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Effects of lisuride hydrogen maleate on the development of secondary brain damage following Controlled Cortical Impact (CCI) injury in rats

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Traumatic brain injury (TBI) is a devastating condition causing a wide range of pathologies. The primary insult is followed by a cascade of secondary reactions which generate metabolic failure, excitotoxicity, oxidative stress, brain edema formation and inflammation. These secondary events lead to enlargement of the primary lesion and deterioration of clinical condition, and they are potentially amenable to targeted therapeutic intervention. Lisuride is a dopaminergic agonist used in treatment of early Parkinson's disease. It possesses a varied and complex pattern of activity, acting as a dopamine agonist (D2 and D4), 5HT1A serotonin agonist, epinephrine agonist and NMDA glutamate antagonist, in addition to decreasing the release of prolactin, thus reducing the amount of inflammatory mediators. In the lack of previous experimental and clinical data on lisuride in TBI, we speculated that these properties would provide neuroprotection at the acute and post-acute stage of experimental TBI. We decided to test our hypothesis in a relevant and highly reproducible TBI model in rats, the Controlled Cortical Impact Injury model.

In the preceding study, we showed that the administration of lisuride significantly reduced the duration and number of post-traumatic seizures, but did not influence the contusion volume or neurological functioning of the animals (Zweckberger et al, 2010). However, the administration of lisuride caused a significant hypotonic response. Therefore, the first phase of the study included a dosage-tapering study, with the aim of determining a dosage that provided neuroprotection but did not cause physiological deterioration. In this first series of experiments, the effect of lisuride on physiological parameters in the acute post-injury period was investigated. Although we were able to determine the dosage of the drug that did not cause hypotension, no effect of treatment was seen on intracranial pressure or microdialysis profiling of pericontusional tissue metabolites.

Secondly, brain edema formation was assessed 24 hours after CCI injury. Here, we saw an increase in total water volume between traumatized and non-traumatized hemispheres, reflecting trauma-induced edema formation. However, there was no effect of lisuride treatment on brain edema formation.

It the third part of the study, the neurological status of animals was investigated using a battery of behavioral tests over a period of 7 days. The neurological status focused on the motor function and revealed no effect of treatment. In addition, we examined the development of the contusion volumes using magnetic resonance imaging and, likewise, saw no effect of lisuride treatment. We observed, however, an increase in the contusion volume during the first two days following CCI injury, corresponding to the development of secondary brain injury.

Taken together, our results suggest that lisuride does not provide neuroprotection in our model of TBI at the acute and subacute stages. Based on available literature it is, however, possible that dopamine agonists such as lisuride can improve outcome in terms of cognitive function in a chronic setting. This aspect would be an area worthwhile of future investigation.