Inhibition of autophagy as a therapeutic strategy of iron-induced brain injury after hemorrhage

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Premenopausal women have better survival than men after intracerebral hemorrhage, which is associated with iron overproduction and autophagy induction. To examine the participation of neuronal autophagy and estrogen receptor α (ER α) in the E2-mediated protection, PC12 neurons treated with Atg7 (autophagy-related protein 7) siRNA, rapamycin (an autophagy inducer), or ERα siRNA were applied. To study whether autophagy involves in β-estradiol 3-benzoate (E2)-mediated neuroprotection against iron-induced striatal injury, castration and E2 capsule implantation were performed at 2 weeks and 24 h, respectively, before ferrous citrate (FC) infusion into the caudate nucleus (CN) of Sprague Dawley male and female rats. Furthermore, the role of neuronal autophagy in the sex difference of FC-induced CN injury was confirmed by using conditional knockout Atg7 in dopamine receptor 2 (DRD2)-containing neurons in mice. The results showed that the suppression of FC-induced autophagy by E2 was abolished by ERα siRNA preincubation. Atg7 silencing simulates and rapamycin diminishes E2-mediated neuroprotection against FC-induced neurotoxicity. In vivo, FC induced a lower degree of autophagy, autophagic cell death, injury severity, histological lesion and behavioral deficit in female rats than in males. E2 implantation decreased the levels of both FC-induced autophagy and injury in ovariectomized rats. Moreover, the sex difference of FC-induced CN injury was diminished in Atg7 knockout mice. Thus, suppression of autophagy by E2 via ERα contributes to less severity of iron-induced brain injury in females than in male. This finding opens up the prospect for a therapeutic strategy targeting autophagic inhibition for patients suffering from intracerebral iron overload.