NEUROPROTECTIVE EFFECT OF MELANOCORTINS IN FOCAL CEREBRAL ISCHEMIA

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We have recently shown that, in gerbils subjected to transient global cerebral ischemia, melanocortin peptides produce long-lasting protection with a broad time window, and through the activation of central nervous system melanocortin MC_4 receptors (1). Because stroke human conditions are mainly due to focal brain ischemia owing to thrombotic occlusion of a cerebral vessel, we aimed to investigate whether melanocortins are neuroprotective also in a rat model of focal cerebral ischemia induced by intrastriatal microinjection of endothelin-1. The vasoconstrictor agent endothelin-1 caused an impairment in spatial learning and memory, as well as in sensory-motor orientation and limb use. These effects were associated with activation of inflammatory and apoptotic pathways in the striatum (increase in the activity of JNKs, p38, ERKs and caspase-3, and in TNF-α levels), and severe striatal morphological damage including a marked neuronal death and an almost complete myelin degradation. Treatment of ischemic rats with a nanomolar dose (340 μg/kg/day i.p. for 11 days, starting 3 h or 9 h after endothelin-1 microinjection) of the synthetic melanocortin analog [Nle[4], D-Phe[7]]α-MSH (NDP-α-MSH) suppressed the inflammatory cascade and the apoptotic process, reduced striatal morphological damage, and improved subsequent functional recovery, with all schedules of NDP-α-MSH treatment. Pharmacological blockade of melanocortin MC_4 receptors with the selective MC_4 receptor antagonist HS024 (260 μg/kg i.p. every 12 h) prevented the protective effect of NDP-α-MSH. Our findings give evidence that melanocortins are neuroprotective with a broad time window, and through the blockade of several ischemia-related mechanisms of damage, also in a severe model of focal cerebral ischemia. Moreover they suggest that selective melanocortin MC_4 receptor agonists could be taken into account as potential new drugs for a novel approach to the management of different types of ischemic stroke.

1) Giuliani D. et al. (2006) Endocrinology 147: 1126-1135.