AUTOPHAGY INHIBITION DECREASES IRON-INDUCED STRIATAL INJURY IN MALE MICE BUT NOT IN FEMALES

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After intracerebral hemorrhage (ICH), men have worse survival than young women. ICH is associated with overproduction of iron, free radical formation, and autophagy induction in brain tissue. In rat ICH model using ferrous citrate (FC) infusion, a higher degree of injury-severity including functional deficit was observed in males than in females. Recently, conditional knockout of autophagy related gene 7 (Atg7) in neurons expressing dopamine receptor D2 (DRD2), which are enriched in striatum, diminished the sex difference of FC-induced injury-severity significantly. Here we present evidence that neuronal autophagy modulation is beneficial for the FC-induced brain injury in a sex-dependent manner. The results showed that levels of FC-induced autophagy, injury severity, and autophagic cell death were higher in males than those in females. Enhancement of autophagy by pre-treatment with rapamycin exaggerated the FC-induced injury-severity and increased the percentage of TUNEL (+) DRD2 neurons, particularly in female mice. Whereas, reduction of neuronal autophagy by conditional knock-out of Atg7 in DRD2 neurons diminished the FC-induced injury severity and decreased the percentage of TUNEL(+) DRD2 neurons in striatum of male but not in female mice. These results suggest that autophagy plays a sex dimorphic role in FC-induced brain injury and autophagy inhibition exhibits a beneficial effect on the iron-induced striatal injury only in males. These findings open up the prospect for a sex-specific therapeutic strategy targeting autophagic inhibition for male patients suffering from ICH or neurodegeneration caused by iron overload.