STRETCH-EVOKED COMPOSITE MONOSYNAPTIC Ia EPSPs IN MOTOR UNIT TYPED ANKLE EXTENSOR MOTONEURONS FOLLOWING CHRONIC SPINAL CORD TRANSECTION

A Thesis
Presented to the
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In Partial Fulfilment of the Requirements
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MASTER OF SCIENCE
IN
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by

Allen Sohrab Jones

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ACKNOWLEDGMENTS

"I do not know what I may appear to the world; but to myself I seem to have been only like a boy, playing on the seashore, and diverting myself, in now and then finding a smoother pebble or a prettier shell than ordinary, while the great ocean of truth lay all undiscovered before me."

Sir Isaac Newton, 1727

So that historians of another time or other planets may better understand our culture, I have decided to begin these acknowledgments with some of the comments that I faithfully recorded in the Protocol during the experiments that formed my thesis. This "Banter of 20th Century Electrophysiologists" will no doubt be required reading for school children in the millennia to come.
(This font indicates what was actually written in the Experimental Protocol, and *italics is just to clarify things.*)

June 15 1989
DAVE: We don't want to stimulate triceps surae, therefore less than ideal conditions to track for triceps surae motoneurons.

18:00 Whaler fish filet and choc shake *[What I ate at Burger King.]*

DAVE: This is your basic Fast. *[Fatiguable motor unit]*

SHAWN: This goes up more. This comes down. *[Shawn adjusts the bridge balance.]*

June 20 1989
SHAWN: We've forgotten to put on the EMG. *[EMG = ElectroMyoGraph]*
DAVE: This looks very weird. It's AC coupled - that's why. Bad boy.
DAVE: Everything in the world will sag at the right frequency. So you have to be careful about frequency. It's the 1.25 we care about.
DAVE: Cell looks like dog doo.

SHAWN: That's the EPSP that ate New York. *[EPSP = Excitatory Post-Synaptic Potential]*

August 16 1989
[We just impaled a] Renshaw cell - fastest firing cell in spinal cord. 2000 Hz for about 25-30 spikes.

Nov 15 1989
SHAWN: You gotta love these young cats. The nerves come apart so easily. (After dissecting LG from TIB.) *[LG = Lateral Gastrocnemius, TIB = Tibial]*

DAVE: Hannibal could have used it *[Shawn's wire from muscle to force transducer and muscle puller]* to pull his elephants over the Alps.

DM saw on the IC trace a "monosynaptic recurrent." This is translated as a monosynaptic EPSP followed by a recurrent IPSP. The NB point is that MN 1 need not spike in order to get Renshaw inhibition. The RC of MN 2 (MN 2 spiked; Maybe it received more Ia afferents or had bigger EPSPs.) gives an IPSP to MN 1. *[IC = IntraCellular, IPSP = Inhibitory Post-Synaptic Potential, MN = MotoNeuron, RC = Renshaw Cell]*

Bacon double cheeseburger, choc shake, sm garden salad, apple turnover

SHAWN: Cell !@#$ now. !@#$. Write that down Al.

Cell 3 MG *[Medial Gastrocnemius]*
SPCT 12 nA *[Short Pulse Current Threshold]*
SHAWN: Still bloody nice. Still bloody stable.
Rheobase 3 nA
DAVE: So we're a slow.
DAVE: Look at that EMG. The muscle is going crazy.
SHAWN: Is the muscle being stretched too much?

SHAWN: Electrode resistance is just disgusting.

Nov 23 1989
DAVE: It's not a slow. I can see the whole muscle twitching.

Cell 2 MG. Shawn uses bridge balance
SHAWN: Electrode is polarizing. It's a !@#$ electrode.

DAVE: How's your electrode?
SHAWN: 13 MΩ. That's the relevant question. Forget it *[membrane time constant]*.

DAVE: Have stretch EPSPs ever been done in motor unit typed cells?
SHAWN: Never.
DAVE: Yes. Never.

[Later, electrode resistance is 1.1 MΩ.]
DAVE: I'm pretty sure I didn't break it.
[Al's note]: Remember, as tip size decreases, resistance increases. Hence the small resistance suggests a broken tip.

SHAWN: I'm gonna do rheobase for the folks back home.

Feb 22 1990
We get electrical EPSP. We can't get stretch EPSP, however. Nor can we get a twitch from the muscle.

BP is 60.
DAVE: That's what you get when your BP is 60. Your peripheral circulation shuts off.

Jan 17 1990
SHAWN: You are a big cat.

SHAWN: Sharon is a great assistant because she concentrates.

SHARON: You're worrying me. How come you have nothing in your bladder?

Feb 27 1990
SHARON: I took off 6,5,4. *[L4-L6 laminectomy.]*

DAVE: Electrode resistance changes with cat's breathing.

DAVE: There's many people on this planet, Al, who don't believe you can do this.
AL: What?
DAVE: Penetrate a cell and leave and come back. *[Dave just re-penetrated cell 6.]*

DAVE: Rheo 19. Very hard to say. Electrode is bouncing away all over the place.

March 15 1990
AL: Do you want to play loosen-tighten? *[Adjusting the stimulating electrodes on the peripheral nerves.]*
SHAWN: No, Dave will be coming back right away.

The IC trace moves up and down on scope screen in phase with movements of the spinal cord.
DAVE: This is what the cervical cord looks like. (i.e., the up and down movements with respiration.)
DAVE: That's amazing.

DAVE: So is Al gonna learn to drink scotch tonight!
AL: No, it's tainted the smell of my cup from last week.
SHAWN: I would say given everything *[tonight]* we shouldn't trust any data.
DAVE: I agree. *[pause]* !@#$. *[pause]* !@#$.

March 22 1990
DAVE: I know whereof I speak. *[re: separating plantaris nerve a bit more for mounting.]*

DAVE: God, these are huge PSPs.

DAVE: OK. Onward and downward.

DAVE: This is like the first cell we had and I don't know what the hell it is. I'd sure like

to know what those cells are that get MG EPSPs but don't cause MG EMG.

[We penetrate a cell with a long AHP. AHP = After-Hyperpolarization Potential]
DAVE: Mother. *[say like Sylvester]*

SHAWN: 20 μm recruits the bugger even at H6.

DAVE: Cell getting !@#$.

Burger King: Whopper with cheese, sm garden salad with 1000 Is, choc shake.

DAVE: Just do a Rin to satisfy the powers that be.

SHAWN: It's not one of ours.

SHAWN: I'm going to give you *[Al]* a trophy for best protocol taker. *[Al blushes and feels hot in the face.]*

Camera acting funny: LED goes off and shutter stays open.
DAVE: Weird logic state.

DAVE: Double anti. *[So]* could be an FF. *[I give Dave that uncomprehending blank look of a dumb dog.] [FF = Fast Fatiguable motor unit]*
SHAWN: It's a fast for sure. It's got a short AHP.

DAVE: It's pretty violent contractions you're giving it there kid.

DAVE: EMG not good for some reason, but APs *[Action Potentials]* are OK.

DAVE: I just lost it. I just got it again. Ye of little faith. 85 *[mV]*.

DAVE: LGS. Big as a house. *[LGS = Lateral Gastrocnemius/Soleus]*
SHAWN: Major sag city. *[Sag in conductance (as opposed to sag in sag test)]*
SHAWN: So this is gonna be a FF. *[Rheobase was 26 nA]*
DAVE: We've never seen a Slow motoneuron with an EMG of this size.
DAVE: EMG is fine.

SHAWN: Sags like crazy.
DAVE: Almost no AHP.
DAVE: EMG looks fine.

00:45 This cell we got on the 3rd track, which was to be our last. Bwana McCrea and Bwana Hochman.

DAVE and SHAWN in unison: Onward and downward.
DAVE: Not a hint of PL. *[PL = Plantaris]*

We lived in fear at all times ce soir that one Gregory Karmy might blow us all to smithereens with his perfusion equipment and 900 mm Hg air pressure.

March 29 1990
At about 08:45 Sharon performs tracheostomy while humming to some tune by Edie Brickell and the New Bohemians, or was that Bonnie Raitt.

16:30 Eyes fairly big.
17:27 DAVE: That looks like a real EC. *[ExtraCellular field potential]*
BRIAN NOGA: Quite a large AP. 80? 90?

[3 μm is threshold for stretch EPSP]
DAVE: That's half the diameter of a red blood cell. Blows my head, every time I see it. I can't get over it.

17:55 Eyes like slits - like a dime couldn't pass thru edge-on.

19:35 24 breaths/min 3% CO_2

21:39 EMG looks good.

23:08 Good EMG.

23:50 Al's pulse: 47-48/min.

[We can no longer get cells at midnight]
DAVE: Al, I hate to say it, but I think we're licked.

Gregory Karmy, a most unusual émigré from Riga, does a perfusion when we could no longer get cells.

April 19 1990
DAVE: Sag city. Could be an FF. *[Sag in middle of voltage deflection due to 50 ms 2 nA hyperpolarizing current pulse to determine input resistance.]*

DAVE: Beautiful delayed depolarization.

SHAWN: Here's a picture for Al.
SHAWN: Here's a picture for Al's buddies.

Shawn goes into cell and sets "DC nullifier" *[Dave's term]* (red LED digital display on Dagan Interface) to 0. Then he saw it depol to 10. When pull out of cell DC goes to 48. 48 +10 = 59 mV $V_{resting}$.

18:46 Choc shake, whaler, sm gdn salad with 1000 Is. DM leaves for his band practice after Burger King.

SHAWN: That's a slow if I ever saw one.

21:23 *[Al's note]*: DM returns from band practice, which is held in his basement, which right under TV, which is why Maria can't watch TV, which is why she'll go home to her mother in Sweden, which why DM will go to Sweden and say sorry Maria.

SHAWN: We're not a 3 (MG). *[3 is number of stimulating electrode for MG nerve.]*
SHAWN: We're not a 5 (PL).

22:10 We are back onto Masscomp now. DM rebooted computer from a terminal in another lab. DM, i.e. Spock, to the rescue yet again. Where would the USS Neuroprise be w/o him?

SHAWN: That's the first cell we've lost while trying to type.
DAVE: !@#$. Who knows? *[re: time to peak of potentiated muscle twitch.]*

SHAWN: Spike at end only in our imagination. *[re: action potential height of cell when we leave it.]*

23:10 Shawn barbs cat to "Love makes no promises" by Candy. Something morbid in that.

SHAWN: There were small PSPs in this cat.

As we clean up DM splashes urine on cat's tail (tail was in urine cup which bladder catheter emptied into) into his face and my hair. I tell Sharon on Friday. She says "Did you take a shower when you got home?" I say no. *[Which is pretty disgusting don't you think?]* She says "Boy, I wouldn't let you get into bed with me unless you had a shower." I say "Great, no date, all I have to do is take a shower!!" Pat Carr nods in agreement.

<u>September 6 1990</u>
DAVE: The AHP was as long as tomorrow.

DAVE: PL gets EPSPs from FDHL. There's a PL field here. *[PL = Plantaris, FDHL = Flexor Digitorum/Hallucis Longus]*

17:30 DM leaves to get his Med I teaching award.

<u>September 13 1990</u>
Al successfully set thresholds. Miracles never cease and miracles will continue n'est ce pas?

DAVE: Virtually no EPSP. Looka that.
DAVE: Cell lost. Damn.

DAVE: I think there's no doubt it's a slow. With half a gram tension.

DAVE: I'm pretty confident that fatigue test was OK. EMGs hard to see.

No EMG *[60 seconds into fatigue test]* b/c cell lost b/c Zeus disapproves of something Dave or I did.

DAVE: Electrode is dog doo.

[2T electrical stimulation of PL]
DAVE: There was nothing, so it's all homonymous in this cell.

September 24 1990
DAVE: Have you ever heard of an unlesioned Fast *[in Soleus]*?
AL: No.
DM nods in utter and total agreement.

DAVE: So we're holdin' em real well today.

DAVE: It's gonna be FF. It's gonna be FR. I can feel it in my bones.
DAVE: Well it's gonna be a slow. There's no doubt about that with that 120 ms AHP. I'd bet a large sum of money on it.

17:35 Back from BK. Choc shake, bacon double cheeseburger (no pickles), lg fries, sm salad, Paul Newman's 1000 island dressing.

DAVE: It's an honest 60 *[mV]* now.

DAVE: It gets a big EP from Tib *[Cell was PL]*

Well, with that Brief History of Electrophysiological Time complete, there are an innumerable number of people whom I would like to acknowledge for their direct involvement or association with this Master's degree.

Dr. Dave McCrea, my supervisor, to whom I owe so much, how can I thank you enough for teaching me to think and to appreciate the majesty of the scientific process. You supported me through my times of difficulty and never lacked in concern for my well-being. Your warmth, your wisdom, your patience, your great intellect - I shall always admire your qualities. Thank you, Dave. Here's a little ditty dedicated to you (maybe the Big Roll Band can play it sometime):

> "These are the Dave's I know I know, these are the Dave's I know. Some of them are David's, but most of them are Dave's. They all have hands, but they come from different moms." ("Dave's I Know" by The Kids in the Hall).

To Dr. Larry Jordan, of my thesis committee, who said to me during my first student evaluation: "You have a pub level understanding of neuroscience," I am proud to say, Larry, that I now have a lounge level understanding.

To Dr. Judy Anderson, my external examiner, thank you for your support and the smiles you always greeted me with.

To Dr. Shawn Hochman, I am greatly indebted, for he had the onerous task of

answering the many questions I was too embarrassed to ask Dave, lest he think me more of a Philistine, eg., "Uh, Shawn, where's the power button for the rack?" It was Shawn who introduced me to "the most important word in science, and in life, the P word - perspective" (Or would that be peanuts, Brent?), and I thank him for that. And of course thanks to Dr. Karen Hochman, who, in her chats with me, dispelled my misconceptions about conception.

To Sharon McCartney, my thanks and my hugs. You were never without a smile, and your laughter always filled the lab. Where would my posters, presentations, and thesis have been without your AutoCadding, WordPerfecting, and Letrasetting? And who else could lie so smoothly to girls on the phone for me?!

To Dr. Susan Shefchyk, rapier wit always at the ready, thank you for your support, and your kind words. May we continue to meet annually at the Dayminder's of America Conference on Organization.

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Thanks to the ever-amiable Matt Ellis, who could easily host a PBS news show called "The Ellis Group" or something like that. Matt, where on earth do you acquire your bountiful collection of bizarre T-shirts? That has always puzzled me. And where is Jimmy Hoffa buried? That has puzzled me too.

To Dr. Chris Livingston, thank you for your concern - it was always appreciated. Thanks for the great conversations about wine, women, and song. Say hi to Jennifer, and for God's sake, do something about that rabbit.

To Maria Setterbom, my lunch companion and rival for calories consumed, thanks for your laughter and your cheer. Say hi to Victoria.

To Dr. Lisa LaBella, thanks for the advice on school and relationships.

To Dr. Brian Noga, alias Dr. Brian Friendly, thanks for your tizanidine files, and your constant corny humor.

Thanks to Nancy Eidsvig, who always had a smile and a birthday cake on the way.

Thanks to Jennifer Douglas, for your enthusiasm and your gentle nature.

As I write these thanks, I notice this recurring theme that everyone is always smiling. Why is that? Matt Ellis surely must know the answer.

Thanks to Lei Song, for telling me that when you're writing your thesis, "It doesn't have to be perfect."

Thanks to Xiao Hong Dai for your smiles, your conversation, and this greeting whenever I met you: "Hi, Al! I thought you were gone."

Thanks to that juggler/unicyclist/comparative vertebrate anatomist Mike Sawchuk. Thanks to Andy Ochalski and good luck with your mathematical modeling of the cultural traits of the Haida Indians of the B.C. coast. (Yikes! No word of lie, that is what he said to me.)

Thanks to Kim Madec for your good cheer. One day I hope to have ripped forearms like you.

To Gilles and Gilbert Detillieux, those 2 fellows of a single egg, my thanks for all that colossal software you created for the Masscomp. Gilles, I noticed that you still have that Castle GreySkull PEZ dispenser from Phoenix. Do you really think the housekeeping lady ate the PEZ? Gilbert, I still think that story that you told on the way to Phoenix about you as a child seeing the Apollo spacecraft orbiting the moon, using your K-Mart telescope, is totally hokey.

Thanks also to Dr. Dr. Rob Brownstone, Dr. Dean Kriellaars, Dr. Jim Nagy, Dr. Toshi

Yamamoto, Dr. Dwight Nance, Dr. Pat Nance, Peter Cunningham, Qiying, Yiching, Dave, Mark Nachtigal, Andrew Halayko, Ingo, Aris the towering Greek with the Hollywood hair, Antonio Torsello, Gail, Judy, Maureen, and Godzilla.

I give special thanks to Pat Carr, Brent Fedirchuk, Kris Harder, Mike Angel, and Charles Ikejiani for their friendship, much laughter, and valued advice on school and life.

Pat, who else but you would have read the entire Childcraft Encyclopedia by grade VII?. And who else but you would live in abject fear that he would contract the Andromeda Strain from all cans of pop, and therefore carries a disinfectant kit to the cafeteria. The hours spent in conversation with you were so full of laughter, and learning, and introspection. Your passion for knowledge I have always admired, and I wish you a most fruitful scientific career.

Brent, you little rascal, always a grin on your face, and a penetrating question formulating. I envy you for your insight (Mike does too. He told me so in the strictest confidence), but I am happy to know it will carry you far.

Ode to Brent Fedirchuk. Brent tells me (to the best of my recollection) January 30, 1991 how he used his science knowledge:

"There was a leak in the cottage roof, so I put a steel pot underneath it, but I didn't want it to overflow while I was sleeping.

I figured each drop was 0.05 ml, and the drops were falling at 1 hertz, therefore the roof leaked about 3 ml per minute, therefore 180 ml per hour.

If I slept for 10 hours, the pot would have 1800 ml of water in it.

The pot was 3 1/2 litres, therefore I was OK."

This astonishing display of mental bronco riding leaves little doubt in my mind that Brent will one day "figure out how the brain works" (as Dave always says).

Kris, you of the mischievous smile and the great charm, you are so cool. Are you still fretting over that "region of negative slope conductance"? You are the only person in the department who is as immature as me, and I am deeply grateful for your company in that respect.

Charles "Sleight of hand, slight of mind" Ikejiani, how I miss those nights at Strawberries! So does Vic. The memory of your hysterical laugh and your great love of life brings a smile to me. The last time I saw you, you were about one action potential away from hurling (again) - most unbecoming of a future physician!

Mike "Big Man on HippoCampus" Angel, wherever did you get your twisted sense of humor? I can recall many the diagram drawn with erasable marker on the board in Rm 411 that, were it seen by eyes other than Pat, Brent, Mike, and Al, would surely have resulted in a dismissal to the Greater Siberian Electrophysiology Gulag. Well, what can be said about Mike Angel that hasn't already been said before at AA meetings? Mike is the kind of guy who makes jokes about the SI unit of conductance to girls at the Marble Club. But to his credit, he's a hell of a tennis player, a comedian, and one cool guy. p.s. If you do not send me $500 monthly, I shall be forced to tell your examining committee how you lied to a car-full of innocent girls after Octoberfest in order to procure transport to your home. By the way, your name has not opened any doors here in Toronto, rather a great scowl and a cauldron full of boiling oil dumped upon my head.

To those who would say this acknowledgment is merely a weak attempt to increase the length of my thesis (eg., Pat Carr, Kris Harder), I reply that you are suffering from the fatuous, mental meanderings of your 5 nanogram brains (2 and 3 nanograms respectively).

My thanks to The Medical Research Council of Canada and the Canadian Paraplegia Association for their generous funding.

I also extend my thanks to Dr. Albert Bush for his great pride in science and having

sparked my interest in it.

To my good friends Karl "The Enigmatic Cellist" Toews, Gord "I've had more women than vertebrae in the human spine" Rust, Cam "'Milton at the Hilton: English Professor Caught With Harlot In Scarlet'" Stewart, Kerri "Mr. Sardonic Wit" Auriat, Alex "Bavarian Motor Works is Justification for Higher Education" Pappas, Michael "Those guys at U of M/W are such assholes" Cayer, Chris "Hydrant Painter from Hell" Donnelly, Mignon "She moves in mysterious ways" Alphonso, Jack "The King of Leisure Activities" Witt, Adolph "Fool for a client" Gameiro, Shy "Mrs. Robertson, I am not a felcher" Kurtz, and last but certainly not least, Terry "The Wil E. Coyote Never Pays Full Price" Hermanson, thanks for the laughs and support along the way.

To my taekwondo family, I say thanks to Master Am Lee, Rob "I'm already two drinks ahead of you" Pavlicic, Victor "This GAP belt cost me 60 bucks" Luke, and Tim "Those Bangers Have Amazing Endurance" O'Toole.

Lastly, many thanks to my family. To my mother, Khorshed, for her total support and love to me throughout this master's degree. Mummy, always a smile on your face, always a laugh when I call collect as "Ali Baba or Toto or Ibrahim or Jawaharal Nehru", God bless you. And of course, thanks for the weekly supply of groceries you put together. To my philosopher father, Richard, who brought me my groceries ("provisions", as Dad put it) every week, my dinner companion at Deen's, and who kept up a vigil of the rewards of an academic life, thank you for exposing me to your humor, your wisdom, and your love. To my sister Ura, who always brightened my life with her magical laughter and her abiding love, you never fail to inject some sense into my life and put things in perspective. Yes, I know I never came to Toronto! Hugs and kisses and punches, dear Ura. And John Paul too.

