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The Role of Pannexins in Cerebral Ischemia

Promotionsfach: Neurologie

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In addition to the connexins, the recently discovered pannexins (Px) comprise also a family of channel-forming proteins. It is still not clear if pannexins are able to form gap junctions, but there is increasing evidence that they are able to form functional channels in the membrane but intracellularly as well.

Although the physiological role of pannexins is still unclear, recent studies provided evidence for the *in vitro* implication of pannexin-based channels in several molecular mechanisms that occur during cerebral ischemia and lead to expansion of the brain damage such as glutamate excitotoxicity, cortical spreading depression, ion dysregulation and IL-1β-related inflammatory cascade. However *in vivo* data are still missing.

Using pannexin-deficient mice, which were generated in our lab, and a well-established mouse model of cerebral ischemia, the permanent distal middle cerebral artery occlusion (pdMCAO), we were able to show that the absence of both pannexins (Px1 and Px2) resulted in significant smaller infarct size in comparison to wild-type littermates 48 hours after ischemia.

Additionally, using several behavioral tests, we were able to show that the smaller infarct size in these mice results in reduced neurological deficits in the days following cerebral ischemia.

Furthermore, in order to investigate whether Px1 modulates the inflammatory response in cerebral ischemia, we measured IL-1β by a commercial ELISA kit and by western blot in wild-type and knockout animals. Our experiments suggest that pannexins are not required for the ATP-induced release of IL-1β.

Hemichannels and gap junctions have been implicated in the propagation of cortical spreading depression (CSD), a post-ischemic depression of brain electrical activity which contributes to lesion progression. To evaluate the role of Px1 and Px2 in this process, we recorded direct current potentials and laser doppler flow from the cortex of the mice before and after pdMCAO. Between double Px1/Px2 knockout mice and their wild-type littermates, no differences were observed in the number and the specific parameters of CSD events, suggesting that the occurrence of CSD after cerebral ischemia does not depend on pannexins.

The results of the current study highlight the neuroprotective effect of pannexin deletion following an ischemic brain damage.