AVE 0991

Lee et al. tested the efficacy of a selective MasR agonist, AVE0991, in in vitro and in vivo models of ischemic stroke.

AVE 0991 (AVE) was administered intranasally 1 h after SAH induction. A779, a selective inhibitor of Mas, and small interfering ribonucleic acid (siRNA) for UCP-2 were administered by intracerebroventricular (i.c.v) injection at 1 h and 48 h before SAH induction respectively. Neurological tests, immunofluorescence, TUNEL, Fluoro-Jade C, DHE staining, and Western blot experiments were performed. We found that Mas activation with AVE significantly improved neurobehavioral scores and reduced oxidative stress and neuronal apoptosis in SAH+AVE group compared with SAH+vehicle group. Moreover, AVE treatment significantly promoted phosphorylation of CREB and the expression UCP-2, as well as upregulated expression of Bcl-2 and downregulation of Romo-1 and Bax. The protective effects of AVE were reversed by i.c.v injection of A779 and UCP-2 siRNA in SAH+AVE+A779 and SAH+AVE+UCP-2 siRNA groups, respectively. In conclusion, our data provides evidence that Mas activation with AVE reduces oxidative stress injury and neuronal apoptosis through Mas/PKA/p-CREB/UCP-2 pathway after SAH. Furthermore, our study indicates that Mas may be a novel therapeutic treatment target in early brain injury of SAH [1)].

Primary cortical neurons were cultured from E15-17 mouse embryos for 7-9 d, subjected to glucose deprivation for 24 h alone or with test drugs, and percentage cell death was determined using trypan blue exclusion assay. Additionally, adult male mice were subjected to 1 h middle cerebral artery occlusion and were administered either vehicle or AVE0991 (20 mg/kg i.p.) at the commencement of 23 h reperfusion. Some animals were also treated with the MasR antagonist, A779 (80 mg/kg i.p.) 1 h prior to surgery. Twenty-four h after MCAo, neurological deficits, locomotor activity and motor coordination were assessed in vivo, and infarct and edema volumes estimated from brain sections. Following glucose deprivation, application of AVE0991 (10-8 M to 10-6 M) reduced neuronal cell death by ~60% ($P<0.05$), an effect prevented by the MasR antagonist. By contrast, AVE0991 administration in vivo had no effect on functional or histological outcomes at 24 h following stroke. These findings indicate that the classical MasR agonist, AVE0991, can directly protect neurons from injury following glucose-deprivation. However, this effect does not translate into an improved outcome in vivo when administered systemically following stroke [2)].

1)
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2)
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