Did I miss anybody? I guess I'll also thank the operating room staff at the Aga Khan Hospital in Nairobi, where I was born.

Finally, I acknowledge perhaps the most important scientific paper ever written, which has had a profound influence on my life: Sherrington, Sir Charles. 1905 Dec 02. The importance of longer hours of sleep at public schools. Brit. Med. J. 2:1469-1471.

Hear yea for the great neuroscientists!!

Le Fin

ABSTRACT

Excitatory postsynaptic potentials (EPSPs) produced in medial gastrocnemius, lateral gastrocnemius, soleus, and plantaris motoneurons by 3-5 ms duration triangular wave stretch of the homonymous and heteronymous muscles simultaneously was observed on anaesthetized, six-week L1-L2 chronic spinal (CS) cats and unlesioned (UL) cats. With the muscles held at an initial tension of 100-500 g a stretch of 1-100 μm amplitude was applied and the composite monosynaptic Ia EPSP from homonymous and heteronymous Ia afferents recorded in the motoneuron. Mean Ia EPSP amplitude was significantly larger in the pool of all motoneurons of the CS preparation than the UL preparation, being 1.9 mV and 1.18 mV respectively for a 20 μm stretch at 100 g initial tension, and 2.92 mV and 2.23 mV respectively for a 20 μm stretch at 200 g initial tension. Mean Ia EPSP amplitude was significantly larger in medial gastrocnemius motoneurons of the CS preparation than the UL preparation, being 2.95 mV and 1.95 mV respectively for a 20 μm stretch at 200 g initial tension. Similarly, in lateral gastrocnemius motoneurons, stretch-evoked Ia EPSPs were 1.05 mV in the CS preparation and 0.45 mV in the UL preparation following a 20 μm stretch at 100 g initial tension.

All motoneurons were motor unit typed as fast-twitch fast-fatiguable (FF), fast-twitch fatigue-resistant (FR), or slow-twitch fatigue-resistant (Slow). The population of FF motoneurons showed an increased mean Ia EPSP amplitude in the CS preparation, being 2.15 mV versus 1.57 mV in the UL preparation following a 20 μm stretch at 200 g initial tension. The same pattern was observed in medial gastrocnemius motoneuron of motor unit type FF, with the mean Ia EPSP amplitude being 2.37 mV and 1.7 mV in the CS and UL preparation, respectively. The most likely explanation, it is argued, for the increased mean Ia EPSP amplitude in homonymous and heteronymous triceps surae and plantaris motoneurons of the chronic spinal preparation is a loss of descending presynaptic inhibition of Ia afferent terminals.

LIST OF ABBREVIATIONS

CS	Chronic Spinal
EPSP	Excitatory Post Synaptic Potential
FF	Fast Twitch Fatiguable
FINT	Fast Twitch Intermediate Fatigue
FR	Fast Twitch Fatigue Resistant
LG	Lateral Gastrocnemius
LGS	Lateral Gastrocnemius/Soleus
MG	Medial Gastrocnemius
MSR	Monosynaptic Reflex
MU	Motor Unit
PAD	Primary Afferent Depolarization
PL	Plantaris
PSR	Polysynaptic Reflex
SOL	Soleus
T	Threshold
TS	Triceps Surae (LG, MG, and SOL)
UL	Unlesioned

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INTRODUCTION

The present experiments were undertaken to further elaborate the neurophysiological mechanisms underlying spasticity - the altered proprioceptive (stretch) reflexes occurring after spinal cord injury. What follows in this Introduction is a short description of the types of spinal cord injury and their manifestations in the human patient, then a definition of spasticity (rather broad as it turns out), some of the animal models that have led to our understanding of the control of stretch reflexes, the experiments that focus on the monosynaptic stretch reflex, and finally the hypothesis of the present work.

TYPES OF INJURY AND THEIR MANIFESTATION

Acute traumatic injuries to the human spinal cord fall into one of three categories. In the first case, that of the transected spinal cord, there is complete functional and structural separation of proximal and distal parts of the cord, so that motor and sensory functions below the level of the lesion are lost (Dimitrijevic, 1988). In the second case, the incomplete lesion, an example of which is hemisection of the spinal cord, there is preservation of some of the normal motor and sensory abilities. The third case, the dis-complete lesion, is more allied with the completely transected spinal cord because of the severity of the lesion; there are only minimal structural connections between the proximal and distal portions of the cord so that motor and sensory functions appear absent upon clinical observation, but may be revealed electrophysiologically (Dimitrijevic, 1988).

The behavioral signs that appear following spinal cord injury are termed "release phenomena" because structures below the level of the lesion are removed, that is, released, from facilitatory or inhibitory influences above the lesion (Barnes and Schadt, 1979). The

so-called "negative" behavioral signs are characterized by a decrease in normal function, and include loss of volitional control of the somatic muscles, muscle weakness, and loss of dexterity (Burke D., 1988). A negative sign that may occur following severe spinal cord trauma is spinal shock (to be elaborated upon later in this Introduction), a period of areflexia that may last for weeks in humans (Barnes and Schadt, 1979).

The "positive" behavioral signs appear as an exaggeration of previously normal cutaneous and proprioceptive reflexes. By 1-3 weeks after a complete spinal cord transection in the human a flexion withdrawal reflex is present. By 3-7 weeks tendon jerks reappear and are exaggerated (Kuhn, 1950). In some patients there are exaggerated tendon jerks, unsustained clonus, and short-lasting ipsilateral withdrawal reflexes. In others there is excessive hypertonicity of the paralyzed limbs in the extended or flexed position after proprioceptive or cutaneous stimuli (Dimitrijevic, 1988). These reflexes may be so profound as to fracture bones in the leg, or to cause a paraplegic patient considerable difficulty in remaining in a wheelchair. At 6-12 months there are predominantly extensor spasms, and maximal reflexes are seen 9-12 months after the injury (Burke D., 1988). Those patients with incomplete lesions report more interference with activities, more pain, and less functional usefulness, that those with complete lesions. Extensor spasms interfere with transfers, whereas flexor withdrawal spasms are more frequent at night and interfere with sleep (Little et al., 1989). Positive signs should not necessarily be thought due to the removal of inhibitory influences, nor negative signs purely the result of the removal of facilitatory influences.

DEFINITION

In medical parlance, spinal spasticity is defined as a motor disorder characterized by exaggerated phasic stretch reflexes and a velocity-dependent increase in tonic stretch reflexes

(Landau, 1974, Lance, 1980). The exaggerated phasic stretch reflex, also known as tendon jerk hyperreflexia, can be elicited by tapping the patellar tendon with a hammer or sharply with the fingertip, and results in a supranormal extension of the knee. A tendon tap that is subthreshold for a stretch reflex in an unlesioned patient may result in one in a patient with spasticity. The second criterion, the velocity-dependent increase in tonic stretch reflexes, is felt by the examiner as a resistance to passive stretch of a muscle, where the resistance is proportional to the velocity of the imposed stretch. This can be demonstrated upon passive supination or pronation of the forearm, passive stretch of the biceps, or passive stretch of the quadriceps.

The definition of spasticity also includes the clasp-knife reflex and clonus. Clonus is the appearance of uncontrollably repetitive stretch reflexes. It is characterized by a 5-8 Hz oscillation at a joint that can be elicited by stretch of the muscle, for example by rapid dorsiflexion of the ankle or by tendon tap (Burke D., 1988). The clasp-knife reflex is a phenomenon that occurs when a hypertonic muscle, for example the quadriceps, is passively stretched. After an initial resistance to the passive stretch, there is a sudden relaxation. The initial resistance is due to increased transmission from Ia afferents to homonymous motoneurons (those motoneurons innervating the same muscle from which the Ia afferent arose). The sudden relaxation was formerly thought due to an inhibition of the homonymous motoneurons by group I inhibitory interneurons activated by group Ib (golgi tendon organ) afferents (Granit, 1955). It is now considered due to group III and IV muscle afferents that may cause a flexion reflex withdrawal through the flexion reflex afferent pathway and therefore inhibit the extensor quadriceps (Holmqvist and Lundberg, 1961, Rymer et al., 1979, Cleland and Rymer, 1990).

The use of the word spasticity in the literature may be so broad as to include flexor

spasms due to exaggerated cutaneous reflexes (Meinck, 1985), and impairment of volitional movement and postural control (Hoogstraten et al., 1988). To summarize, spasticity results from the loss of descending control of spinal neurons because of damage to fibers of the pyramidal (corticospinal) tract and parapyramidal pathways (Lance, 1980), which may result from lesions to the cerebral cortex, internal capsule, brainstem, or spinal cord. Hence we distinguish between "central spasticity" and "spinal spasticity". Semantics aside, an improved understanding of the pathophysiology of the gain in reflexes following both spinal cord and supraspinal injury can be achieved by focusing on the mechanism underlying spinal spasticity.

ANIMAL MODELS

Spinal spasticity in the human can be mimicked with appropriate animal models. Preparations that demonstrate altered stretch reflexes include the decerebrate cat, the hemisected cat, the acute spinal cat, and the chronic spinal (CS) cat.

Two types of decerebrate cat preparations, the intercollicular and the anemic, have shown that there is much complexity in the organization of the afferents, motoneurons, and interneurons subserving stretch reflexes. In the intercollicular decerebration there is a transection of the midbrain between the inferior and superior colliculi. The effect of removing cortical input to the midbrain is that extensor gamma-motoneurons and extensor alpha-motoneurons receive a larger input from the reticular extensor facilitatory area than the reticular extensor inhibitory area. The gamma drive to muscle spindles of extensor muscles is increased (Hunt and Perl, 1960), and the result is that the sensitivity of muscle spindles to stretch is greatly enhanced, producing a rigidity of the limbs known as "gamma rigidity" (Sherrington, 1898, Granit, 1955, Barnes and Schadt, 1979). In particular, the activity of the static gamma motoneuron is increased in the decerebrate cat (Matthews, 1972), the effect of

which is to increase sensitivity to static stretch. If the ankle extensor muscles of the decerebrate cat are held in a stretched position a continuous EMG discharge is recorded (Brothers et al.,, in preparation). This observation can be partially explained by three factors. One, the static gamma motoneuron innervates the nuclear chain intrafusal muscle fiber more than the bag type 1 or bag type 2 intrafusal muscle fibers. Two, the static gamma motoneuron drive is increased, and therefore the nuclear chain intrafusal muscle fiber is more taut. Three, the nuclear chain intrafusal muscle fiber is innervated preferentially by the Group II afferent, which is sensitive to static stretch and much less to dynamic stretch (The nuclear chain intrafusal muscle fiber is also innervated by the Ia afferent, which is sensitive to both static and dynamic stretch) (Matthews, 1981, Hasan et al., 1984).

If the midbrain transection of the intercollicular decerebrate cat is accompanied by ligation of the basilar and carotid arteries, the so-called "anemic decerebration", then a condition known as "alpha rigidity" results (Pollock and Davis, 1930, 1931, Barnes and Schadt, 1979). The anemic decerebration ablates the anterior lobe of the cerebellum, such that the Purkinje cells of the cerebellar cortex no longer inhibit the cells of the vestibular (Deiter's) nucleus. The latter, via the lateral vestibulospinal tract, tonically depolarize extensor alpha-motoneurons. The extensor rigidity of alpha rigidity (intercollicular decerebration plus anemic decerebration) is greater than gamma rigidity (intercollicular decerebration) since both extensor gamma-motoneuron drive to muscle spindles is increased and extensor alpha-motoneuron drive to extensor muscles is increased (Pollock and Davis, 1930, 1931). If the dorsal roots are now cut, the extensor rigidity is not abolished. The reason is that the excitatory drive from the vestibular nucleus to extensor alpha-motoneurons is so great, that in spite of removing the excitatory input from spindle afferents to the extensor motoneurons, the extensor rigidity is maintained. If decerebration is followed by spinal cord transection,

which severs the lateral vestibulospinal tract, then the greatly enhanced stretch reflexes are lessened (Fulton et al., 1930, Liddell, 1934, Ellaway and Trott, 1975). This is reversed by the administration of 5-hydroxytryptophan, which is thought to directly facilitate the Ia pathway to alpha motoneurons (Ellaway and Trott, 1975).

The problem with the decerebrate cat preparation as a model of human spasticity is that although it mimics the increase in muscle tone and increase in stretch sensitivity seen in human spasticity, it does so primarily through an increased excitatory drive to gamma-motoneurons. Studies have shown, however, that fusimotor (gamma) activity is not increased in cats with spasticity (which is best produced by the chronic spinal transection preparation, as will be discussed shortly) (Fujimori et al., 1966, Bailey et al., 1980). Furthermore, an increase in static stretch sensitivity is not seen in human spasticity (Hagbarth et al., 1973).

The rationale for the hemisected cat is a good one; the limb ipsilateral to the lesion is predicted to be hyperreflexic, and the limb contralateral to the lesion is to serve as a control. The fact, however, that some descending pathways contralateral to the lesion may have bilateral effects on spinal circuitry may contribute to the hemisected cat being an unreliable model of spasticity (Ashby and McCrea, 1984). Some investigators have noted an increased monosynaptic reflex on the hemisected side several weeks after mid-thoracic spinal hemisection in cat (McCouch et al., 1958). Others have noted no increase in the monosynaptic reflex of hemisected cats, but an increase in the polysynaptic reflex (Teasdall et al., 1958, 1965). Still others have noted an increase in both monosynaptic and polysynaptic reflexes 3-5 weeks after T8 hemisection (Fujimori et al., 1966).

In cats hemisected at the L2 level, muscle tone was elevated in extensor muscles 2-3 days after the lesion but returned to normal levels 1-2 weeks later (Hultborn and Malmsten,

1983). Only minimal increases in muscle tone and tendon jerks of ankle extensors were reported in cats hemisected at the L2 level (Brothers et al.,, in preparation). The authors of both studies concluded that the hemisected cat was an unsatisfactory model of human spasticity.

The acute spinal cat model suffers from a serious limitation - it does not allow time for the possible changes that occur in human spasticity, that is, plasticity of the reflex pathways. It has, however, provided insight into the synaptic changes occurring immediately after spinal cord transection, as will be noted in the Discussion.

A syndrome of spasticity develops slowly in the chronic spinal cat, as it does in the human. By one week after a complete L2 transection, the hindlimbs are mildly hypertonic and moderately hyperreflexic, and by 4 weeks are markedly hypertonic and markedly hyperreflexic (Bailey et al., 1980). Also present are clonus, an exaggerated flexion reflex, flexor and extensor spasms, reflex stepping, and reflex standing (Sherrington, 1906, Bailey et al., 1980, Naftchi, 1980) This reflex activity is maintained over weeks and months (Nelson and Mendell 1979, Brothers et al.,, in preparation).

EMG studies of the L2 chronic spinal cat revealed that short latency (11 ms) and long latency (25-40 ms) reflexes in medial gastrocnemius muscle in response to ankle dorsiflexion were increased in amplitude (Brothers et al.,, in preparation). The short latency reflex is known to be largely monosynaptic based on the latency of the H-reflex (Lloyd, 1943a,b, Teasdall et al., 1958). Based on the findings, the chronic spinal cat is the most appropriate model of spinal spasticity, and the monosynaptic reflex the most suited for an examination of hyperreflexia.

What are the causes of the increased MSR in the chronic spinal cat?

The monosynaptic reflex is mediated by the primary muscle spindle afferent (group Ia afferent)(annulospiral ending) - the largest diameter fiber in the hindlimb muscle nerves. It is therefore the first recruited by liminal electrical stimulation, which is designated as an electrical threshold (T) of 1.0T (Hunt, 1954, Sumner, 1961). The advent of intracellular recording permitted the synaptic actions of muscle spindle group Ia afferents (Eccles et al., 1957a, Eccles and Lundberg, 1958, Eccles et al., 1962), Golgi tendon organ (Eccles et al., 1957b), and higher threshold afferents (Eccles and Lundberg, 1959) to be examined. Activity in group Ia muscle spindle afferents causes monosynaptic excitation of homonymous and synergist motoneurons (Eccles et al., 1957a); disynaptic, trisynaptic, and late polysynaptic excitation have been observed as well (Jankowska et al., 1981a,b, Jankowska and McCrea, 1983). Group Ia afferents disynaptically inhibit antagonist motoneurons via the Ia inhibitory interneuron ('reciprocal inhibition') (Hultborn et al., 1971a,b), and disynaptically inhibit homonymous motoneurons via the group I inhibitory interneuron ('non-reciprocal inhibition') (Fetz et al., 1979, Jankowska et al., 1981a). Also, Ia afferents may inhibit gamma motoneurons via the group I inhibitory interneuron (Fetz et al., 1979). Finally, primary muscle spindle afferents of the cat hindlimb project in the dorsal columns as far as the upper lumbar segments and commonly to low thoracic segments (Fern et al., 1988a). At L3 and L4 the Ia afferents relay onto neurons of the dorsal spinocerebellar tract (Clarke's column) (Lundberg and Winsbury, 1960b, Fern et al., 1988b).

A number of studies have examined the effects of spinal cord transection on both unitary and composite Ia EPSPs in ankle extensor motoneurons, most commonly medial gastrocnemius (MG) motoneurons. Unitary EPSPs are those in which the EPSP recorded in the motoneuron is due to the activation of a single Ia afferent fiber, while a composite

EPSP is due to the activation of a population of Ia afferent fibers, for example the roughly 60 Ia afferents that innervate the MG muscle (Boyd and Davey, 1968). These studies of unitary and composite EPSPs reveal a transient increase in homonymous or heteronymous Ia EPSPs in MG motoneurons following spinalization. Homonymous EPSPs are those in which the Ia afferent monosynaptically contacts a motoneuron which innervates the same muscle from the Ia afferent arises (for example, an MG Ia afferent monosynaptically contacting an MG motoneuron). Heteronymous EPSPs are those in which the Ia afferent monosynaptically contacts a motoneuron which innervates a muscle other than the one from which the Ia afferent arises (for example, an MG Ia afferent monosynaptically contacting an LG motoneuron).

Composite Ia EPSPs. Munson and colleagues (1986), in a study of L4-L5 chronic spinal cats, found that the amplitude of composite heteronymous Ia EPSPs in MG motoneurons was increased significantly at 1-3 weeks post-lesion, but returned to pre-lesion levels 4 to 7 months post-lesion. Mayer and colleagues (1984), in a study of T13-L1 chronic spinal cats, reported that neither homonymous or heteronymous Ia EPSPs were increased 6 months post-lesion. Hence the composite EPSP studies indicate an enlargement of Ia EPSPs in MG motoneurons early after the lesion, and then a return to pre-lesion amplitudes.

Unitary Ia EPSPs. The conclusions that can be drawn from unitary versus composite Ia EPSP studies with regard to amplitude increases are necessarily limited. The reason for this is that the latter examine the combined effects of many MG Ia afferents (at least 30 even if only half are recruited) onto MG motoneurons, whereas the former examine only one. Thus composite EPSP studies provide a more realistic view of the synaptic changes following cord transection.

(This is not to say that unitary studies are not useful; in fact they can be most instructive in terms of the information they beget.) Bearing this in mind, the results are as follows. In cats with the spinal cord transected at L4-L5, unitary homonymous Ia EPSPs in MG motoneurons were increased in amplitude more than 3 times that in the intact preparation (from 100 μV to 350 μV) one month after the lesion, but returned to normal levels 4 months post-lesion (Nelson and Mendell, 1979). In another study with transection also at L4-L5, unitary homonymous Ia EPSPs in MG motoneurons were unchanged 2 months after the lesion (Munson et al., 1986). These findings prompted the comment that "the transient nature of this augmentation as well as its dependence upon level of lesion render it an unlikely candidate as a basis for sustained hyperreflexia following spinal injury" (Munson et al., 1986). Such a statement, however, ignored the unreliability of unitary Ia EPSP. Secondly, in the study of Nelson and Mendell (1979), only one cat was used for each of 12 post-lesion experiments measuring unitary Ia EPSP amplitude. Such a small sample size (n=1) per period neglects the considerable variability in EPSP amplitude from cat to cat (composite EPSPs at that), so that an EPSP less than the actual mean value could be interpreted as a return to normal EPSP amplitude (Compare Fig. 7 in Hochman and McCrea, 1992a with Fig. 3 in Munson et al., 1986). Hence the conclusion by Nelson and Mendell (1979) that unitary Ia EPSPs in MG motoneurons of L4-L5 spinal cats returned to normal levels by 4 months post-lesion is somewhat debatable. Furthermore, the authors of the statement above (Munson et al., 1986) used small samples in each of their post-lesion experiments on unitary Ia EPSPs in L4-L5 chronic spinal cats (3 months n=1, 4 months n=1, 7 months n=2).

