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Demystifying Spasticity: Reply to Dietz

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REPLY: I was glad to read Dr. Volker Dietz recent letter to the editor (Dietz 2007) comparing his work on spasticity in humans to my studies of spasticity in the sacral spinal rat (Bennett et al. 2004). His comments highlight many of the confusions that have shrouded the study of spasticity and give me a chance to clear the air on this topic.

The first confusion relates to the complexity of spasticity and the lack of consensus on which aspects of spasticity are most relevant. The spastic syndrome in humans (or what Dietz calls the “spastic movement disorder”) is a complex collection of clinical conditions, including excess muscle tone (hypertonus), changes in muscle properties (like contractures), excess reflex activity (hyperreflexia), muscle oscillations (clonus), and massive uncontrolled motoneuron firing and contractions (spasms; Bennett et al. 2004; Dietz and Sinkjaer 2007; Kuhn and Macht 1948). In my laboratory, we mostly study spasms triggered by brief cutaneous stimulation and we have shown these to result from excess motoneuron excitability (Bennett et al. 2004; Li et al. 2004a). Dietz has spent a lot of time studying muscle properties (Dietz et al. 1986) and emphasizes their importance in his letter to the editor (Dietz 2007). From this perspective, he criticizes research that does not focus on muscle properties, suggesting that it is not relevant to the study of spasticity. This seems a bit odd because upward of 80% of spinal cord injured humans suffer from spasms caused by excess motoneuron activity (Maynard et al. 1990), and thus understanding spasms is important.

The second confusion has arisen because spasticity research has for decades focused exclusively on correlating spastic behavior with short-lasting reflexes (mono- and polysynaptic) that can be conveniently measured in the laboratory in humans, as though these reflexes were the only forms of neuronal activity possible from the spinal cord. I think that research should instead focus on measuring neuronal activity during actual spastic episodes, such as during spasms, even though this means studying complex long-lasting reflexes, rather than simple short-lasting reflexes (Bennett et al. 2004). Dietz rightly points out that after years of studying short-latency monosynaptic reflexes and other short-lasting polysynaptic reflexes, it is clear that they do not “contribute greatly to the spastic movement disorder” (Dietz 2007; Dietz and Sinkjaer 2007). However, he then seems to fall into the classic trap of assuming that these reflexes are the only forms of neuronal activity possible from the spinal cord, and thus makes the overgeneralization that human spasticity is not “primarily caused by an *increased* neuronal activity” (Dietz 2007). Because muscle

properties change somewhat in spastic patients (Dietz and Sinkjaer 2007), Dietz then concludes, without any further evidence, that properties of muscles must instead be primarily responsible for spasticity (Dietz 2007; Dietz and Sinkjaer 2007). Importantly, Dietz has not considered longer-lasting reflexes more closely related to the pathological motor behavior. For example, in spinal cord injured patients cutaneous stimulation evokes a long-lasting reflex that underlies muscle spasms. We have shown in both humans and rats with spinal cord injury (Gorassini et al. 2004; Li et al. 2004a) that such long-lasting reflexes are produced by sustained motoneuron discharges maintained by currents intrinsic to the motoneuron (persistent sodium and calcium currents, PICs). After a brief synaptic input (cutaneous), these currents remain activated and produce uncontrolled firing that cannot be turned off because of the loss of descending inhibitory control following spinal cord injury. Thus, in patients that suffer from muscle spasms, neuronal activity in the form of aberrant motoneuron firing plays a major role in their clinical spasticity condition.

The question of whether changes in properties of muscles or changes in neuronal activity are more important depends on the particular patient and the muscle studied. Following spinal cord injury some muscles suffer from atrophy, contractures, and tendon shortening, and I would agree with Dietz that in these muscles the intrinsic muscle property changes dominate the clinical picture (Dietz 2007). However, in many muscles (both leg flexor and extensor muscles) there can be significant motoneuronal activity following spinal cord injury, in the form of clonus and muscle spasms (Gorassini et al. 2004; Kuhn and Macht 1948; Thomas and Ross 1997). It is also very telling that BOTOX injections can rapidly reduce muscle tone (Richardson et al. 2000), which can happen only if the muscles are centrally activated, rather than under peripheral contractures. Thus, it is somewhat of an overgeneralization for Dietz to claim that changes in muscle properties, rather than neuronal activity, always determine spasticity. It is sometimes even quite the opposite. Indeed, we have recently shown that neuronal activity in the form of muscle spasms actually prevents muscle atrophy and changes in muscle properties (Harris et al. 2006, 2007). So the nonspasming muscles atrophy and the spasming muscles do not atrophy, which raises the question of how vigorously we should treat spasticity with drugs like baclofen (Li et al. 2004c).

