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Loewi's old saying "Ja, Kalzium, das ist alles" is still valid in the degenerative processes of motor neurons

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Amyotrophic lateral sclerosis (ALS), this fatal disease of the motor nervous system has an outstanding importance in relation to basic research, since parts of the diseased neurons, the motor axons and nerve terminals can be sampled in humans with no ethical concerns. Thus, since the first demonstration of the dysregulated neuronal calcium (Ca^{2+}) in degenerating human motor nerve terminals (1), series of experiments were conducted in animal models of ALS and, on the basis of the similarity of findings in the appropriate motor axon terminals of mice and man, extrapolative conclusions were drawn for the dysregulated Ca^{2+} in the human spinal motor neurons (2,3). Clinical and pathological observations, however, suggested that a differential susceptibility of neurons to the disease may exist, with higher resistance of those cells which are rich in certain Ca^{2+} binding proteins, possibly acting as Ca^{2+} buffers, thus defending Ca^{2+} homeostasis. This concept got further support from axotomy experiments: the lesion induced contrasting changes in intracellular Ca^{2+} level in parvalbumin (PV) rich oculomotor- and hypoglossal neurons lacking such proteins (4), which lower buffering capacity could be compensated by overexpressing PV (5). Further axotomy experiments in PV-transgenic animals demonstrated that by lending improved Ca^{2+} buffer capacity to motor neurons, they can be protected from Ca^{2+} overload, thus reducing Ca^{2+} -mediated injury, which leads to a more general effect, a reduced local inflammatory reaction in these animals (6). PV overexpression also prevented acute immune-mediated Ca^{2+} increase in motor neurons (7). Unfortunately, in chronic stress condition, in a transgenic model of familial ALS by upregulating PV, though the loss of motor neurons could be reduced and the survival of the animals could be prolonged, the progression of the disease could not be halted, likely due to the saturation of the finite Ca^{2+} -buffer (7). The notion that in these transgenic animals the intracellular Ca^{2+} increase could be prevented in the vulnerable cells in another way, by pharmacologically reducing Ca^{2+} influx through AMPA receptors, but only if the treatment was started presymptotically (8), points to a possible cause of the failure of the clinical trial with talampanel, which treatment was started late relative to the course of the disease, after the onset of symptoms.

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