These objections aside, hyperreflexia is a phenomenon associated not just with increased reflex activation of medial gastrocnemius muscle, but with all the ankle extensor muscles. With this in mind, Hochman and McCrea (1992a) predicted that in chronic spinal

cats, monosynaptic EPSPs would be increased in other ankle extensor motoneurons at a period of time about six weeks after the lesion. Using electrical stimulation of hindlimb muscle nerves, they recorded homonymous and heteronymous composite monosynaptic Ia EPSPs in medial gastrocnemius, lateral gastrocnemius (LG), soleus (SOL), and plantaris (PL) motoneurons of unlesioned and L1-L2 chronic spinal cats, making theirs the most extensive study to date of the changes in Ia EPSPs after spinalization. The EPSPs in the chronic spinal cats were recorded at only one postoperative period, 6 weeks, so that a large number of motoneurons from a total of 20 animals (UL=10, CS=10) could be compared. Homonymous and heteronymous Ia EPSPs in the TS and PL motoneuron populations were significantly larger in the CS preparation ($p < 0.01$) (their data shown in Table 3). Like previous investigators, they found no increase in homonymous Ia EPSP amplitude in MG motoneurons; heteronymous EPSPs in MG motoneurons were, however, increased. In LG motoneurons, both homonymous and heteronymous EPSPs were increased. In SOL and PL motoneurons, homonymous EPSP were increased; heteronymous EPSPs were not tested. In addition, the same motoneurons were grouped according to motor unit type, the three major classes being FF (Fast twitch, Fatiguable), FR (Fast twitch, Fatigue Resistant), and Slow (Slow twitch, Fatigue Resistant) (Burke et al., 1973). Heteronymous Ia EPSPs were increased in all three motor unit types, and homonymous Ia EPSPs were increased only in FR and Slow motoneurons (Hochman and McCrea, 1992c).

A limitation of Hochman and McCrea's experiments (1992a,b,c) concerned the recruitment of Ia afferent fibers in the muscle nerve using bipolar stimulating electrodes. Firstly, the use of a stimulation strength which could recruit all Ia afferent fibers in a hindlimb muscle nerve, approximately 1.9T, was precluded due to the fact that at approximately 1.7T the alpha-motoneuron axon in the peripheral nerve is excited - the resulting antidromic action

potential in the motoneuron obscures the homonymous Ia EPSP (Sumner, 1961). Homonymous Ia EPSPs were therefore elicited at stimulation strengths less than 1.7T, which is submaximal for recruitment of the Ia fiber population. Secondly, electrical stimulation capable of recruiting all the Ia afferents also resulted in inhibition of the motoneuron, which altered the decay phase of the monosynaptic Ia EPSP. This had the effect of altering the risetime and half-width of the EPSP, which were important in modeling the Ia bouton location onto the motoneuron (risetime is the time in milliseconds from the onset of an EPSP to the peak EPSP amplitude; half width is the time in milliseconds from 50 percent of peak EPSP amplitude on the rising phase of the EPSP to 50 percent of peak EPSP amplitude on the falling phase of the EPSP).

These inhibitory processes included: (1) Recurrent inhibition of the motoneuron by Renshaw cells, and (2) Autogenic inhibition of the motoneuron by the group I inhibitory interneuron excited by group Ib afferents at 1.4-1.5T (Sumner, 1961, Fetz et al., 1979). Hence, the electrical studies of Hochman and McCrea were conducted at stimulation strengths of 1.1T, 1.2T, and 1.4T, with the majority of parameters examined at 1.2T.

Some questions unanswered by their study were as follows: Why should heteronymous but not homonymous Ia EPSPs be increased in MG and FF motoneurons following six week chronic spinalization? Was it due to the experimental design? That is, did electrical stimulation for homonymous effects at 1.2T and heteronymous effects at 2T allow a fair comparison of homonymous and heteronymous effects? How closely did electrical stimulation mimic a Ia volley as would occur physiologically?

The present work continued the examination of Ia EPSPs in triceps surae and plantaris motoneurons. The above questions could be addressed in experiments where the

Ia afferent fibers were recruited by a physiological stretch of the ankle extensor muscles. MG, LG, SOL, and PL motoneuron pools would receive a combined input from homonymous Ia afferents and heteronymous Ia afferents. The hypothesis would be that motoneurons of the chronic spinal cat would receive a larger Ia afferent input, whether it be due to homonymous effects alone, heteronymous effects alone, or a combination of the homonymous and heteronymous effects.

A physiological activation of Ia afferents via a pull on the Achilles tendon models the clinical observation of hyperreflexia in response to a patellar or Achilles tendon tap. Furthermore, where electrical stimulation recruits the Ia afferents according to fiber diameter (Hunt 1954), physiological stretch may recruit Ia fibers differently, depending on the location of the muscle spindle location within the muscle and the manner in which the Ia fiber innervates chain, bag1, and bag2 intrafusal muscle fibers. A physiological stretch also has the advantage of maximally recruiting all Ia afferent fibers, which was not possible with electrically evoked Ia EPSPs for two reasons.

Stretch-evoked responses from Ia afferents have been recorded from dorsal root filaments (Lundberg and Winsbury, 1960a, Buller et al., 1960, Ellaway and Trott, 1978) and intracellularly from motoneurons (Lundberg and Winsbury, 1960a, Stuart et al., 1971, Fetz et al., 1979). This paper will examine stretch-evoked EPSPs under two novel circumstances. First, and most importantly, the stretch-evoked EPSPs will be compared in UL and CS motoneurons, the reasons for this having been outlined above. Secondly, the UL and CS motoneurons will be motor unit typed, so that a better understanding of the pattern of recruitment between the two preparations can be gained.

The hypothesis of these experiments was that the combined homonymous and heteronymous monosynaptic Ia EPSP evoked by physiological stretch of the ankle extensor

muscles would be of greater mean amplitude in all ankle extensor motoneurons in the six-week L1-L2 chronic spinal cat than in the unlesioned control cat. The MG, LG, SOL, and PL MN pools as well as FF, FR, and Slow MN pools were predicted to receive larger stretch-evoked composite monosynaptic Ia EPSPs in the chronic spinal cat. It should be noted that the "stretch-evoked" EPSPs referred to throughout this paper are combined homonymous and heteronymous composite monosynaptic Ia EPSPs (Fig. 1).

METHODS

Composite monosynaptic Ia EPSPs evoked by stretch of the triceps surae and plantaris muscles were recorded from homonymous and heteronymous motoneurons in the L7 and S1 segments in 12 unlesioned control cats and 8 cats whose spinal cord had been completely transected at the L1-L2 level 6 weeks prior to the experiment. All animals were young females. The average weight of the chronic spinal cats prior to spinalization was 2.9 kg (range 2.7 - 3.3 kg), and six weeks later the average weight was 3.0 kg (range 2.6 - 3.3 kg).

Dissection and Surgery for the experiment

Surgery was performed using a mixture of oxygen (O_2), and the inhalation anaesthetics Halothane (2-bromo-2-chloro-1,1,1-trifluoroethane) and nitrous oxide (N_2O). The gases were initially delivered into a closed box in which the cat had been placed, and approximately 5 minutes later the unconscious cat was transferred to the surgery table where the gas administration was continued via a mask placed over the mouth and nose. A tracheostomy followed, and the gases were then delivered through a metal catheter sutured into the trachea. A heating pad on the under surface of the surgery table was maintained at the body temperature of the cat (38 °C).

The barbiturate sodium pentobarbital (Nembutal) was introduced into a cannula inserted into the right femoral vein, and Halothane and nitrous oxide anaesthesia discontinued. The cumulative dosage of Nembutal was recorded, and 10-12 hours after the first administration it was approximately 65 mg/kg. The level of anaesthesia was adjusted so that systolic blood pressure was 100-120 mm Hg and pupillary diameter was usually less than 1 mm. An intraperitoneal injection of barbiturate at the onset of the experiment was not

favored due to the variability of the time required for induction of anaesthesia. A heparin-filled cannula inserted into the right femoral artery was connected to a pressure transducer, and blood pressure monitored. A subcutaneous injection of the muscarinic cholinergic blocking agent atropine (0.1 mg/kg) decreased salivation, gastrointestinal motility, and micturition. A cannula inserted into a vein of the right forelimb was used to deliver 0.5 ml (4 mg) of dexamethasone to reduce edema of the spinal cord. The same intravenous cannula was used for continuous administration at 2 mL/hour of a buffer solution containing glucose (5%) and sodium bicarbonate (0.84%).

Muscles and nerves of the left hindlimb were dissected to prepare the limb for muscle stretch and peripheral nerve stimulation. The muscle nerves to MG, LG, SOL, and PL muscles were left intact. Due to the technical difficulty of separating the LG and SOL nerves far enough proximally to mount both nerves on separate bipolar stimulating electrodes, the two nerves were mounted together as the LGS nerve. To ensure that the stretch of the Achilles tendon activated only afferents in the triceps surae and plantaris nerves, the following nerves were cut: quadriceps, sartorius, anterior biceps, posterior biceps, semitendinosus, semimembranosus, flexor hallucis longus, flexor digitorum longus, tibial, common peroneal, saphenous, lateral cutaneous sural, caudal cutaneous sural, and joint.

In order that the triceps surae and plantaris muscles could be attached to a muscle puller, the muscles were cleared of the fascia adjoining them to the skin and other muscles, and the insertion of the biceps femoris onto the lateral edge of the triceps surae was removed. The calcaneus bone was severed distal to the insertion of the Achilles tendon onto the tuberosity of the calcaneus, and bone wax was applied to control bleeding. A hole was made through the bone using a drill, and a wire was passed through and later connected to either a muscle puller or force transducer (see following section on "muscle stretch"). Care

was taken to ensure that the blood supply to the triceps surae and plantaris muscles was intact. During the dissection 0.9% saline at 38 °C was sprayed on the muscles and nerves to keep them moist, which markedly reduced spontaneous muscle contractions.

An L4-L6 laminectomy was performed, and the exposed spinal cord kept covered with moist gauze until transfer of the cat to a Göteborg type spinal frame, where mineral oil pools over the spinal cord and left hindlimb were formed from skin flaps sutured to the frame. To prevent movement of the spinal cord due to the cat's breathing, freely moving clamps which could be attached to the frame were adjusted so that they pushed down on the L7 vertebral body on either side of the spinal cord. If gross movements of the spinal cord interfered with intracellular recording, a bilateral pneumothorax was produced by thoracotomy, and the cat artificially respired through the tracheal catheter. Temperature was measured using thermistors in the esophagus and in either the back pool or leg pool, and body temperature maintained at 38 °C by means of heat lamps. End-expired CO2 was monitored using a Beckman Medical Gas Analyser (Model LB-1).

The intact nerves MG, LG, SOL, and PL were mounted on silver bipolar stimulating electrodes, as were the cut nerves anterior biceps, posterior biceps, semitendinosus, semimembranosus, tibial, and common peroneal. An electrically isolated stimulator applied constant current stimuli (duration 200 μs) to the peripheral nerves; the potential difference between the bipolar stimulating electrodes could be precisely adjusted with a 10-turn variable resistor across the output (Eide, 1972). The threshold voltage (T) for activation of the group Ia muscle afferents was determined by the deflection in cord dorsum potentials due to orthodromic afferent volleys. Liminal electrical stimulation, which was designated as 1.0T, recruited the Ia afferents first since they are the largest diameter fibers in the nerve (Hunt, 1954, Sumner, 1961). Cord dorsum potentials were obtained by placing one foot of a silver

bipolar recording electrode on the dorsal surface of the spinal cord adjacent to the L7-S1 dorsal root entry zone, and the other electrode foot on a back muscle, the two inputs being fed into a differential amplifier and displayed on an oscilloscope screen.

Electromyographic (EMG) activity was recorded from the MG, LG, and SOL muscles. Lacquer coated copper wire was threaded through the tip of a hypodermic needle, and the wire then given a small bend at the tip. The needle was next pushed into the belly of the muscle, and withdrawn, leaving the wire attached to the muscle via the bend at the tip. The inverting and non-inverting inputs of these EMG electrodes were fed into a differential amplifier and displayed on the oscilloscope.

Surgery and care of chronic spinal cats

Anaesthesia was induced by intraperitoneal injection of sodium pentobarbital (30-35 mg/kg), and the cat then transferred to the surgery table, where a mixture of Halothane, nitrous oxide, and oxygen was delivered through a mask placed over the mouth and nose. Atropine (0.1 mg/kg) was delivered subcutaneously. Surgery was conducted using aseptic technique so as to minimize the chance of post-operative infection. The topical germicide Betadine (10% pividone-iodine) was rubbed onto the shaved back of the cat, and a longitudinal incision made over the caudal thoracic and rostral lumbar vertebrae. The muscle between the L1 and L2 spinous processes was removed, and the central arch over the spinal cord was chipped away with rongeurs. The dura mater was opened and the exposed spinal cord was irrigated with 0.9% NaCl. Lidocaine hydrochloride (Xylocaine) was dripped onto the cord as it was teased apart at the L1-L2 level with fine forceps. Small pieces of Gelfoam were inserted between the separated regions of the cord. The spinal cord transection completed, sterile silk (Ethicon 4-0 braided silk) was then used to suture the muscle layer, the

thoracolumbar fascial layer, and finally the skin. A catheter was inserted into the urethra. The cat was moved to a cage, covered with a drape, and kept warm with radiant heat. A subcutaneous injection of morphine was administered (0.15 mg/kg) several hours post-operatively for the management of pain. The antibiotic penicillin G (Wycillin) was given intramuscularly once a day for 5 days (250,000 I.U.). No infections were encountered. The bladder was expressed manually two times per day, and if the catheter had come out of the urethra, it was cleaned with 70% ethyl alcohol before reinsertion. Animal use procedures were approved, according to the Canadian Council on Animal Care guidelines, prior to the experiments.

Intracellular recording and muscle stretch

Glass microelectrodes of 1.5-2.2 μm outside tip diameter and 2-7 MΩ resistance were filled with 2 molar potassium citrate, and mounted on a micromanipulator. The spinal dura was opened under a dissecting microscope, and the pia covering dorsal roots L6, L7, and S1 was removed with fine forceps. motoneurons of the L7-S1 segments were impaled with the microelectrode, and their species was identified by an antidromic action potential in response to peripheral nerve stimulation at approximately 1.7 T. When motoneuron species was confirmed as triceps surae or plantaris, membrane electrical properties were investigated only in cells with a membrane potential of 60 Mv or more. Measurements included short pulse current threshold (the minimal current needed to evoke an action using a 0.5 ms current pulse), rheobase (the minimal injected current that will produce an action potential using a 50 ms current pulse), input resistance (determined from the voltage deflection due to a 50 ms 1-2 Na hyperpolarizing current), and afterhyperpolarization duration.

With the motoneuron still impaled, a stretch was applied to the TS and PL muscles.

Several factors had to be considered for the applied stretch: duration, amplitude of displacement, and tension of the muscle. For the present study we chose a triangular stretch of 3-5 ms duration, and 1-120 μm amplitude applied at 100-500 g initial tension, based on the reasonable selectivity of such parameters in recruiting Ia afferents (Lundberg and Winsbury, 1960a, Stuart et al., 1970, Stuart et al., 1971, Fetz et al., 1979). An initial tension of 500 g (5 Newtons) corresponds roughly to an 8-12 mm stretch of the muscle from a slack position (Buller et al., 1960, Fetz et al., 1979). The range of 100-500 g muscle tension is physiological, considering that a 2 kg cat would have a weight distribution of 500 g per limb.

The knee was flexed approximately 30° from the horizontal plane by pins attached to the frame, and the direction of muscle pull was along the axis of the hindlimb. The wire that had been passed through the drilled hole in the severed proximal end of the calcaneus bone (onto which the ankle extensors insert via the Achilles tendon) was fastened to a steel washer which could be placed on a hook at the end of the shaft of an electromagnetic muscle puller (built in this laboratory on the design by Reinking and Stuart, 1974). The linear motor (Ling) of the muscle puller was fed a triangular waveform from a function generator, which resulted in stretches of 1-120 μm and 3-5 ms duration applied to the MG, LG, SOL and PL muscles simultaneously. The output of a length transducer mounted on the shaft of the muscle puller was amplified and displayed on the oscilloscope, allowing visualization and capture of the number of microns of stretch imposed on the muscle. The output of a force transducer also mounted on the shaft indicated the tension of the stretched muscle, so that an initial muscle tension of 100 - 500 g could be maintained while a series of muscle stretches was applied.

The resulting stretch-evoked composite monosynaptic Ia EPSP was recorded and 32 sweeps captured at 5 kHz and averaged on-line (Cromemco or Masscomp 4350), using software programs written in the laboratory. Oscilloscope traces of the EPSPs were

photographed with a Grass Kymograph camera (Model C4R) using Kodak photofluorographic (PF) film. Using either a photographic enlarger or analysis software, the captured EPSPs were later measured for amplitude, time to peak amplitude, 10-90% risetime, and half-width. Unlesioned and chronic spinal Ia EPSP amplitudes were compared using the Student's T-test. The probability of $p < 0.05$ was used to reject the null hypothesis.

Motor unit typing

Motoneuron electrical properties and stretch-evoked EPSPs having been measured, the Achilles tendon was detached from the muscle puller and connected to a force transducer for measuring the tension exerted by single motor units in response to intracellular stimulation of the motoneuron. The muscle tension was set at 200 g, and the output of the force transducer was amplified and displayed on the oscilloscope.

The motor unit was typed as FF, FINT, FR, or Slow, according to its mechanical and fatigue properties, a technique developed by Burke and colleagues (1973). The method, summarized in Figure 2 was as follows. The first step was to determine if the motor unit was Slow or Fast. Fast motor units exhibit a characteristic decrease ("sag") in force development over time in response to a train of stimuli to the innervating motoneuron, while slow units do not. This formed the basis for a test for the presence or absence of sag by the motor unit. A single intracellular suprathreshold current pulse was delivered to elicit a contraction of the motor unit. The time to peak muscle tension (in ms) of the resulting muscle twitch was measured (Fig. 3A) from the onset of electromyographic activity in the muscle (not shown). This value was multiplied by 1.25 (The rationale for this is in small print on page 22); the product was used as the inter-stimulus interval (in ms) for a train of 23 suprathreshold stimuli to the motoneuron (The rationale for this is also in small print on page 22). The tension

envelope of the resulting unfused tetanic twitch was visually inspected for the presence of a decrease, that is, a sag, in force development by the 5th or 6th stimulus. If there was no sag present, the motor unit type was Slow.

If there was sag, however, the motor unit was either FF, FINT, or FR, and these were differentiated according to their susceptibility to fatigue. This consisted of delivering a train of 13 suprathreshold stimuli (single stimulus duration = 0.5 ms; interstimulus interval = 25 ms) to the motoneuron once per second for 120 seconds. The motor unit tension was captured, and the force output of the 120th train expressed as a percentage of the force output of the 1st train, as a means of illustrating the decrement in force output. If the tension at the end of 2 minutes was 75-100% of the original tension, the motor unit was FR. If the motor unit tension at the end of 2 minutes was 0-25% of the original tension, the motor unit was FF. Motor units that fatigued more than FR, but less than FF, were FINT. All motor units that did not sag were by definition Slow, but were nevertheless confirmed to be Slow by a fatigue test. In summary:

FF < 25% of original tension < FINT < 75% of original tension < FR (or Slow).

The use of the value 1.25 as a multiplier of the time to peak tension of the muscle twitch was found by Burke and colleagues (1973) to produce the best examples of sag in the tension profile. Sag is thought to result from differences between the sarcoplasmic reticulum in mammalian fast twitch and slow twitch fibers, that is, the kinetics of intrafiber calcium movement during electrochemical coupling (Burke R.E., 1990).

The use of 23 stimuli for the sag test was arbitrary, and could as easily have been 20 stimuli, the point being that the tension envelope had to consist of an appropriate number of stimuli so that a sag could be identified.

To minimize the differences between motor units due to previous activation history the

motoneuron was first potentiated with a 1 second 100-200 Hz burst of intracellular suprathreshold stimuli (Burke et al., 1976a).

Motor unit typing assisted in distinguishing LG motoneurons from SOL motoneurons, a task not possible using antidromic activation since the LG and SOL nerves were mounted together. If an LGS motoneuron was motor unit typed as FF or FR, it was necessarily an LG motoneuron because the soleus muscle is composed of nearly 100% Slow motor units in the cat (Ariano, 1972, Burke et al., 1974). If an LGS motoneuron was motor unit typed as Slow, its identity was not certain because LG muscle is composed of both Fast and Slow motor units (Hochman and McCrea, 1992c).

EMG recordings made from the MG, LG, and SOL muscles assisted in the confirmation of motor unit type and in gauging the general health of the motor unit during the motor unit typing procedure. The whole muscle tension of the MG, LGS, and PL muscles was measured throughout the experiment, using 10T stimulation of the peripheral nerve to recruit all motor units. When whole muscle tension fell to less than 75% of the very first measurement the experiment was stopped and the animal euthanized with an overdose of barbiturate.

RESULTS

Results were obtained from 70 motoneurons in 12 unlesioned cats, and 87 motoneurons in 8 six week chronic spinal cats. Stretch of the triceps surae and plantaris muscles evoked a combined homonymous and heteronymous composite monosynaptic Ia EPSP. Before a comparison of unlesioned and chronic spinal EPSPs, these Results will present examples of how motor unit typing was performed and behavioral observations on the chronic spinal cats.

