Studies on the Spastic Rat: An Adequate Model for Human Spastic Movement Disorder?

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TO THE EDITOR: For the successful translation of basic research to humans, the adequacy of the animal model being studied is of crucial importance. With respect to the frequently occurring spastic syndrome, as a consequence of brain or spinal cord damage, the spastic rat tail is commonly applied as a model. Animal studies using this model focus on the mechanisms underlying increased neuronal activity following spinal cord transection. However, a major factor of the human spastic movement disorder is a secondarily occurring change in muscle mechanics and not a neuronal overactivity. Thus the “spastic” rat tail may not represent a suitable model to help understanding human spasticity.

To a significant degree, animal research is devoted to elucidating physiological mechanisms underlying a human pathological state, to develop therapeutic treatments. Research on human movement disorders is usually limited to behavioral studies and to surface recordings of gross motoneuronal (electromyogram) and kinematic activities. Only by a detailed analysis, i.e., by studies on the (intra-)neuronal function in the isolated animal preparation, including the function of cell membrane channels, can basic mechanisms underlying a disease be explored. The crucial question for the success of such basic research for its translation to human beings is whether and to what extent the animal models that are used are adequate, or even whether an appropriate model exists at all.

A frequently occurring pathological condition in humans relates to the spastic syndrome that occurs as a consequence of a brain or spinal cord damage. Clinically, it is characterized by exaggerated short-latency reflexes and muscle hypertonia. As a consequence, it was assumed that enhanced reflex activity is responsible for muscle hypertonia and that this leads to spastic movement disorder (for review see Dietz 2002; Dietz and Sinkjaer 2007). Therefore most treatments are directed at reducing reflex activity (e.g., by the application of baclofen). However, in human spasticity this is not the case. In none of the actual animal models have changes in muscle properties been addressed.

During the past 20 yr it could convincingly be shown that in spastic humans the enhanced activity of short-latency stretch reflexes does not contribute greatly to the spastic movement disorder. It is contrasted by a loss of functionally essential long-latency reflex activity. Spastic movement disorder is characterized by a reduced ability to modulate leg muscle activation. Changes in mechanical muscle fiber properties take place and compensate for the lack of muscle activation associated with paresis (for review see Dietz 2002; Dietz and Sinkjaer 2007).

What is the nature of these muscle changes? In spastic humans, histochemical and structural changes of the spastic muscle have been described (Dietz et al. 1986; Edstrom 1970) and a loss of sarcomeres (O’Dwyer et al. 1996) was assumed to play a major role in the development of muscle hypertonia. Nevertheless, it remained unclear to what degree these muscle alterations contribute to spastic muscle tone and the overall movement disorder.

In developing an appropriate treatment, it would be of interest to obtain a detailed analysis of the complex mechanisms involving reflexes and muscle changes on the development of spasticity in an animal model. In the decerebrate cat model, the relevance of the myotatic reflex for the increased muscle tone was stressed (Liddell and Sherrington 1925). However, this animal model clearly failed to adequately mimic the slowly developing spasticity that occurs following CNS damage, such as after a stroke. Surprisingly, central motor lesions in nonhuman primates did not lead to a spastic movement disorder (Kuypers 1978).

During the past few years, a rat model involving chronic sacral spinal cord transection has been used to study spastic tail muscles (Bennett et al. 2004; Li et al. 2004, 2007). It was found that motoneuronal excitability increased and was associated with long-lasting reflexes and muscle spasms. The motoneurons were found to develop large voltage-dependent persistent sodium and calcium inward currents, which were assumed to cause exaggerated reflexes and muscle spasticity. Parallel with the development of “spastic tail,” a progressive decrease in the overall number of dendritic branches of motoneurons was observed (Kitzman 2005). This was associated with an increase in the overall level of excitatory neurotransmitters (Kitzman 2006) and of H-reflex amplitude (Kakinohana et al. 2006). These effects were assumed to be responsible for the emergence of spasticity.

Thus most current studies on animal models for spasticity are biased by their assumption that spasticity is primarily caused by an increased neuronal activity (for review see Hultborn 2003). However, in human spasticity this is not the case. In none of the actual animal models have changes in muscle properties been addressed.

Thus several objections exist against the adequacy of current rat models for spasticity. 1) The rat tail is hardly comparable with the human legs, which represent the basis for the spastic movement disorder. In addition, the clinical signs of spasticity are reflected poorly in the rat tail. 2) Increased muscle tone, as described in the rat model, does not necessarily correspond to spasticity in humans. Several conditions can lead to increased muscle tone in humans, such as rigidity, dystonia, peripheral muscle cramps, or spasms. 3) Spasticity represents a multifac-
Editorial syndrome. Research focused on isolated muscle tone or on increased neuronal activity fails to adequately address the complex disorder.

Consequently, research on the “spastic” rat tail can hardly meet all of the requirements necessary for understanding human spasticity. Thus such a model for muscle hypertonia should not be called “spastic” with respect to the human condition.

REFERENCES