The third confusion in the study of spasticity has arisen over the years because researchers have mixed together studies of patients with stroke and spinal cord injury. The clinical spasticity syndrome following stroke is characterized in large part by excess muscle tone (especially in arm flexors and leg extensors) and a relative absence of spasms, whereas the clinical spasticity syndrome following spinal cord injury is characterized by less muscle tone and, instead, flexor and extensor muscle spasms triggered by cutaneous stimulation are the hallmark (Kuhn and Macht 1948). Dietz's early research largely focused on stroke (Dietz et al. 1986), and from this stroke work he came to the somewhat extreme conclusion that changes in muscle properties (contractures) dominate spasticity following stroke (see Dietz and Sinkjaer 2007). He then makes a sweeping generalization that changes in muscle property dominate all forms of spasticity, including that arising from spinal cord injury. Here he makes the classic error of mixing stroke and spinal cord injured patients, and ultimately jumps to the conclusion that spasticity is not "caused by *increased* neuronal activity" (Dietz 2007). Because muscle contractures are more prominent in stroke than in spinal cord injury, it is thus not surprising that Dietz focuses exclusively on muscle property changes. However,

following spinal cord injury, the clinical picture is dominated by spasms, in both humans and rats, as I have detailed earlier.

The fourth confusion surrounding spasticity relates to animal models. Because spasticity is such a complex syndrome, no one single animal (or even human) can exhibit all the aspects of the syndrome. Thus, multiple animal models are required to study the various aspects of spasticity. Dietz dismisses all the animal models, especially our sacral spinal rat, because he thinks that they do not have changes in muscle properties similar to those seen in his stroke patient groups (Dietz 2007; Dietz and Sinkjaer 2007). Ironically, however, it is our sacral spinal rat model that might be most useful to his investigations of muscle properties (Harris et al. 2006, 2007) because we have shown that the muscle properties of sacral spinal rats do change very much as in humans after spinal cord injury (Thomas and Ross 1997; Zijdwind and Thomas 2003). Interesting, in muscles that exhibit lots of spasms, this motoneural activity tends to help preserve muscle properties, preventing atrophy, although not completely preventing increased contractures (Harris et al. 2006, 2007). In contrast, when spasms are prevented by cutting the dorsal roots in chronic spinal rats, pronounced muscle property changes occur, including atrophy and emergence of new myofiber types (Harris et al. 2007). An important idea that arose from this work of Harris is that impaired intramuscular calcium handling may underlie many of the changes in muscle properties, including changes in fatigability, twitch tension, and contractures (Harris et al. 2006). Thus, Dietz is wrong in saying that “[I]n none of the actual animal models have changes in muscle properties been addressed” (Dietz 2007).

In summary, I appreciate Dietz’s consideration of our rat model of spasticity. I agree with Dietz on a number of issues. First, muscle property changes are sometimes important to spasticity. Also, short-latency reflexes (like monosynaptic stretch reflex) may not be so relevant to spasticity. However, Dietz (2007) has made a number of errors in judging our rat model, including: mixing stroke and spinal cord injury; ignoring the complexity of the spastic syndrome by focusing only on muscle properties; assuming that the lack of importance of short-latency reflexes means that all neuronal activity is unimportant; and finally underestimating the relevance of current animal models, just because they do not fit precisely with what he thinks is relevant in spasticity. His claim that spasticity does not arise from neuronal activity is just plain wrong, when we consider that muscle spasms are entirely caused by excess motoneuronal activity (Li et al. 2004a), and spasms play a major role in spasticity following spinal cord injury in humans and rats (Gorassini et al. 2004; Li et al. 2004a). It is strange that in his letter Dietz ignores the important work from Gorassini’s laboratory (Gorassini et al. 2004), where it is shown that the same motoneuronal mechanisms that underlie spasticity in our sacral spinal rat (Li et al. 2004a) also underlie spasms in the human after spinal cord injury. Gorassini uses paired motor unit recordings to quantify the sustained motoneuron firing and associated persistent inward currents underlying spasm. We have verified Gorassini’s paired motor unit method of estimating the persistent inward currents using motor unit and intracellular recordings in rats where these currents can be directly measured (Bennett et al. 2001a,b; Li and Bennett 2003). Outside of showing the remarkable utility of motor unit recordings, a surprising coincidence can be seen in the quantitative firing rates of rat sacral motoneurons and human leg motoneurons: both fire with low rates, typically <20 Hz (Bennett et al. 2001a; Gorassini et al. 2004; Li et

al. 2004a). This allows quantitative comparisons of rat and human motor unit firing properties and, in general, suggests that the rat sacral motoneuron is an excellent model of the human lower limb motoneuron.

Our sacral spinal rat model has for the first time allowed combined in vivo and in vitro studies of the mechanisms underlying spasticity following spinal cord injury, including changes in muscle and motoneuron properties (Bennett et al. 1999, 2001a, 2004; Harris et al. 2006, 2007; Li and Bennett 2003; Li et al. 2004a,b). We admit that this model has limitations, such as it addresses only axial musculature. However, we have gone to great lengths to demonstrate that the hypertonus, hyperreflexia, clonus, spasms, and muscle properties seen in the muscles of sacral spinal rats are very similar to those seen in human spastic muscles after spinal cord injury (Bennett et al. 1999, 2004; Harris et al. 2006, 2007), contrary to what Dietz claims. The real power of the sacral spinal rat model comes from the ability to study the injured adult mammalian spinal cord in a dish (in vitro), and thus for the first time enable combined electrophysiological, pharmacological, and molecular studies of chronic spinal cord injury (Anelli et al. 2007; Harvey et al. 2006; Li and Bennett 2007; Li et al. 2004a,c, 2007; Rank et al. 2007). I suggest that we now focus our efforts on understanding the basic neurophysiology underlying spinal cord injury, in general, and leave behind the historical quibbles about definitions of spasticity.

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