MOTOR UNIT TYPING EXAMPLES

Figure 3 shows the mechanical properties of an LG motor unit, used to determine its motor unit type. The tension generated in the muscle due to a single stimulus to the LG motoneuron is approximately 30 grams (Fig. 3A), and the time to peak muscle tension (peak motor unit tension) is 32 ms. When a train of pulses is delivered to the motoneuron, with inter-pulse interval of 40 ms (1.25 X 32 ms = 40 ms. See Methods.), the tension envelope of the muscle exhibits a sag, beginning at the third stimulus (Fig 3B). The presence of sag indicates that the motor unit is Fast twitch. The fatigue test (Fig. 3C,D) reveals that the motor unit tension after the first train of stimuli is 51 g, and after the 120th train, that is, 2 minutes later, the tension is 2 g. Since 2g/51g X 100% = 4% , the motor unit is type FF (See Methods).

The LGS motor unit shown in Fig. 4A had a time to peak tension of 70 ms and a motor unit tension of approximately 0.5 grams. Such a long time to peak tension and small motor unit tension hinted strongly that the motor unit was Slow. This was confirmed by an absence of sag in the motor unit tension profile (Fig. 4B). The tension in the motor unit remained at a constant 4 g throughout the 2 minutes of stimulation of the fatigue test (Fig. 4C,D,E).

BEHAVIORAL OBSERVATIONS OF THE SPINAL CATS

Increased muscle tone of the hindlimbs was apparent two weeks after the L1-L2 transection. An increased tendon reflex was elicited by a tap of the patellar and Achilles tendons, and was accompanied by clonus in some cases. Clonus would sometimes occur spontaneously, with a frequency of approximately 5 Hz. A clasp knife reflex was not observed.

There was increased resistance to passive dorsiflexion or plantar flexion of the rear foot, the former in general much more evident. If the cat was held aloft by supporting its chest with the hand, the hindlimbs would dangle toward the floor, and tremble for several seconds before becoming still. There was a noticeable stiffness in the knee and ankle joints. From this position, if the foot was passively stretched by dorsiflexion, there was resistance to the stretch followed by a rapid, brief hip flexion, and then a slow relaxation of the hip so that it once again was straight. This was accompanied by approximately 10 seconds of twitching of the leg until it was still, or fanning of the toes of the tested limb, or movement of the tail from side to side. There was also increased resistance to passive flexion of the hip.

Reflex stepping (spinal walking) involving both hindlimbs was apparent 5 days post-transection. One cat in particular would display bouts of reflex stepping of 5-10 seconds duration, with each leg "stepping" at a frequency of approximately 2 Hz.

Passive extension of the quadriceps was on one occasion met with considerable resistance, which was followed by a rapid (5 Hz) extension and retraction of the hindlimb, this movement alternating between both hindlimbs. The movement was similar in appearance to reflex stepping. A small degree of reflex standing was observed.

Pinch of the toes resulted in a withdrawal of the limb, but a crossed extension reflex was not observed.

Manual expression of the bladder evoked hindlimb hip flexion followed by hip

extension, this behavior alternating from one hindlimb to the other, and persisting for as long as the pressure was maintained on the bladder. The intensity of the movements ranged from mild to quite vigorous contraction. This behavior could not be elicited by merely supporting the cat under the belly - only pressure exerted on the urinary bladder elicited the response.

These observations are similar to those in 4 and 8 week L1 chronic spinal cats where increased muscle tone, increased patellar tendon reflex, increased withdrawal reflex, clonus, reflex stepping, and reflex standing were reported (Bailey et al., 1980). Brothers et al., (in preparation) reported increased muscle tone, exaggerated tendon taps, and muscle activity resembling stepping in 10-16 week L2 chronic spinal cats.

STRETCH-EVOKED EPSPs

Growth of EPSPs as a function of initial tension and stretch. The amplitude of the Ia EPSPs was dependent upon two variables that could be controlled in the experiment - initial muscle tension of the muscles and the extent of the imposed stretch by the muscle puller. The initial muscle tension was set at 100, 200, 300, 400, and 500 g, and for each setting the Achilles tendon was pulled from 1-100 μm, usually in 10 μm increments.

With regard to the first factor, initial tension, Fetz and colleagues (1979) estimated that a tension of 500 g (5 Newtons) on the triceps surae corresponded to a static stretch of 8-12 mm from an initially slack position (0 g of tension). At maintained muscle lengths of 0, 8, and 12 mm, primary muscle spindle afferents from MG have a firing frequency of 15, 18, and 22 Hz respectively (Bailey et al., 1980). Hence, as initial tension on the muscle increases from 100 to 500 g, the firing of primary spindle afferents increases. As initial tension increases, and the intrafusal muscle fibers become more taut, an increasing number of primary spindle afferents are recruited (Matthews, 1981), and the composite EPSP measured in the

motoneuron is increased. Figure 5 shows monosynaptic Ia EPSPs in a PL motoneuron evoked by 20 μm stretch at initial tensions of 100, 200, and 300 g. EPSP amplitude at 100 g is just over 2 Mv, and increases slightly at 200 g and 300 g initial muscle tension. Panel D in Figure 5 shows a composite monosynaptic Ia EPSP evoked by 1.2T stimulation of the PL nerve. It is slightly smaller than the EPSP evoked by a 20 μm stretch in panel A.

Figure 6 is essentially a conglomeration of many Figure 5's. It shows the mean Ia EPSP amplitude for all triceps surae and plantaris motoneurons in response to 20 μm stretch at varying muscle tensions. Chronic spinal EPSP amplitudes were larger at 100, 200, and 300 g initial tension. At 100 g initial tension the mean EPSP amplitude was 1.18 mV in the unlesioned cat and significantly ($p < .05$) increased by 61% in the chronic spinal cat to 1.90 mV (Fig. 6, Table 2A). At 200 g initial tension and 20 μm stretch the mean EPSP amplitude was 2.23 mV in unlesioned motoneurons and 2.92 mV in chronic spinal motoneurons, a significant increase of 31% ($p < .025$). These findings support the hypothesis of the experiments that the stretch-evoked monosynaptic Ia EPSPs that are a summation of homonymous and heteronymous monosynaptic EPSPs are enlarged in chronic spinal motoneurons. Further, it is a physiological corroboration of the work of Hochman and McCrea (1992a) in which electrically-evoked homonymous and heteronymous Ia EPSPs were both larger in the entire pool of chronic spinal motoneurons of triceps surae and plantaris. At 300 g, 20 μm, the mean EPSP amplitudes were 2.33 mV and 2.74 mV in UL and CS motoneurons respectively, but not significantly. At 400 g, 20 μm, the sample size was too small as to be significant (UL n=30, CS n=2).

Because of time constraints on identification of the motor unit type of a motoneuron before the cell deteriorated in health, the number of Ia EPSPs recorded at each initial muscle tension evoked by several stretches of different amplitude was limited. As shown in Table

2A, mean EPSP amplitude in CS motoneurons was usually larger at all tensions and all stretch amplitudes than in UL motoneurons. Had the sample sizes been larger, it is possible that the differences in amplitude would have been statistically significant. The standard deviation was occasionally quite high, and appeared to be partly varying with the size of the mean.

The second factor affecting EPSP amplitude was stretch of the ankle extensor muscles, thereby activating group Ia muscle spindle afferents. As stretch of the triceps surae and plantaris muscles is increased, the number of Ia afferents recruited is increased (Matthews, 1981). Monosynaptic Ia EPSPs in the LG motoneuron shown in Fig. 7 increase in amplitude as the displacement increases from 5 to 30 μm (initial muscle tension = 200 g). The effects of increasing initial muscle tension and increasing muscle stretch on EPSP amplitude are shown in Fig. 8. For this particular fast-fatiguing MG motoneuron from the unlesioned preparation, stretches of 5-75 μm were applied at 200-500 g initial muscle tension. Increasing the initial tension increased the EPSP amplitude for a given stretch, and lowered the stretch amplitude at which maximal EPSP amplitude was achieved. At the lower initial tension of 200 g, the EPSP amplitude was maximal when 40-50 μm of stretch was applied to the muscle. At the higher initial tension of 500 g, the EPSP amplitude was maximal at 30 μm of stretch.

The trend of the stretch-evoked EPSP to reach a maximum value, shown in Figure 8 for a single motoneuron, was seen to occur for the entire ankle extensor population. Figure 9 shows the mean EPSP amplitude in pooled data from all unlesioned and chronic spinal ankle extensor motoneurons in response to stretch of 0-80 μm at 200 g initial tension. The stretches are grouped into bins of 10 μm width. Clearly, the trend is for Ia EPSP amplitude across the entire stretch range to be larger in the chronic spinal motoneuron population than in the unlesioned motoneuron population. The stretch ranges of 20-30 μm, 30-40 μm, and

40-50 μm produced significantly ($p < .05$) larger composite monosynaptic Ia EPSPs in chronic spinal motoneurons. In the stretch ranges of 0-10 μm, 50-60 μm, 60-70 μm, 70-80 μm, and 80+ μm there was no significant difference between unlesioned and chronic spinal Ia EPSPs. This lack of significance may have been due in part to the smaller sample sizes in these bins, where the number of chronic spinal motoneurons especially was limited (Table 1). The stretch range of 10-20 μm, in which there was an adequate sample size (UL n=44, CS n=36), was an anomaly, with the unlesioned EPSP average larger than chronic spinal, albeit insignificantly.

In the pool of all unlesioned motoneurons, stretches greater than 30-40 μm (initial muscle tension = 200 g) did not usually elicit EPSPs larger than approximately 2.5-3 mV (Fig. 9), although in individual motoneurons EPSP amplitude would occasionally reach a peak value only when stretches of 80-100 μm were applied to the muscle. In the pool of all chronic spinal motoneurons, maximal EPSP amplitude was greater (3.5 mV) (initial muscle tension = 200 g) than unlesioned. Maximal EPSP amplitude occurred at about the same stretch amplitude in both preparations (Fig. 9). Fetz and colleagues (1979) found that Ia EPSPs in triceps surae motoneurons (n = 12) evoked by 3-5 ms triangular stretch (c.f. 2 ms triangular stretch in this study) reached a maximum amplitude when stretches were 50-60 μm at 500 g initial tension (see their Figure 1C). They interpreted this as 100 percent recruitment of the Ia afferents. They estimated that 90 percent of the Ia fibers were recruited by stretches of 30-35 μm at 500 g initial muscle tension, which is comparable to our value of maximal recruitment by stretches of 30-40 μm at 200 g initial muscle tension. In a study of isolated soleus Ia afferents activated by muscle stretch, maximal Ia recruitment occurred at 60 μm of stretch at muscle tensions of 25-50 g (Stuart et al., 1970). An earlier study of isolated soleus Ia afferents found maximal recruitment at 60 μm of stretch also, but

in this case the initial tension was only "a few grams" (Lundberg and Winsbury, 1960a). It is not surprising then, that with the standard initial tension of 200 g used in this study, maximal Ia recruitment was elicited at a stretch amplitude (30-40 μm) that was less than that for 25-50 g initial muscle tension (60 μm) and slightly greater than that for 500 g initial muscle tension (30-35 μm) (Stuart et al., 1970, Fetz et al., 1979). The finding in this study that maximum EPSP amplitudes in both UL and CS motoneurons (although increased in the latter) were elicited by approximately the same magnitude of stretch conforms to previous findings that muscle spindle Ia afferent discharge is not increased in the chronic spinal preparation (Bailey et al., 1980, Burke D., 1983).

EPSPs in differing ankle extensor species. Ia EPSP amplitude was consistently enlarged in MG, LG, and SOL motoneurons in the chronic spinal preparation compared to the unlesioned (Fig. 10, Table 2B). Mean Ia EPSP amplitude in MG motoneurons in the unlesioned preparation in response to 20 μm stretches at 100 and 200 g initial muscle tension was slightly less than 2 mV, and was 2.4 mV at 300 g initial muscle tension (Figure 10, Table 2B). The mean amplitude of Ia EPSPs in MG motoneurons in the CS preparation was larger for each initial tension, being 2.4 mV at 100 g initial muscle tension, and slightly less than 3 mV at 200 g and 300 g initial muscle tension. The UL and CS amplitudes at 200 g initial muscle tension were significantly different ($p < 0.05$), being 1.95 mV and 2.95 mV respectively. The lack of significance between UL an CS values in MG motoneurons for 20 μm stretch at 100 g initial muscle tension was probably due to the small number (n=3) of EPSPs tested in the unlesioned preparation. In fact, at 100 g initial muscle tension in the UL preparation, a 20 μm stretch would frequently not elicit a composite Ia EPSP in MG motoneurons. Stretches which did not evoke a Ia EPSP were not included for analysis. The

greater number of samples in the CS preparation (n=19 at 100 g initial muscle tension/20 μm stretch) was not due to the fact that more MG motoneurons were encountered, rather that Ia EPSPs were larger and more easily elicited.

Stretch EPSP amplitude in LG motoneurons was also larger in the chronic spinal preparation. The mean Ia EPSP amplitude evoked by stretch of 20 μm at 100 g initial muscle tension was 0.45 mV in UL motoneurons, and increased significantly ($p < 0.05$) by 133% to 1.05 mV in CS motoneurons (Fig. 10, Table 2B). At 200 g initial muscle tension, the mean Ia EPSP amplitude in LG motoneurons was not significantly larger in the chronic spinal preparation. The mean Ia EPSP amplitude evoked in MG versus LG motoneurons was considerably larger for the 20 μm stretch at 100 g initial muscle tension (Fig. 10). However, at 200 g initial muscle tension, the mean amplitudes were more comparable. This could indicate that small stretches at low muscle tensions are more effective in MG than LG motoneurons.

The number of positively identified SOL motoneurons was few (UL n=0, CS n=4), and therefore assessment of EPSP changes with spinalization was difficult. If the LGS motoneurons were a fair representation of SOL motoneurons, and not untyped or Slow LG motoneurons, then the increases in mean EPSP amplitude in LGS motoneurons at 200 g and 300 g initial muscle tension agree with previous findings of an increase in Ia EPSP amplitude in SOL motoneurons after spinalization (Hochman and McCrea, 1992a). The mean Ia EPSP amplitude in PL motoneurons evoked by 20 μm stretch at 200 g initial muscle tension was 2.56 mV and 2.55 mV in the UL and CS preparations respectively, but sample size was quite small (UL n=9, CS n=10).

EPSPs in different motor unit types. As mentioned in the methods section, an attempt was

made to classify the motor unit type of all impaled ankle extensor motoneurons. Table 2C and Figure 11 show that the mean Ia EPSP amplitude was greater in CS FF motoneurons and CS Slow motoneurons. EPSPs evoked by 20 μm stretch at 200 g initial muscle tension in FF motoneurons averaged 1.57 ± 0.77 mV in unlesioned controls and increased significantly ($p < 0.05$) by 37% to 2.15 ± 0.91 mV in chronic spinal. Approximately one half of these FF motoneurons (UL n=21, CS n=15) were from the MG pool (UL n=9, CS n=10) (Table 2C). In these MG FF motoneurons, the mean Ia EPSP amplitude evoked by 20 μm stretch at 200 g initial muscle tension was 1.70 mV in the UL preparation and 2.37 mV in the CS preparation, a significant 39% increase ($p < 0.05$).

Interestingly, homonymous Ia EPSPs are not increased in MG FF motoneurons following spinalization (Hochman and McCrea, 1992c, their data shown in Table 3). The mean amplitude of composite homonymous monosynaptic Ia EPSPs in response to 1.2T electrical stimulation of the MG nerve was 1.67 mV and 1.57 mV in the UL and CS states respectively. The increase in combined homonymous and heteronymous EPSP amplitude following spinalization, in the present study, from 1.70 mV to 2.37 mV is therefore attributable to an increase in the efficacy of the heteronymous component.

There was a trend for motoneurons of motor unit type Slow to be increased in mean Ia EPSP amplitude in the CS preparation at 100 g and 200 g initial muscle tension (Table 2C, Figure 11). The number of CS Slow motoneurons sampled was quite small however, and a statistically significant increase was not observed. Likewise, for FR and FINT motoneurons, the number of CS motoneurons samples was often only one, thus EPSP changes were difficult to assess. Hochman and McCrea (1992c) found that both homonymous and heteronymous Ia EPSPs were significantly increased ($p < 0.05$) in presumed FR and Slow motoneurons following spinalization.

Electrical Typing of Motor Units. Zengel and colleagues (1985) were able to predict with 90% accuracy the motor unit type of MG motoneurons from measured membrane electrical properties, a procedure known a "electrical typing". In particular, a plot of rheobase (nA) versus input resistance (MΩ), placed FF motoneurons above a line of slope m=18, Slow motoneurons below a line of slope m=7, and FR motoneurons between the two lines (Figs 14,15). Electrical typing is important because it does away with the need for mechanically determining motor unit type, and more so because it indicates that there is a close match between membrane electrical properties and the mechanical properties of the motor units (Mendell, 1988). The electrical typing concept was applied in this study to all ankle extensor motoneurons of both the UL and CS cat. Its effectiveness in predicting the motor unit type of motoneurons other than MG and also in the chronic spinal preparation could be gauged since the actual motor unit type of the motoneurons had already been determined during the experiments. As shown in Figures 12 and 13, motoneurons of mechanically determined motor unit type fell quite accurately within the boundaries for electrical typing. Of a total of 52 UL and CS motoneurons, only 9 were outside of their prescribed boundaries, which makes the electrical typing 83% accurate for the motoneurons of the 4 ankle extensors. Of the 9 out of place motor units, only 2 were in the CS preparation, indicating the utility of electrical typing for that preparation; this is perhaps due to the fact membrane electrical properties are largely unchanged with respect to the unlesioned state following spinalization. Therefore the rheobase and input resistance relationship is unchanged (Gustafsson et al., 1982, Hochman and McCrea, 1992b). Further, the results of electrical typing of mechanically typed motor units in these experiments indicate that the electrical typing of triceps surae and plantaris motoneurons in UL and CS cats by Hochman and McCrea (1992c) was accurate.

In summary, the results show statistically significant increases in group Ia EPSP amplitude in response to muscle stretch in the chronic spinal preparation. These increases are found in the entire pool of ankle extensor motoneurons, in individual motoneuron species, and in the different motor unit types. Further, these increases occur at differing muscle tensions and at differing amplitudes of muscle stretch.

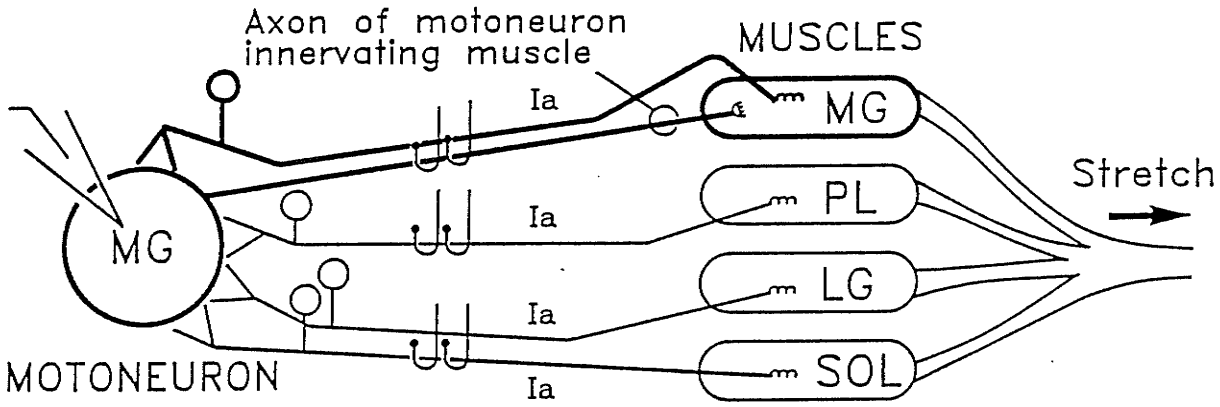

Figure 1. Paradigm for recording either stretch-evoked EPSPs or electrically-evoked EPSPs in ankle extensor motoneurons. Stretch of the Achilles tendon results in combined homonymous and heteronymous monosynaptic Ia EPSPs in ankle extensor motoneurons. An intracellular microelectrode records changes in membrane potential. The Achilles tendon could also be attached to a force transducer to measure the force generated by a single motor unit.

