Tissue-type plasminogen activator exacerbates memory impairment related to amyloid-beta toxicity in a mouse model of Alzheimer's disease

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Amyloid-beta is among the major players in the neurodegenerative process of Alzheimer's disease. Its metabolism, however, is not fully understood. In vitro studies show that the proteolytic system of tissue-type plasminogen activator (tPA) /plasmin degrades amyloid-beta and attenuates its toxicity. We studied the consequence of a neuronal overexpression of tPA on amyloid-beta pathogenesis in vivo. tPA transgenic mice were crossed with mice overexpressing amyloid precursor protein (SwAPP). Learning abilities of the bi-transgenic mice (SwAPPT4) were analyzed in the spatial water-maze test and in the automated IntelliCage at two different ages. When tested in the long term memory version of the water-maze task, the aged SwAPPT4 mice exhibited a similar performance as their age-matched SwAPP littermates. In the episodic-like version, however, young SwAPPT4 mice showed a significant impairment. Mice were also analyzed in a three-phase schedule in the IntelliCage device, in which activity and learning skills of mice can be measured automatically through their visits to four reinforced corners. The habituation phase resulted in a significant difference in the activity, strongly marked by the SwAPPT4 mice with the lowest number of visits to the corners. An acquisition phase of a three-day learning schedule followed, in which each individual had to remember the spatial location of a single reinforced corner. This phase was replaced by a reversal place learning task, where mice had to learn a new location of the reinforced corner. Although the level of amyloid-beta deposits was unchanged in the SwAPPT4, our results show that tPA may intensify the deleterious effect of amyloid-beta on learning and memory abilities. This conclusion highlights the need of caution in the use of tPA for the treatment of stroke in Alzheimer patients.

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