Protective effect of duloxetine against cerebral ischemia-reperfusion injury through TRPM2 inhibition

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The activation of transient receptor potential melastatin 2 (TRPM2), which is an oxidative stress-sensitive Ca^{2+} -permeable channel, implicates in the aggravation of cerebral ischemia-reperfusion (CIR) injury. Recent studies have shown that duloxetine, one of the antidepressants, attenuates TRPM2 activation in response to oxidative stress induced by H_2O_2 in neuronal cells. In the present study, we firstly characterized the inhibitory effects of antidepressants on H_2O_2 -induced TRPM2 activation in TRPM2-expressing HEK 293 cells. Duloxetine exhibited the strongest inhibitory effect on TRPM2 activation among tested seven antidepressants, and the maximum inhibitory effect was observed in 10 μM . However, duloxetine had no effects on H_2O_2 -induced activation of TRPA1 and TRPV1, which are also the members of TRP channel and activated by oxidative stress. We next examined the effects of duloxetine on CIR injury. The administration with duloxetine (10 mg/kg, i.p.) into wild-type mice reduced the infarct area, LDH activities in plasma and IL-6 levels in the brain comparable to *Trpm2*KO mice. However, duloxetine did not further reduce them induced by CIR in *Trpm2*KO mice. These observations strongly suggest that duloxetine has a protective effect against CIR injury through the inhibition of TRPM2 activation. Duloxetine could be a useful drug for treatment with reperfusion therapy in cerebral ischemia.