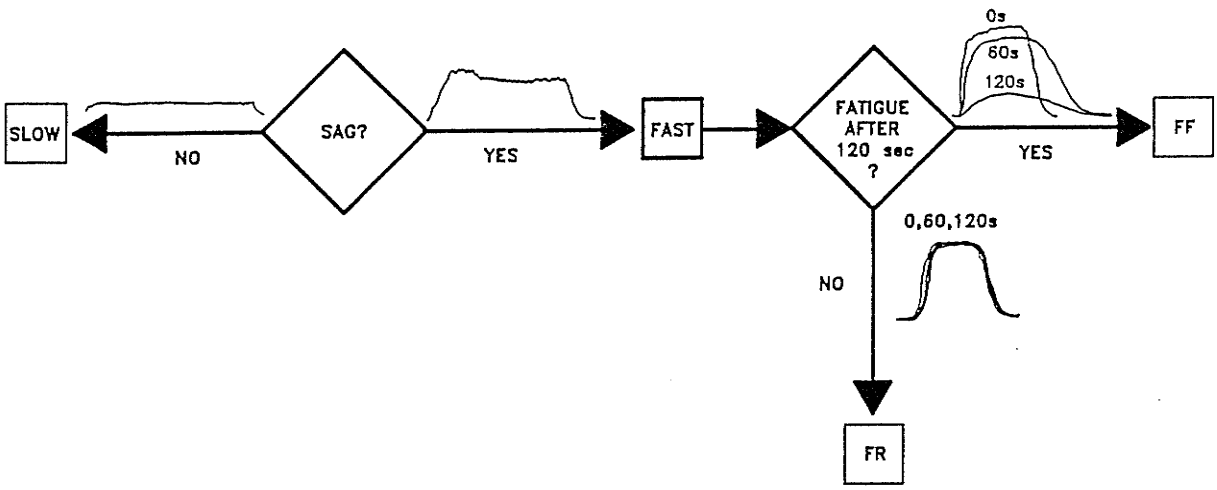

Figure 2. Mechanical typing of motoneurons. Slow and Fast motor units can be separated on the basis of a "sag" in the tension profiles of unfused tetanus. FF and FR motor units can be separated according to the extent of their fatigue following a train of pulses.

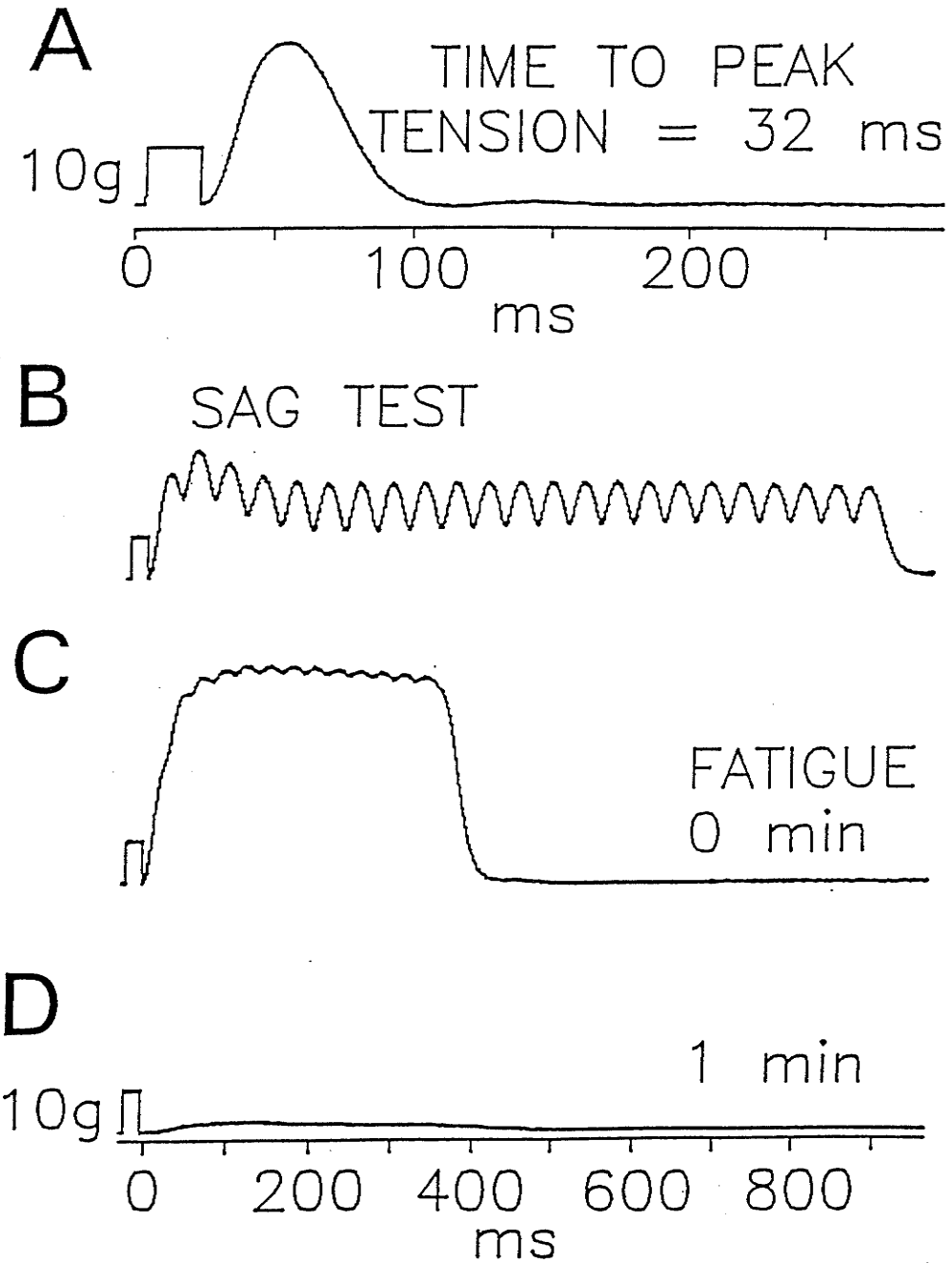

Figure 3. Mechanical properties of an FF motor unit from LG muscle of unlesioned cat. (A) Tension generated by a single stimulus (current strength 18 nA, duration 0.5 ms) to motoneuron is 30 grams. (B) Sag test to determine whether motor unit is Slow or Fast. The tension profile exhibits sag, beginning with third stimulus to motoneuron, therefore the motor unit is Fast. (C,D) Fatigue test to determine whether Fast motor unit is FF or FR. (C) Fused tension developed at onset of train of stimuli (13 pulses of 0.5 ms duration at 40 Hz, current strength 18 nA) to motoneuron delivered once per second. (D) After only 60 seconds of stimulation, the tension generated by the motor unit is minimal, therefore the motor unit is FF. Calibration pulse is 10 g, 20 ms.

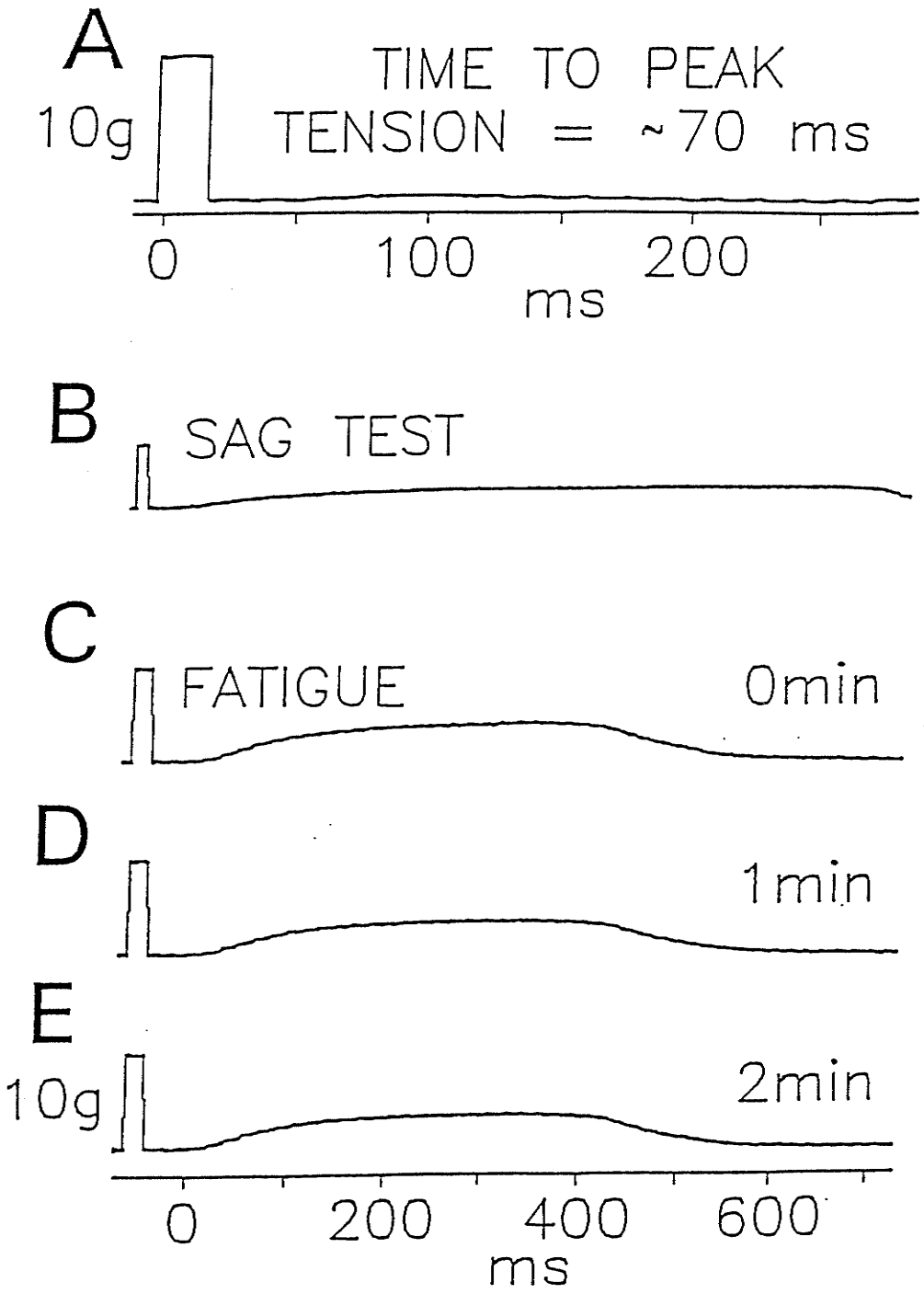

Figure 4. Mechanical properties of a Slow motor unit from LGS muscle of unlesioned cat. (A) Single stimulus to motoneuron produces 0.5 grams tension. (B) No "sag" in unfused tetanus. (C,D,E) The Slow motor unit does not fatigue after 2 minutes of stimulus trains. Calibration pulse is 10 g, 20 ms.

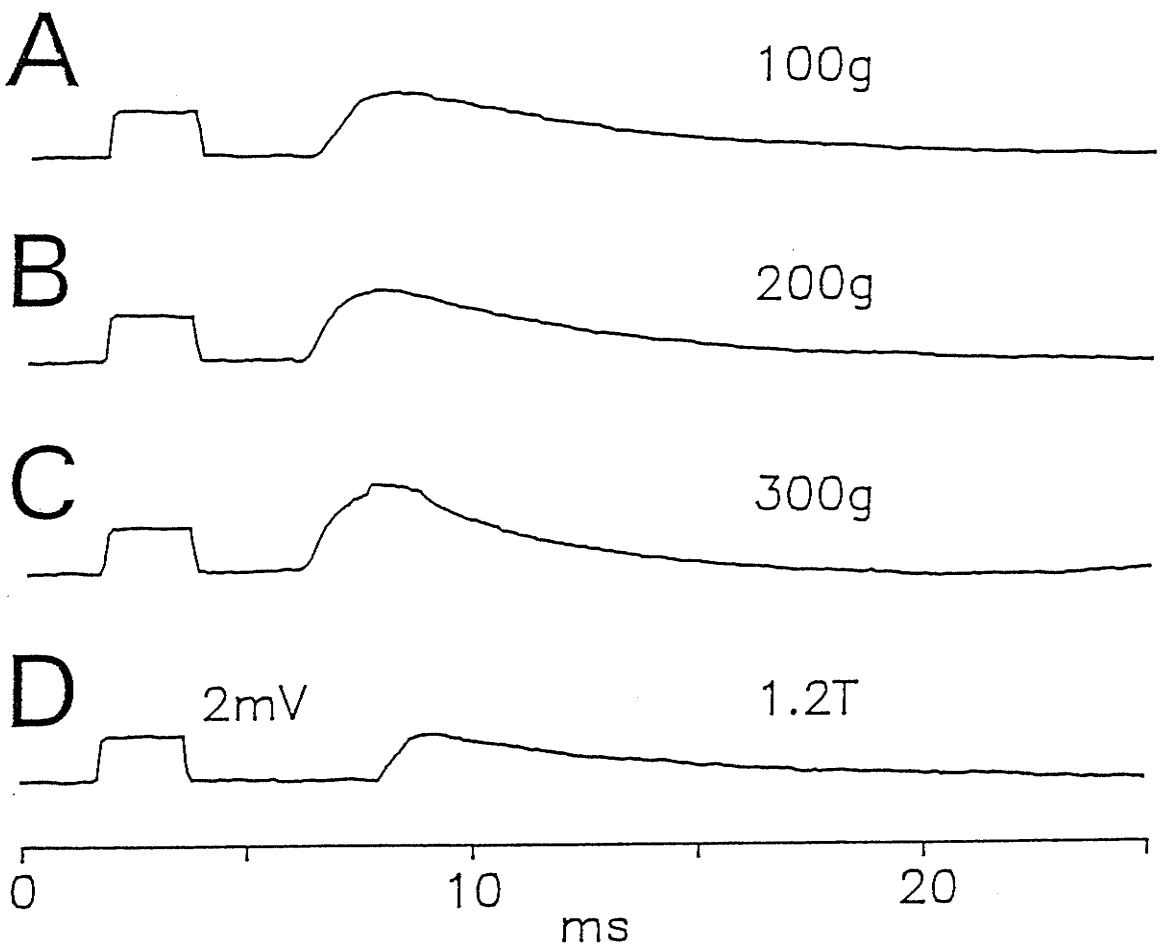

Figure 5. Combined homonymous and heteronymous composite monosynaptic Ia EPSPs in a PL motoneuron from the unlesioned spinal cord evoked by 20 μm muscle stretch at 100-300 g initial muscle tension. A group Ia EPSP evoked by electrical stimulation of the PL nerve at 1.2T is shown for comparison. Calibration pulse is 2 mV, 2 ms.

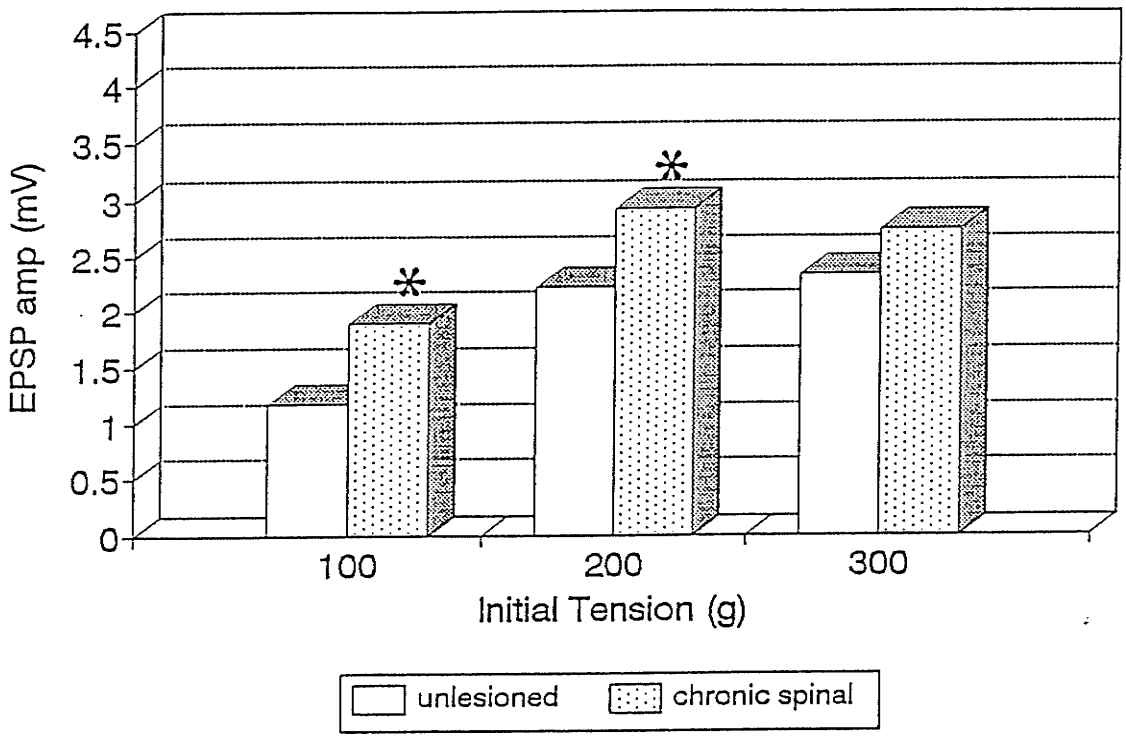

Figure 6. Combined homonymous and heteronymous composite monosynaptic Ia EPSPs in all ankle extensor motoneurons. EPSPs were evoked at initial muscle tensions of 100-300 g by muscle stretches of 20 μm. * denotes significant difference in EPSP amplitude ($p < .05$).

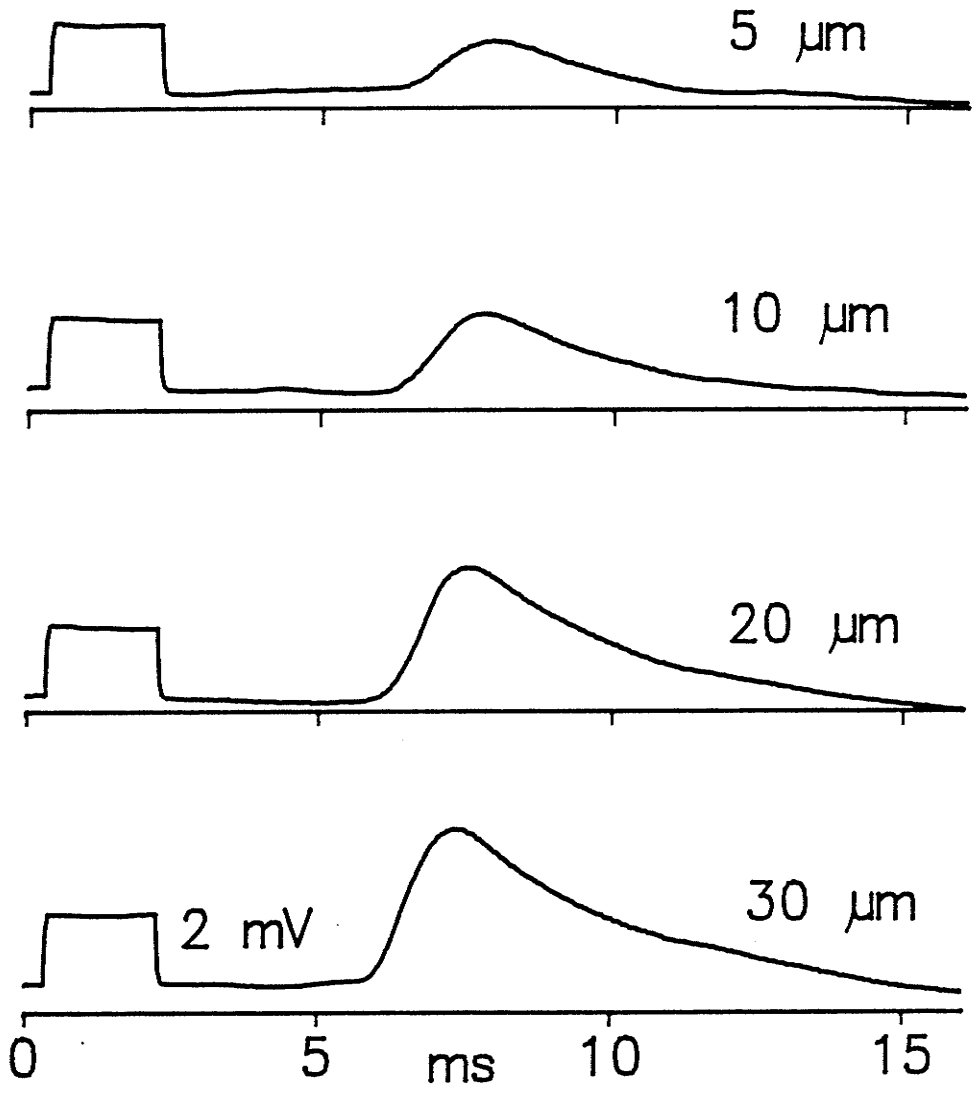

Figure 7. Combined homonymous and heteronymous composite monosynaptic Ia EPSPs in chronic spinal LG motoneuron evoked by 5-30 µm stretch of the ankle extensor muscles at 200 grams initial muscle tension. Calibration pulse is 2 mV, 2 ms.

