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The Effect of Tolperisone in Neuropathy – Efficacy in Animal Experiment and Mechanism Behind

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Introduction: Slow onset of action and numerous side-effects limit the use of current pharmacological options in the treatment of neuropathic pain. Tolperisone, a centrally acting muscle relaxant with a favorable side effect profile, has been reported to alter ion channel activity, similarly to current first-line medications in neuropathic pain therapy. Though an inhibitory effect on both voltage-gated sodium and calcium channels has been suggested, its exact mechanism of action still remains elusive.

Aims: Our aim was to explore the antinociceptive effect of tolperisone in partial sciatic nerve ligated rats displaying allodynia, a symptom of painful neuropathy, as well as to better understand the molecular mechanisms involved.

Methods: Nerve ligation-induced allodynia was assessed by Randall-Selitto test and measured as decrease in paw pressure thresholds. Glutamate content of cerebrospinal fluid (CSF) of nerve ligated rats was measured. In order to understand its mechanism of action, the direct effect of tolperisone on glutamate release was examined using rat brain synaptosomes. Glutamate levels were determined using a capillary electrophoresis laser induced fluorescence method.

Results: Acute oral tolperisone treatment restored allodynia indicated by an increase in paw pressure thresholds. Sciatic nerve ligation caused a significant elevation in CSF glutamate content compared to sham-operated animals, which was normalized by single-dose tolperisone treatment suggesting it may inhibit its neuronal release. The effects of tolperisone on allodynia and CSF glutamate level were comparable to those of pregabalin, a first-line medication in neuropathy. Tolperisone caused a concentration-dependent inhibition of sodium channel-dependent glutamate release elicited by 4-aminopyridine from synaptosomes. The largely sodium channel-independent release induced by high concentration potassium chloride was also inhibited by tolperisone albeit at much higher concentrations, while co-treatment with adrenergic α_2 antagonist, idazoxan failed to reverse the inhibitory effect of tolperisone.

Conclusion: We have demonstrated for the first time [1] that tolperisone both restores nerve injury-induced allodynia in rats and normalizes the increased CSF glutamate levels observed in neuropathic pain likely by inhibiting synaptic glutamate release. Furthermore, its mechanism of action is now better understood as our results strongly suggest that the inhibition of synaptic sodium channels rather than calcium channels is responsible for its analgesic effect, while its activity on α_2 receptors was found negligible.

Literature: [1] Lakatos, P.P.; Int. J. Mol. Sci. 2022, 12, 9564.