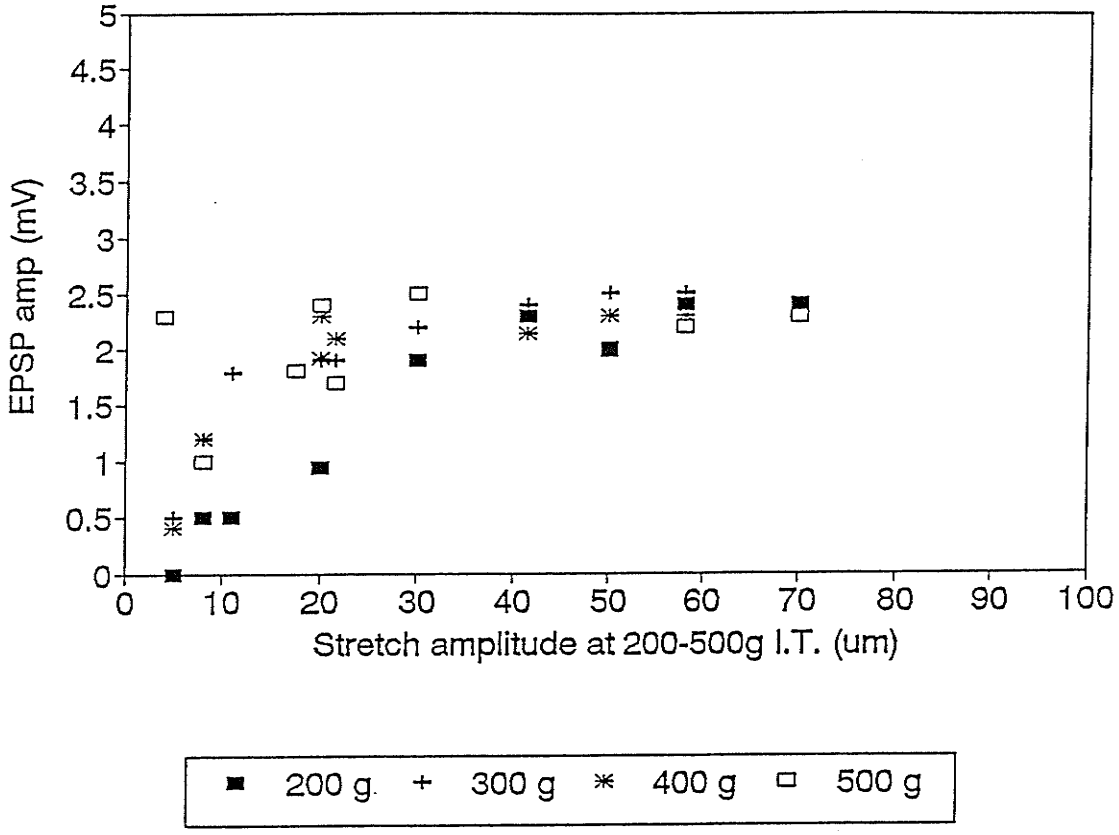

Figure 8. Combined homonymous and heteronymous composite monosynaptic Ia EPSPs evoked by muscle stretch in an MG motoneuron of motor unit type FF in the unlesioned preparation. The initial muscle tension (I.T.) prior to each stretch was either 200, 300, 400 or 500 grams.

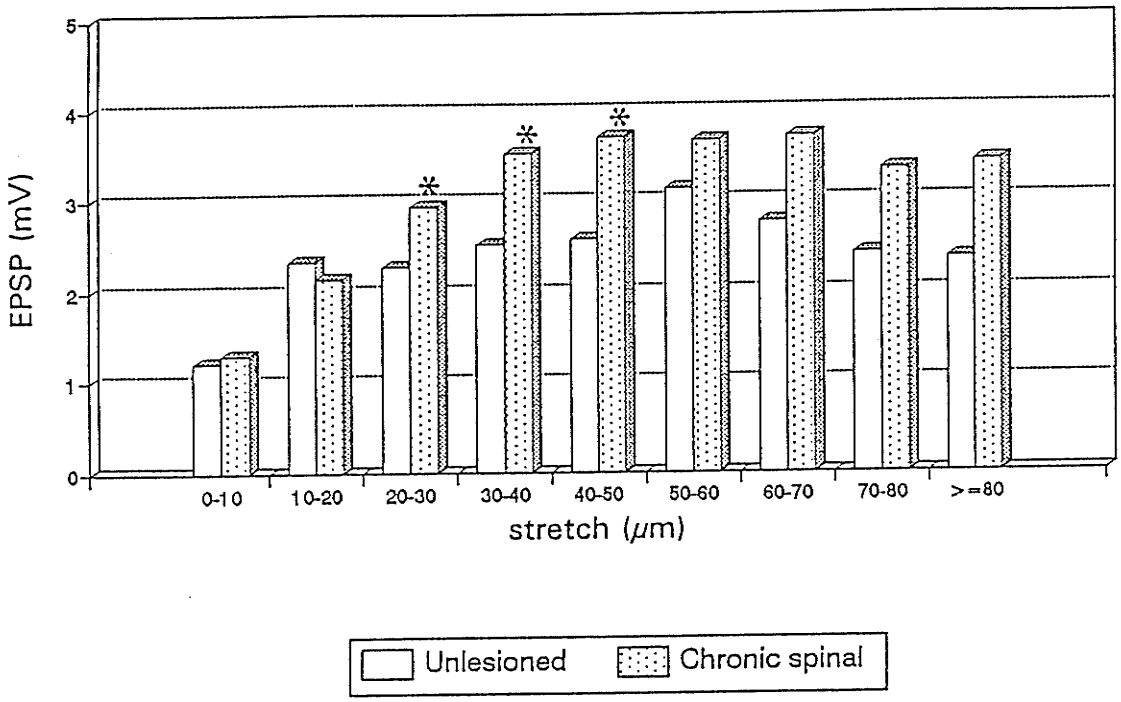

Figure 9. Combined homonymous and heteronymous composite monosynaptic Ia EPSPs evoked by muscle stretch at 200 g initial muscle tension. The stretches have been grouped into 10 μm bins. All triceps surae and plantaris motoneurons pooled. * denotes significant difference in EPSP amplitude ($p < .05$).

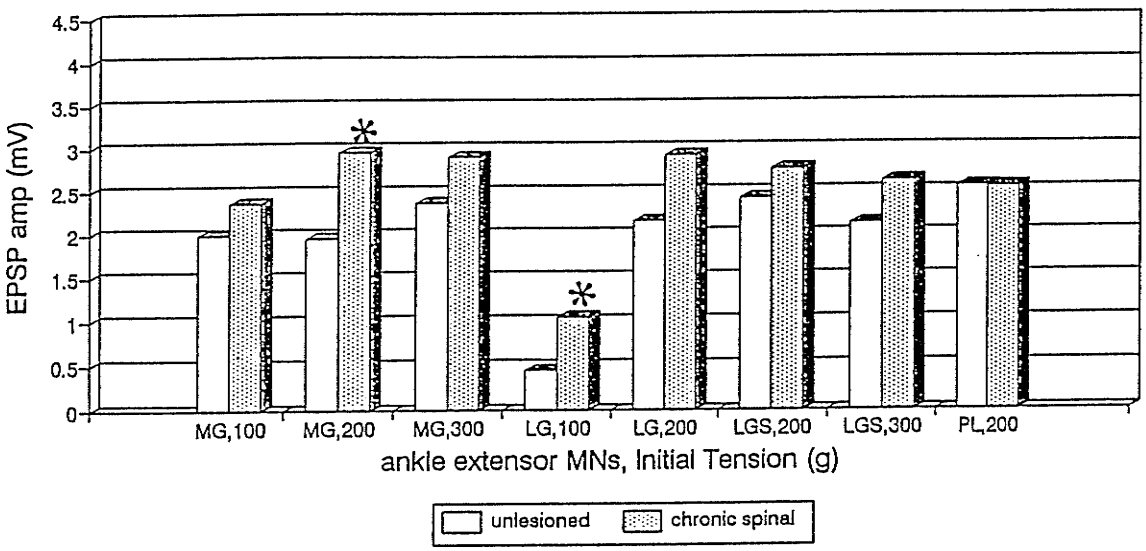

Figure 10. Combined homonymous and heteronymous composite monosynaptic Ia EPSPs in MG, LG, LGS, and PL motoneuron populations. EPSPs were evoked at initial muscle tensions of 100-300 g by muscle stretches of 20 μm. LGS motoneurons are those in which the motoneuron species was either LG or SOL. * denotes a significant difference in EPSP amplitude ($p < .05$).

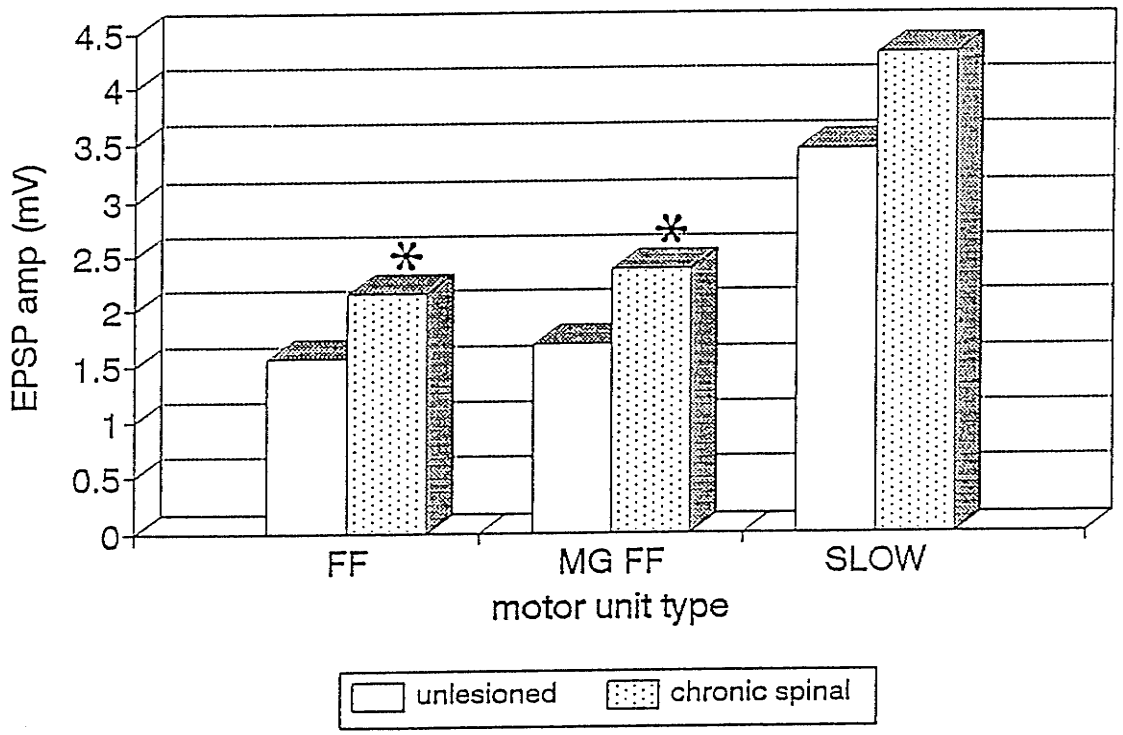

Figure 11. Combined homonymous and heteronymous composite monosynaptic Ia EPSPs in FF motoneurons, MG type FF motoneurons, and Slow motoneurons. EPSPs were evoked at an initial muscle tension of 200 g by stretches of 20 μm. * denotes a significant difference in EPSP amplitude ($p < .05$).

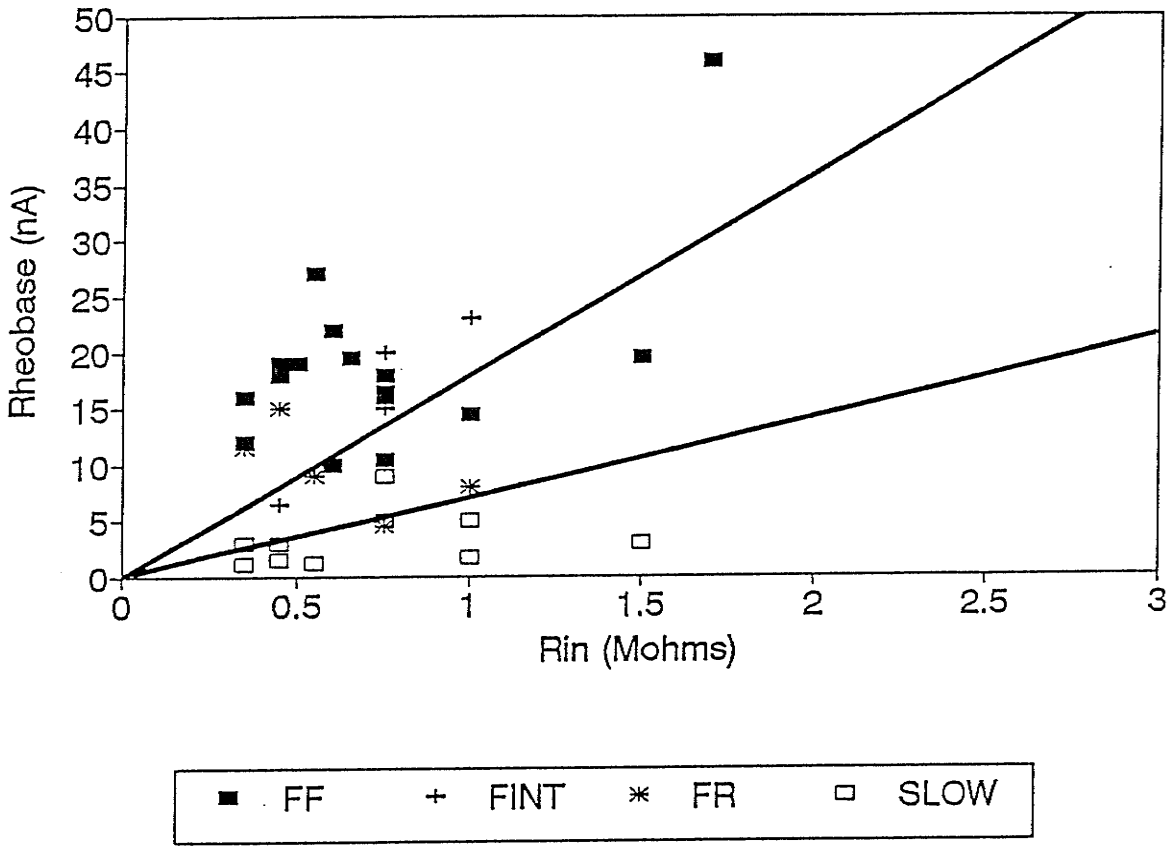

Figure 12. Inferring motor unit type in the unlesioned preparation from the motoneuron electrical properties rheobase and input resistance. Ideally, FF motor units lie above the line of slope m=18, Slow motor units below the line of slope m=7, and FR motor units between the two lines. Adapted from Zengel et al., 1985.

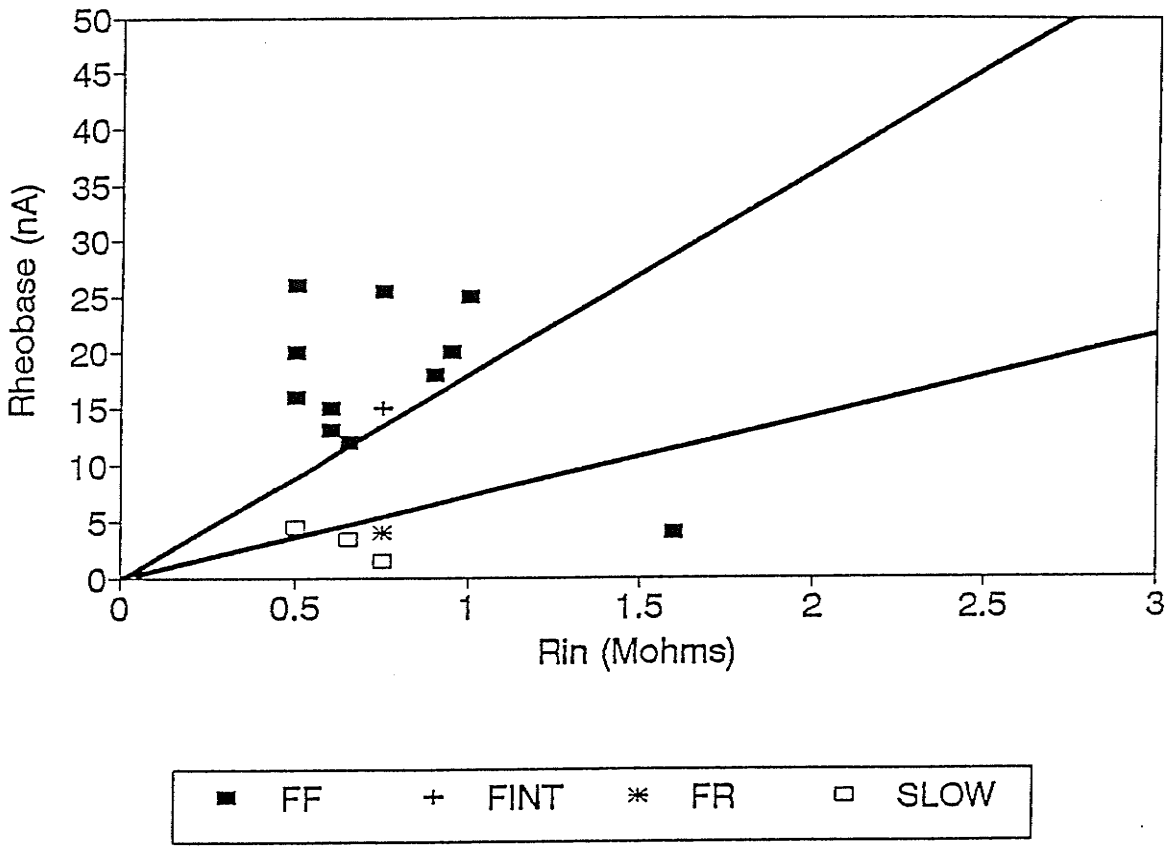

Figure 13. Inferring motor unit type in the chronic spinal preparation from the motoneuron electrical properties rheobase and input resistance. Ideally, FF motor units lie above the line of slope m=18, Slow motor units below the line of slope m=7, and FR motor units between the two lines. Adapted from Zengel et al., 1985.

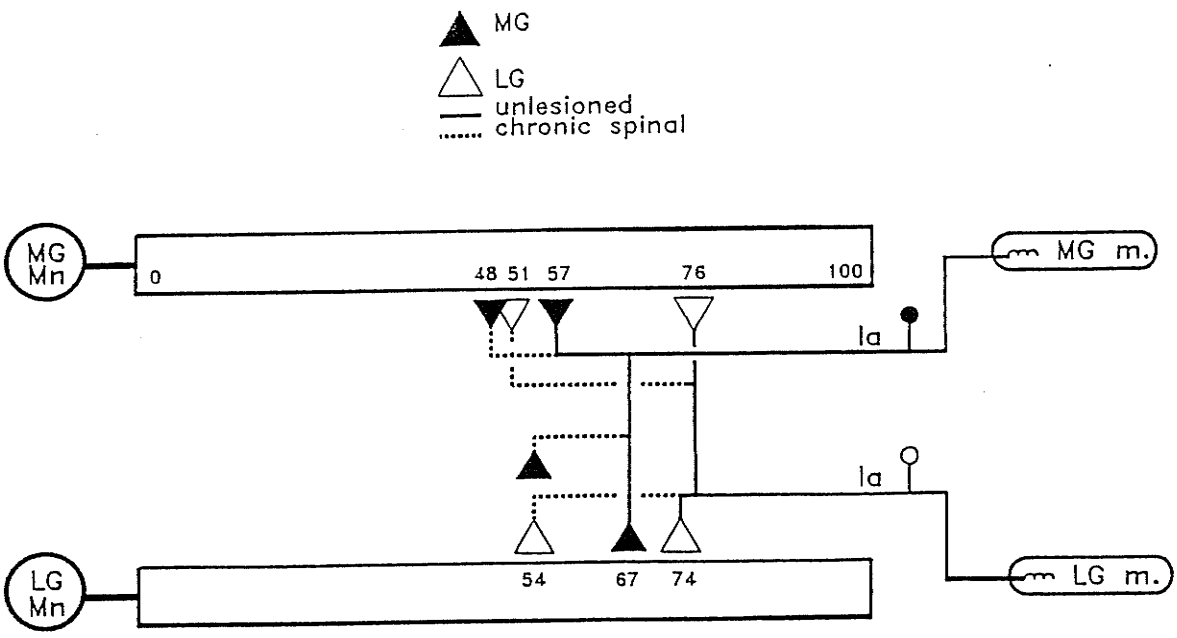

Figure 14. Use of risetime data to infer mean dendritic location of Group Ia boutons. Mean dendritic location of unlesioned and chronic spinal homonymous and heteronymous Ia EPSPs on equivalent cylinder models of MG and LG motoneurons. The equivalent cylinder may have risetimes of greater than 100 ms, which is shown here for scale only. Data from Hochman and McCrea (1992a). See Table 3 for their risetime data.

TABLE 1

Stretch (um)	UL EPSP (mV)	n	CS EPSP (mV)	n	p<
0-10	1.20	44	1.29	36	ns
10-20	2.33	40	2.14	33	ns
20-30	2.27	59	2.93	85	0.05
30-40	2.52	39	3.53	28	0.05
40-50	2.57	32	3.69	20	0.05
50-60	3.12	27	3.66	9	ns
60-70	2.76	22	3.71	13	ns
70-80	2.42	17	3.34	5	ns
80+	2.36	27	3.42	10	ns

Table 1. Stretch-evoked homonymous-heteronymous Ia EPSPs in all ankle extensor motoneurons. The stretches have been grouped into 10 μm bins. 200 grams initial muscle tension throughout. * denotes a significant difference in EPSP amplitude ($p < .05$).

TABLE 2A All MNs

		Tension (grams)	Stretch (um)	Meanamp (mV)	p<	n	Standard deviation
	UL	100	20	1.18	0.05	31	1.49
	CS			1.9		29	1.37
	UL	200	20	2.23	0.025	55	1.57
	CS			2.92		82	1.88
	UL	300	20	2.33	ns	47	1.38
	CS			2.74		32	1.31
	UL	300	70	2.71	ns	7	0.87
	CS			3.71		4	2.24
	UL	400	20	1.77	ns	25	1.16
	CS			2.03		1	—

TABLE 2B MG, LG, SOL, and PL MNs

		Tension (grams)	Stretch (um)	Meanamp (mV)	p<	n	Standard deviation
MG	UL	100	20	1.99	ns	3	1.59
	CS			2.36		19	1.48
MG	UL	200	20	1.95	0.01	22	1.35
	CS			2.95		37	1.52
MG	UL	300	20	2.36	ns	19	1.3
	CS			2.9		19	1.11
LG	UL	100	20	0.45	0.005	14	0.27
	CS			1.05		5	0.48
LG	UL	200	20	2.15	ns	17	1.44
	CS			2.92		24	2.21
LG+LGS	UL	200	20	2.42	ns	23	1.69
	CS			2.76		31	2.02
LG+LGS	UL	300	20	2.13	ns	18	1.16
	CS			2.62		12	1.61
PL	UL	200	20	2.56	ns	9	1.84
	CS			2.55		10	2.57

Table 2. Stretch-evoked homonymous-heteronymous Ia EPSPs in A) pooled data from all motoneurons, B) MG, LG, LGS (either LG or SOL motoneurons), and PL motoneuron populations, C) motor unit typed motoneuron populations.

TABLE 2C Motor Unit Typed MNs

		Tension (grams)	Stretch (um)	Meanamp (mV)	p<	n	Standard deviation
FF	UL	200	20	1.57	0.025	21	0.77
	CS			2.15		15	0.91
MGFF	UL	200	20	1.7	0.05	9	0.3
	CS			2.37		10	0.98
SLOW	UL	100	20	2.3	ns	11	1.9
	CS			2.71		4	1.28
SLOW	UL	200	20	3.44	ns	12	2.07
	CS			4.3		5	1.97
SLOW	UL	300	20	3.19	ns	9	1.83
	CS			2.38		3	0.42

Table 2. Stretch-evoked homonymous-heteronymous Ia EPSPs in A) pooled data from all motoneurons, B) MG, LG, LGS (either LG or SOL motoneurons), and PL motoneuron populations, C) motor unit typed motoneuron populations.

TABLE 3

		amplitude (mV)	risetime (ms)
MG	Homonymous		
UL		1.50	0.57
CS		1.57	* 0.48
LG	Homonymous		
UL		1.23	0.74
CS		* 1.80	* 0.54
LGS to MG			
UL		1.36	0.76
CS		* 2.58	* 0.51
MG to LG			
UL		1.55	0.67
Cs		* 2.73	* 0.54

Table 3. Electrically-evoked composite monosynaptic Ia EPSPs in MG and LG motoneuron pools. Homonymous EPSPs evoked by 1.2T electrical stimulation. Heteronymous EPSPs evoked by 2T electrical stimulation . * denotes a significant difference in EPSP amplitude ($p < .05$). (Data from Hochman and McCrea 1992a).

DISCUSSION

The experiments outlined in this thesis were concerned with the synaptic mechanisms underlying the increased proprioceptive reflexes that follow spinal cord transection. Previous work in this laboratory showed that while the amplitude of homonymous and heteronymous composite monosynaptic Ia EPSPs was increased in the pool of all ankle extensor motoneurons in six week L1-L2 chronic spinal cats, some differences existed between homonymous and heteronymous EPSPs in certain groups of motoneurons, notably MG and type FF. The present experiments extended these observations to stretch activation of Ia afferents, thereby mimicking clinically elicited reflexes. As well, the present approach summated homonymous and heteronymous EPSPs evoked by stretch. This better assesses the effects of chronic spinalization than EPSPs evoked electrically at different stimulation strengths. In this study, stretch-evoked EPSPs are combined (temporal and spatial summation) homonymous and heteronymous composite monosynaptic Ia EPSPs.

To summarize the results, Ia EPSPs evoked by a 20 μm stretch of the ankle extensor muscles were significantly increased in pooled data from all ankle extensor motoneurons at 100 and 200 grams initial muscle tension, in MG motoneurons at 200 g, LG motoneurons at 100 g, FF motoneurons at 200 g, and MG FF motoneurons at 200 g. Ia EPSP amplitude was larger in the chronic spinal motoneurons in almost every group of motoneurons tested, though not always with statistical significance (Tables 2A,B,C). This was the case for all motoneurons at 300g/20μm (UL=2.33mV, CS=2.74mV), 300g/70um (UL=2.71mV, CS=3.71mV), and 400g/20um (UL=1.77mV, CS=2.03mV). Likewise, CS Ia EPSPs were larger, but not always significantly in each species: MG 100g/20um (UL=1.99mV, CS=2.36mV), MG 300g/20um (UL=2.36mV, CS=2.90mV), LG 200g/20um (UL=2.15mV,

CS=2.92mV), LG and LGS 200g/20um (UL=2.42mV, CS=2.76mV), LG and LGS 300g/20um (UL=2.13mV, CS=2.62mV). Finally, there was a trend for an increase in Ia EPSP amplitude in motor unit typed motoneurons of the chronic spinal cat: Slow 100g/20um (UL=2.30mV, CS=2.71mV), Slow 200g/20um (UL=3.44mV, CS=4.3mV).

The need to motor unit type the impaled motoneuron before it became unhealthy imposed a time constraint, making it difficult to record the EPSP at several stretch amplitudes using several initial tensions. Since the sample size was often small the consequent lack of significance does not necessarily imply a lack of physiological difference between unlesioned and chronic spinal EPSPs. Table 2B shows that stretch-evoked EPSPs in MG motoneurons at 100 g initial tension were not significantly larger in the chronic spinal preparation. This would likely not have been the case had the unlesioned sample size not been so small (n=3), which is ascribable to the fact that EPSPs evoked at 100 g in the unlesioned animals were often too small to measure. This in itself indicates that stretches unable to evoke an EPSP in unlesioned motoneurons could evoke an EPSP in chronic spinal motoneurons. Similarly, Figure 9 underestimates chronic spinal EPSP amplitude because stretches which evoke a spike are not included. The standard deviation of the mean Ia EPSP amplitudes were occasionally quite high, as for example in PL motoneurons for a 20 μm stretch at 200 g initial muscle tension (Table 2B). Here the standard deviation for the chronic spinal group (2.57) was larger than the mean value itself (2.55 mV). As stated above, it is strongly felt that were the sample sizes larger in many of the groups studied, then statistically significant differences would have been demonstrated, as would smaller standard deviations. Certainly, some of the variation is due to quite different Ia afferent responses to stretch from cat to cat, and from muscle to muscle, as well as changing responses as the experiment wore on. It was important to terminate the experiments when the whole muscle tension of the triceps surae and

plantaris was less than 75 per cent of the first recorded whole muscle tension. However, at whole muscle tensions between 100 per cent and 75 per cent, some loss of Ia afferent fibers may have occurred, and contributed to a smaller EPSP amplitude. This reduction of Ia EPSP size with time was not assessed. Similarly, when blood pressure fell to low levels, for example 60 mm Hg, Ia EPSPs could not be evoked by stretch, but could be evoked by electrical stimulation of the muscle nerves. This observation points to a loss of the stretch receptor function, but not to a loss of impulse propagation along the Ia afferent nerve.

The previous work of Hochman and McCrea (1992a) demonstrated that in chronic spinal MG and FF motoneurons the heteronymous EPSPs were increased, but the homonymous EPSPs were not. Since the combined homonymous and heteronymous stretch-evoked EPSPs in this study were increased in chronic spinal MG and FF motoneurons (Tables 2B,C), it is concluded that the heteronymous EPSPs are responsible for the increase. What synaptic events could account for increased transmission in the heteronymous pathway, but not the homonymous pathway is uncertain. And why the homonymous transmission is increased in LG motoneurons, but not MG or FF motoneurons is not certain.

Group II effects. It is of concern to what degree the monosynaptic EPSP measured in the motoneuron was purely Ia in origin. Group Ia and group II muscle spindle afferents are similar in their response to static stretch, and although the Ia's are especially more sensitive to dynamic stretch, the group II do have some dynamic responsiveness (Matthews, 1981, Hasan and Stuart, 1984, Hunt, 1990). Homonymous monosynaptic group II EPSPs were recorded from intercostal motoneurons and later from triceps surae motoneurons (Kirkwood and Sears, 1974, 1975). These findings were confirmed in ankle extensors and flexors (Stauffer et al., 1976). The group II versus group Ia monosynaptic input to hindlimb

motoneurons, however, is small - and functional connectivity (the percent of motoneurons in the motoneuron pool to which an afferent fiber makes functional contact) is less, as is EPSP amplitude. Functional connectivity of group II afferents in homonymous MG motoneurons was found to be only 52 percent, as compared with 87 percent for group Ia afferents (Taylor et al., 1976). The functional connectivity to heteronymous LGS motoneurons was 26 percent for group II and 61 percent for group Ia (Taylor et al., 1976). Similarly, MG group II afferent functional connectivity in all triceps surae motoneurons was 42 percent, as compared with 78 percent for MG group Ia (Sypert et al., 1980).

With regard to EPSP amplitude, unitary monosynaptic group II EPSPs evoked by maintained stretch of the MG muscle and measured in all triceps surae motoneurons were less than one half as large as those from MG group Ia afferents (30 μV versus 65 μV, chloralose anaesthetized cats) (Stauffer et al., 1976, Watt et al., 1976). A similar study also using maintained stretch found that MG unitary monosynaptic group II EPSPs in all triceps motoneurons were less that one third the amplitude of those from MG Ia afferents (24 μV versus 82 μV, barbiturate anaesthetized cats) (Munson et al., 1980, Sypert et al., 1980). Lundberg and colleagues (1977) have speculated that since group II functional connectivity and unitary group II EPSP amplitude are both about half of the corresponding Ia values (Taylor et al., 1976), the effective group II monosynaptic input to motoneurons would be about 25 percent of Ia. Their own observations using electrical stimulation of peripheral nerves was that composite homonymous monosynaptic group II EPSPs in hindlimb flexor and extensor motoneurons were only 5-10 percent of the amplitude of Ia EPSPs.

In an examination of electrically-evoked composite monosynaptic Ia and group II EPSPs in decerebrate cats, it was found that group II afferents alone could not evoke an action potential in ankle extensor motoneurons (Tan, 1983). However, one third of the

motoneurons were designated as "group II activated motoneuronal units" because they would only discharge when homonymous Ia input was supported by heteronymous group II input. The consensus is that the group II afferents have a weak monosynaptic effect, especially when considering the following statement by Matthews (1963): "A brief tap of the type used to elicit a tendon jerk induces a much brisker burst of firing from the primary ending than from the secondary ending which may remain almost unaffected and simply continue with its preexisting discharge."

The group II role is important in the modulation of ongoing movements, with the group II activity maintaining the excitability of interneurons in reflex pathways (Lundberg et al., 1987b). The group II afferent may also function as a flexion reflex afferent (Lundberg and Holmqvist, 1961), as it disynaptically excites flexor motoneurons and trisynaptically inhibits extensor motoneurons (Lundberg et al., 1987a). Monosynaptic group II EPSPs onto group II excitatory interneurons are far more efficacious than onto motoneurons. A unitary EPSP from a single MG spindle group II afferent onto a group II excitatory IN is on the order of 800 μV and may be large enough to discharge the IN on its own (See Fig. 11A-E in Lundberg et al., 1987a). By comparison, it is has been suggested that if all 71 (Boyd and Davey, 1968) group II afferents from MG were to fire at 100 Hz, the resulting homonymous monosynaptic tonic depolarization would be only 0.3 mV (Munson et al., 1982). Nonetheless, this does not eliminate a role of the Group II afferent in the enhanced monosynaptic reflex.

Mechanisms of EPSP increase

A number of theories have been put forth regarding the cause of the increased Ia EPSP following spinal transection. In summary, these are loss of descending pathways, sprouting of new boutons from sensory afferents, and unmasking of silent synapses.

LOSS OF DESCENDING PATHWAYS

The extent to which the motoneurons of the lumbar segments are deprived of synaptic input following the interruption of descending pathways by a lesion is an important factor in understanding spasticity. Synapse removal may cause immediate changes in the synaptic efficacy of other fiber systems onto the motoneuron, or more delayed changes due to the degeneration and withdrawal of their boutons from the motoneurons. Synapses may cover 50 percent of the motoneuron membrane, and a single alpha-motoneuron may receive 4000-8000 synaptic contacts (although higher figures have been reported) (Burke and Rudomin, 1977, Sypert and Munson, 1984). The majority are from intrinsic fiber connections and a small percentage from primary afferent and long descending systems (McLaughlin, 1972). Following denervation of neurons, there are vast areas of denuded soma and dendritic surface membrane available for new synapses (Bernstein and Bernstein, 1973).

It is known that 6-7 days after axotomy, axon terminals are pushed away from their contacts with postsynaptic neurons by invading glial cells, and after two weeks are no longer in contact (McLaughlin, 1972). Electron microscopy of boutons of the lumbar segments reveals that following L2 complete spinal cord transection there is maximal degeneration and phagocytosis of boutons in the L3-L5 motor nuclei at 3-4 days, and in S1 motor nuclei at 6-8 days. On the strength of these observations, it was proposed that the pathological changes occurring 3-8 days after the lesion involved a degeneration of propriospinal and supraspinal boutons. There are five supraspinal descending systems that contact motoneurons: the vestibulospinal tract, the reticulospinal tract, the rubrospinal tract, the corticospinal tract, and the tectospinal tract. Knee and ankle extensors receive monosynaptic EPSPs from the lateral vestibulospinal tract (Deiter's nucleus) (Grillner et al., 1970, 1971). These vestibulospinal EPSPs are approximately one quarter of the amplitude of Ia EPSPs, and based on their

smaller risetime and half-width than Ia EPSPs, are largely on the proximal half of the lumbar motoneuron dendrites (Burke and Rudomin, 1977, Sypert and Munson, 1984). The reticulospinal tract in cat projects monosynaptically to motoneurons of the neck, back, forelimb extensors and flexors, hindlimb knee, ankle, and toe flexors, and hindlimb hip and toe flexors; there appear not to be monosynaptic contacts in the cat from the reticulospinal tract to ankle extensor motoneurons (Grillner et al., 1970, 1971, Shapovalov, 1972, Burke and Rudomin, 1977, Sypert and Munson, 1984). The rubrospinal, corticospinal, and tectospinal tracts do not make monosynaptic contacts with motoneurons in cats (Burke and Rudomin, 1977). Hence, it appears that of the descending tracts from supraspinal structures, only the lateral vestibulospinal tract gives monosynaptic EPSPs to ankle extensor motoneurons. As for propriospinal systems that could be severed by the L1-L2 transection of the present study, Jankowska and colleagues (Jankowska et al., 1974) identified monosynaptic EPSPs in lumbar motoneurons from long propriospinal neurons that connect the cervical enlargement with the lumbar enlargement. Thus the denervation of triceps surae and plantaris motoneurons would be expected to occur directly from degeneration of vestibulospinal boutons and long propriospinal boutons, although other descending pathways may be involved in as yet undetermined ways.

SPROUTING

It has been suggested that the increased monosynaptic EPSP amplitude in hindlimb motoneurons following chronic spinal cord transection is due to the sprouting of terminals from Ia afferent fibers. These new terminals are thought to populate vacated synaptic sites on the motoneuron that were previously occupied by the boutons of descending synaptic systems (Nelson and Mendell, 1979). As early as 1958, it was postulated that sprouting was

an important factor in the production of spasticity (McCouch et al., 1958). Evidence in support of this idea comes from Liu and Chambers (1958), who described sprouts from dorsal root fibers in the ventral horn of the thoracic spinal cord in cats following section of the adjacent ipsilateral dorsal roots. No sprouts from dorsal root fibers, however, were recognized in the lumbosacral region in chronic cats with a degenerated pyramidal tract (Liu and Chambers, 1958). It is tempting to suggest that no sprouting occurred in the ventral horn of the lumbosacral cord because the corticospinal tract in cat does not make monosynaptic contact with motoneurons (Burke and Rudomin, 1977).

Additional evidence for sprouting in the central nervous system comes from Tsukahara and colleagues (1974, 1975), who have demonstrated that if the neurons of the red nucleus are deprived of their somally located input from the cerebral cortex, then the fibers from the nucleus interpositus of the cerebellum that innervate the distal dendrites of the red nucleus neurons sprout to fill in these vacated synapses. This conclusion is based on the fact that after the lesion to the fibers from the cortex, EPSPs from the nucleus interpositus recorded in red nucleus neurons have a shorter risetime (risetime is the time in milliseconds from the onset of an EPSP to the peak EPSP amplitude), indicating the addition of more proximally located boutons. This is in turn based on the fact that EPSPs exhibiting faster risetimes and shorter half widths (half width is the time in milliseconds from 50 percent of peak EPSP amplitude on the rising phase of the EPSP to 50 percent of peak EPSP amplitude on the falling phase of the EPSP) are known to be closer to the soma of neurons. In a study of the time course of Ia EPSPs, Redman and Walmsley (1983a) stained lumbar motoneurons and Ia axons of the cat with horseradish peroxidase. The location of the Ia synapses onto the motoneuron as revealed by electron microscopy was compared with electrophysiological data of EPSP shape (risetime, half width), and confirmed the predictions of Rall (1967) that

mathematically modeled EPSPs with fast risetime and short half width should be closer to the soma.

The enlarged Ia EPSP amplitudes in MG and LG motoneurons measured in the current study and in others (Nelson and Mendell, 1979, Munson et al., 1986, Hochman and McCrea, 1992a) could be partially explained by sprouting. The Ia EPSP shape data of Hochman and McCrea (1992a) following chronic spinalization offers some insights into the pattern of sprouting of LG and MG Ia afferents onto LG and MG motoneurons. Figure 14 depicts the predicted mean dendritic location of Ia afferent terminals onto a motoneuron equivalent cylinder model, based on the risetime data of electrically-evoked homonymous (1.2T) and heteronymous (2T) Ia composite monosynaptic EPSPs in MG and LG motoneurons (Data from Hochman and McCrea, 1992a. Their risetime data is shown in Table 3). The model is meant to represent the entire dendritic tree of the neuron as a cylinder, and indicates the electrotonic length of boutons with respect to the soma. The electrotonic length is a dimensionless value (range = 1-2 for cat spinal motoneurons) indicating the number of times a synaptic voltage on the distal dendritic tree decays to 37 percent (1/e) by the time it is recorded as a voltage in the soma (Sypert and Munson, 1984, Schwindt and Crill, 1984). Figure 14 slightly modifies that concept, as it shows the mean dendritic location of Ia boutons as a physical distance from the soma - the distance more or less correlated with risetime. The scale is from 0, indicating an EPSP on or very close to the soma, to an arbitrary upper limit of 100, indicating an EPSP quite distal to the soma (All risetime values from Table 3 have been multiplied by 100.). As the figure shows, following 6 week chronic spinalization, there were statistically significant ($p < 0.05$) reductions in the risetime of Ia EPSPs from LG-to-LG (LG Ia EPSP onto LG motoneuron) (0.74 ms to 0.54 ms), from LG-to-MG (0.76 ms to 0.51 ms), from MG-to-MG (0.57 ms to 0.48 ms), and from

MG-to-LG (0.67 ms to 0.54 ms) (Hochman and McCrea, 1992a). The trend appears to be for the LG and MG terminals in the chronic spinal cat to attain a more proximal location on homonymous and heteronymous motoneurons than the unlesioned cat, with a mean risetime of approximately 0.5 ms for the former (shown as 50 units in Figure 14). This dendritic location could be where there are vacant synaptic sites formerly occupied by degenerated descending, propriospinal, or interneuronal boutons.

Nelson and Mendell (1979), in a study of L4-L5 chronic spinal cats, found that there was an increase in the number of small risetime EPSPs, and this was taken to mean that degenerated boutons had previously occupied synaptic sites close to the cell body in the intact spinal cord. Monosynaptic EPSPs from the lateral vestibulospinal tract are, based on their time course being less than that of Ia EPSPs, largely on the proximal half of the lumbar motoneuron dendrites (Grillner, 1970a, Sypert and Munson, 1984). The proximal dendrites are the most frequent region for Ia synaptic input, although some Ia single-fiber synaptic contacts include terminals at the distal dendrites (Redman and Walmsley, 1983a, Brown and Fyffe, 1981). Therefore, sprouting of Ia afferents should proceed in a proximal direction. Possibly the homonymous mean dendritic location of Ia EPSPs in MG (UL risetime = 0.57 ms) is already quite close to the vacant synaptic sites, which may be the reason that the proximal sprouting is minimal (CS risetime = 0.48 ms) (Table 3). Why does sprouting of Ia afferents only proceed to a "distance" of 0.48 ms of risetime from the soma (Figure 14)? Why not all the way to the soma? Perhaps some new boutons do make contact with the soma, however, the mean "distance" is 0.48 ms of risetime. Perhaps the proximal half of the dendritic tree is occupied by the boutons of intact neuronal pathways.

Does a relationship exist between the lack of change of homonymous Ia EPSP amplitude in MG motoneurons and the lack of change of risetime of homonymous Ia EPSPs

in these same motoneurons? One would argue likely not, since there is only a weak negative correlation between amplitude and risetime (Mendell and Weiner, 1976). Moreover, Redman and Walmsley (1983b), in their single vesicle hypothesis state that the "quantal" EPSP recorded in the soma due to a bouton releasing a single vesicle of neurotransmitter (one quantum) is about 100 μV, regardless of whether the synapse is proximal or distal. They go on to say that a distal bouton may open ten times as many ion channels as a proximal bouton, either because more neurotransmitter is released per vesicle or possibly that the neurotransmitter efficacy is greater distally (Finkel and Redman, 1983).

Should there be sprouting from Ia afferents onto lumbar motoneurons, one would expect that the projection frequency of Ia afferents should increase. Projection frequency, also known as functional connectivity, is measured by stimulating a Ia afferent fiber and recording the number of homonymous (or heteronymous) motoneurons that receive monosynaptic EPSPs from it (Scott and Mendell, 1976). Indeed, projection frequency increases do occur after acute spinalization and chronic spinalization. It was reported that the projection frequency to homonymous MG motoneurons increased from 80 % in the intact cat to 100 % in the T13 chronic spinal cat, 100 % in the L5 chronic spinal cat (Nelson and Mendell, 1979), 100 % in the T13 acute spinal cat, and 100 % in the L5 acute spinal cat (Nelson et al., 1979). These increases are immediate (within minutes) and are therefore not due to sprouting, which appears after 2 weeks, at least in the red nucleus (Tsukahara et al., 1974, 1975).

Assuming that a projection frequency of 80 percent represents an average value, the increase in functional connectivity immediately following spinalization has been ascribed to a functional change in previously inactive synapses (silent synapses) (Nelson et al., 1979). A silent synapse is one in which a bouton is seen morphologically, but no EPSP occurs upon

stimulation of the axon of the bouton (Redman and Walmsley, 1983b). These synapses may be inactive in the unlesioned state because they are presynaptically inhibited. This presynaptic inhibition is thought due to segmental and descending fibers making GABAergic axo-axonic synapses with the Ia afferent boutons (Frank and Fourtes, 1957, Eccles et al., 1961, Eccles et al., 1963). GABA (gamma-aminobutyric acid) is known to activate both $GABA_A$ and $GABA_B$ receptors located on muscle spindle afferent terminals of the isolated frog spinal cord (Peng and Frank 1989a,b). Activation of $GABA_A$ receptors causes an efflux of chloride ions from the terminal, leading to its depolarization ("primary afferent depolarization") (PAD), which reduces the amount of neurotransmitter released when an action potential invades the bouton (Eccles et al., 1961, DeGroat et al., 1972, Gallagher et al., 1978, Alvarez-Leefmans et al., 1988). Primary afferent depolarization decreases the number of vesicles of neurotransmitter (quanta) released by a bouton, but the quantal EPSP due to each vesicle is unchanged (Kuno, 1964). Activation of $GABA_B$ receptors reduces inward calcium currents activated during the action potential, which reduces the amount of neurotransmitter released (Borman, 1988, Dunlap and Fischbach, 1981). Hence, the effect of GABA is to sufficiently reduce the amount of neurotransmitter released by Ia afferent terminals so that they become functionally silent. If the segmental and/or descending inputs causing presynaptic inhibition of Ia afferent synapses (silent) are removed due to a lesion, then one would expect an increased transmission from Ia afferents onto their lumbar motoneuron contacts.

The immediacy of the increases in projection frequency, that is, the unmasking of silent synapses after acute spinalization, suggests that a loss of presynaptic inhibition may be responsible (Luscher, 1990) - a conclusion based on several observations. Firstly, it is known that the Ia monosynaptic reflex evoked by gastrocnemius-soleus peripheral nerve stimulation

is suppressed by a Ia volley in Posterior biceps/Semitendinosus (PbSt) Ia afferents (Naftchi, 1980, Gillies et al., 1969). The PbSt Ia afferents excite a first order PAD interneuron which excites a second order PAD interneuron which depolarizes the gastrocnemius-soleus boutons, therefore decreasing the amount of neurotransmitter released (Rudomin et al., 1983). In human patients with spastic hyperreflexia, there is evidence that suppression of the monosynaptic reflex by PAD is less than in normal subjects, which is taken to mean that presynaptic inhibitory mechanisms are reduced (Burke and Ashby, 1972, Ashby and Verrier, 1980). Secondly, in the chronic spinal cat there is a gradual reduction in presynaptic inhibition. Inhibition of the G-S monosynaptic reflex by a Ia volley in PbSt is markedly reduced 1-12 weeks following the lesion (Naftchi, 1980). Thirdly, this latter observation is attributed to a decreased release of GABA by the PAD interneurons, because the enzymatic activity of glutamate decarboxylase, the enzyme that converts glutamate to GABA, is known to be decreased below the lesion (Naftchi, 1980). Finally, evidence exists for a tonic presynaptic inhibition of Ia terminals in the human (Hultborn et al., 1987a,b, Meunier and Pierrot-Deseilligny,1989, Rudomin, 1990) and in the cat (Andén et al., 1966). The interruption of descending fibres mediating tonic presynaptic depolarization of Ia afferent terminals following spinal cord transection would be expected to enhance the monosynaptic transmission from Ia afferent fibres onto ankle extensor motoneurons. Precisely how increased Ia transmission occurs after chronic spinal cord transection must be complex, since descending systems have both excitatory and inhibitory effects on PAD-evoking interneurons (Rudomin, 1990). For example, the first order interneurons that evoke PAD of Ia terminals (via a second order PAD interneuron) are excited by the vestibulospinal tract (Grillner et al., 1966, Cook et al., 1969, Rudomin et al., 1983) but inhibited by the pyramidal and rubrospinal tracts (Lundberg, 1964, Lundberg and Vyklicky, 1966, Rudomin et al., 1983, Rudomin et al.,

1986); and the second order PAD interneuron is inhibited by the reticulospinal tract (Rudomin et al., 1983).

It has been postulated that the increased Ia EPSP following spinal cord transection may be mediated by factors outside the neuraxis, that is, other than by mechanisms within the spinal cord. It is known from Nelson and Mendell (1979) that T13 transection does not cause a change in unitary homonymous MG Ia EPSP amplitude (nor does L1-L2 transection cause a change in composite homonymous MG Ia EPSP amplitude (Hochman and McCrea, 1992a). But, a T11 transection several weeks after the T13 transection caused an increased Ia EPSP amplitude in MG motoneuron within hours (Cope et al., 1980). The authors of the latter study speculate rather broadly as to why the "double transection" increases Ia EPSP amplitude: release of certain humoral factors onto the motoneurons, autonomic effects on motoneurons, or breakdown of the blood-brain barrier releasing substances onto the motoneurons. That the release of substances onto the motoneurons should cause a change in EPSP amplitude following T11, but not T13 transection, is problematic. The situation seems more aligned to that presented in the Nelson and Mendell paper, where T13 transection caused no change in Ia EPSP amplitude in homonymous MG motoneurons (as stated above), but an L5 transection did cause an increase; this was explained as due to the fact that TS motoneurons in L7-S1 were more denervated following L5 transection and therefore more sprouting and denervation supersensitivity occurred. The upshot of it all is that lesion level plays an important albeit confusing and complex role in the development of enlarged EPSPs following spinalization.

It was formerly thought that increased gamma motoneuron activity causing enhanced stretch reflexes in the decerebrate cat was also a cause of spasticity (Burke D., 1983). Experimental work in support of this idea came from a study of cats whose hindlimb was

immobilized in a cast, whereupon there was atrophy of the extrafusal and intrafusal muscle fibers of the MG muscle, and an increase in the resting discharge and sensitivity of spindle afferents (Maier et al., 1972). In fact, there is no increased spindle afferent activity in cats with CS transection (Bailey et al., 1980) nor in spastic man (Hagbarth et al., 1973).

The monosynaptic reflex recorded in triceps surae ventral roots of peripheral nerves can be increased without an increase in Ia EPSP amplitude (Decima and Morales, 1983, Decima et al., 1986). This was demonstrated following axotomy of the ascending branch of Ia afferents in the L3-L4 dorsal column (Ia afferents send rostrally directed branches into the dorsal columns). The increased MSR was attributed to the observed sharper rate of rise of the Ia EPSPs, although the mechanism was uncertain (Decima et al., 1986).

RECRUITMENT

We have looked at EPSP amplitude from stretch receptors. Following chronic spinalization there are changes in motoneuron electrical properties, increases in EPSP amplitude (as we have shown), and changes in the proportions of the motor unit types that comprise the motoneuron pool of each ankle extensor species. The net result is an altered recruitment of motoneurons leading to an increased MSR and spasticity. But how, for example, does a 1 mV increase (from 1.95 mV to 2.95 mV) in Ia EPSP amplitude in MG motoneurons evoked by a 20 μm muscle stretch (Table 2A) fit into the scheme of things? It is useful to first briefly overview the current thoughts on recruitment. Investigators have stated that the recruitment of motoneurons may be according to several criteria: 1) motoneuron size, 2) motor unit contraction strength, 3) motor unit type, and 4) motoneuron electrical properties.

It was noted early in this century that red (slow twitch) muscle had a lower threshold

to stretch than pale (fast twitch) muscle (Denny Brown, 1929). When muscle was further elaborated into three motor unit types, it was suggested that motor unit recruitment follows the order S -> FR -> FF (Burke R.E., 1981, Fleshman et al., 1981b, Zajac and Faden, 1985, Zajac, 1990). Not surprisingly, the amplitude of homonymous Ia EPSPs was found to be larger in Slow motoneurons than in Fast motoneurons (Burke R.E., 1968, Fleshman et al., 1981a, Zengel et al., 1983, Mayer et al., 1984, Munson et al., 1986, Hochman and McCrea, 1992c).

That recruitment might be based on the size of the motoneuron forms the core of the "size principle", the theory being credited to Elwood Henneman (Henneman et al., 1965). According to the size principle, recruitment order is proportional to the action potential amplitude of the motor axon, which is proportional to the diameter of the axon, which is proportional to motoneuron size (Henneman, 1957, Henneman, 1965), so that small motoneurons are recruited before large motoneurons. Over the years, the word 'size' has been given considerable latitude, in what appears to be an undercurrent of loyalty to Henneman's original size principle. Indeed, John Munson (1990), points out that "there is general agreement that motor units have a usual order of recruitment, i.e., from small to large. There is no universal agreement, however, on small or large what (i.e., motoneuron size? motor axon size? muscle unit size?)". If size is taken to mean total membrane area of the motoneuron, the differences are still not motor unit type specific (Ulfhake and Culheim, 1981). The size principle was altered in 1977, so that recruitment was according to "muscle unit size" in addition to motoneuron size (Henneman, 1977). Muscle unit size refers to the maximal isometric force (P_o) of a motor unit. Recruitment is in the order of increasing P_o, and parallels the recruitment according to motor unit type: the mean P_o of S, FR, and FF motor units 5 g, 20 g, and 60 g respectively (Burke and Rudomin, 1977, Zajac and Faden,

1985). It is probably more correct to say that motoneuron recruitment is according to, rather than due to, motor unit type (S -> FR -> FF) and contraction strength (small -> large).

Today, more than 25 years after its inception, the original size principle hypothesis stating that recruitment is according to motoneuron size is unproven. The redeeming feature of the size principle is that it has encouraged much work and thought on the factors underlying recruitment of motoneurons for purposeful motor tasks and reflex movements. If motoneuron recruitment is according to motor unit type and contraction strength, then what is it due to? Differences in motoneuron electrical properties seem to be the common denominator. Slow motoneurons have a larger input resistance, smaller rheobase, and larger specific resistivity (Mendell, 1988, Gustafsson and Pinter, 1984).

ANTISPASTICITY THERAPIES

A number of clinical therapies aimed at the reduction of spasticity have been tried. Functional electrical stimulation of the quadriceps and hamstring muscles has been shown to reduce spasticity, although the mechanism is uncertain (Homberg, 1989). Cooling the spastic limbs with ice packs decreases spasticity for 15-20 minutes (Knuttsson and Mattsson, 1969). Pharmacological treatment appears to be more effective than either functional electrical stimulation or cryotherapy. The best success has been met with the GABA agonist, baclofen [beta-(4-chlorophenyl) GABA], which activates $GABA_B$ receptors located on the terminals of primary afferents, the result of which is a decrease in calcium influx into the terminal, thereby reducing the release of neurotransmitter onto motoneurons (Davidoff, 1985). Intrathecal baclofen causes profound decreases in the monosynaptic H reflex and in polysynaptic reflexes. Spasticity is reduced from Ashworth Scale 4-5 (marked spasms and/or spasticity) to 1-2 (normal or slightly increased), at doses (100-800 μg/day) much less in

quantity but much more effective than oral baclofen (160 mg/day): "We are convinced it is the drug of choice for these severely spastic patients. It is hard to believe the same drug, namely [intrathecal versus oral] baclofen, is producing the effects" (Penn, 1989). As well, baclofen decreases bladder dyssynergy and decreases external urethral sphincter tone (Penn, 1989). There is an increased concentration of baclofen in lumbar spinal cord tissue with intrathecal administration in cats and humans, because orally administered baclofen does not penetrate the blood brain barrier well (Henry, 1980). Baclofen decreases Ia EPSPs from flexors more than from descending inputs to lumbar motoneuron in cats. This suggests that the reduction of spasticity in humans without significant impairment of voluntary movements, following intrathecal administration of baclofen, can be accounted for by a higher density of baclofen receptors in Ia than descending terminals (Latash et al., 1989).

The drug Tizanidine decreases the PSR but not the MSR. The reason, it is postulated, is that tizanidine is an inhibitor of aspartate, which is released by interneurons in the spinal cord. Inhibition of aspartate would decrease the PSR, whereas the MSR is due to glutamate released by primary muscle spindle afferents (Wiesendanger et al., 1984). Clonidine, also an alpha$_2$ adrenergic receptor agonist, is effective in the treatment of certain reflexes. There is improved locomotion of spastic paretic patients (Stewart et al., 1991) and reduction of external urethral sphincter dyssynergia (Herman and Wainberg, 1991).

In summary, the stretch-evoked Ia EPSPs in triceps surae and plantaris motoneurons were of greater than normal mean amplitude in the six-week chronic spinal cat. Statistically significant increases were seen in pooled data from all motoneurons at initial muscle tensions of 100 g and 200 g when stretches were 20 μm. When the 200 g initial muscle tension was examined in 10 μm stretch bins, there were statistically significant increases in mean Ia EPSP

amplitude for the 20-30, 30-40, and 40-50 μm ranges. Analysis of EPSPs in the motoneuron populations of each of the ankle extensor species revealed increases in amplitude in MG, LG, and SOL. Statistically significant increases in Ia EPSPs evoked by 20 μm stretch were observed in the chronic spinal preparation for MG motoneurons at 200 g initial muscle tension, and in LG motoneurons at 100 g initial muscle tension. Finally, the increase in mean Ia EPSP amplitude in FF motoneurons and MG motoneurons of motor unit type FF of the chronic spinal preparation were statistically significant when 20 μm stretches were applied at 200 g initial muscle tension.

The composite Ia EPSPs evoked in these experiments produced results that were more reliable than those from an analysis of unitary Ia EPSP, for two reasons. One, the effects of all the homonymous and heteronymous afferents contacting MG, LG, SOL, or PL motoneurons were assessed. Two, the Ia afferents were recruited physiologically in both the unlesioned cat and the chronic spinal cat. Also, the results of the quite exhaustive study by Hochman and McCrea (1992a,b,c) of changes in electrically-evoked Ia EPSPs in ankle extensor motoneurons following chronic spinalization were corroborated. Together, all four studies indicate that the increased Ia EPSP amplitudes underlying the increased monosynaptic reflex that partially accounts for hyperreflexia following chronic spinal cord transection are specific to certain species of motoneurons and specific to heteronymous inputs to certain species and motor unit classes of motoneurons. This provides some insight into the nature of the synaptic contacts made by afferent, descending, and interneuronal pathways onto hindlimb motoneurons.

The most probable mechanism of Ia EPSP enlargement recorded in triceps surae and plantaris motoneurons is due to the release of the homonymous and heteronymous Ia terminals from primary afferent depolarization. Future experiments must determine how

much PAD the Ia afferents are deprived of following chronic spinal cord transection. How much PAD do Ia afferents receive in the unlesioned condition? And from what descending sources is the PAD? What sources of Ia PAD would be lost following chronic spinalization.

A topic of uncertainty at present time is the probability of neurotransmitter release by the boutons of an afferent fiber. For example, a typical MG motoneuron receives approximately 60 MG Ia afferents (Boyd and Davey, 1968), each Ia afferent depositing an average of 3 boutons per MG motoneuron (a conservative average according to Sypert and Munson, 1984), for a total of 180 MG Ia boutons per MG motoneuron. If we assume a functional connectivity of 80% (Nelson and Mendell, 1979) and a mean unitary Ia EPSP of 100 μV, then approximately 144 MG Ia boutons (180 X 80%) would cause a 14.4 mV depolarization if all Ia afferents in the MG nerve were recruited. This is clearly larger than the average composite homonymous Ia EPSPs recorded in MG motoneurons, which are on the order of 6-7 mV for 5T stimulation of the MG muscle nerve (Eccles et al., 1957a, Burke et al., 1976b). Hence, the anatomical arrangement is capable of a theoretical depolarization of some 14 mV, yet physiologically only a 7 mV depolarization is recorded. Does this imply that one half of the boutons from the MG Ia afferent population onto an MG motoneuron are functionally silent? The answer to that question remains unknown, but experiments by Redman and Walmsley (1983a,b) examining Ia afferent-motoneuron connections offer some insight. They compared the fluctuations in unitary Ia EPSP amplitude, as revealed by intracellular recording, with the number of boutons that the Ia afferent deposited on the motoneuron, as revealed by horseradish peroxidase staining and electron microscopy. For example, in one Ia afferent-motoneuron pair, the Ia afferent deposited four boutons onto the dendritic tree of the motoneuron. The unitary Ia EPSP amplitude fluctuated between 322 μV (64% of the time) and 443 μV (36% of the time). The 322 μV EPSP was the result of

transmission at three boutons at which failure never occurred. The 443 μV EPSP was the result of transmission at all four boutons. The probability to release transmitter at the fourth synapse was 0.64. While the mechanism for the failure is uncertain, the point is that a considerable fraction of the time a physiologically effective synapse is functionally silent. In the larger scheme of things, this would seem to afford the nervous system with considerable control of the amount of excitation that a motoneuron is to receive from particular afferents. This seems somewhat analogous to situation where the PAD of Ia and Ib afferents is mediated by different sets of PAD interneurons (Rudomin et al., 1983, Rudomin, 1990). If this control mechanism (tonic PAD of a certain fraction of the Ia afferents?) were altered by an interruption of descending pathways, as would occur with spinal cord transection, then it is not be too surprising that reflexes would run amuck.

Future experiments must also compare the anatomical location of Ia boutons on the dendritic tree of ankle extensor motoneurons in the cat before and after chronic spinalization. The hypothesis of such an experiment is that triceps surae and plantaris Ia boutons on the dendritic tree of homonymous and heteronymous motoneurons are more proximal and greater in number following chronic spinal cord transection. This could be accomplished by staining ankle extensor Ia afferents and motoneurons, a procedure that has met with success previously (Redman and Walmsley, 1983a). Both the axon and motoneuron are iontophoresed with horseradish peroxidase and serially reconstructed using a high magnification camera-lucida microscope. A comparison of the dendritic location of the boutons in unlesioned and chronic spinal cats would hopefully demonstrate more proximal and increased numbers of Ia boutons in the latter. This might reveal a differential proximal sprouting of homonymous and heteronymous Ia terminals on MG motoneurons; or similar findings in FF motoneurons if they were motor unit typed according to their electrical

properties rheobase and input resistance. Such a study could only take place in the best of all possible worlds (that is, where Dairy Queen gives away free ice cream), for it would be a colossal undertaking. For example, Redman and Walmsley (1983a) performed experiments on fifty-one cats and only 4 pairs of Ia axon-motoneuron connections were successfully reconstructed after reacting for horseradish peroxidase! Obtaining adequate sample sizes to allow statistically significant comparisons of the anatomical location of homonymous and heteronymous triceps surae Ia boutons in the unlesioned and chronic spinal preparation would entail vast numbers of experiments. Not to mention attempting to calculate the meaning of newly added boutons versus those released from presynaptic inhibition. Nevertheless the "experiment" is food for thought, as it highlights some of the difficulties encountered when elucidating the synaptic plasticity occurring after denervation of the lumbar motoneurons.

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