Memantine produces antidepressant effect through the enhancement of hippocampal neurogenesis in olfactory bulbectomized mice　P. 519

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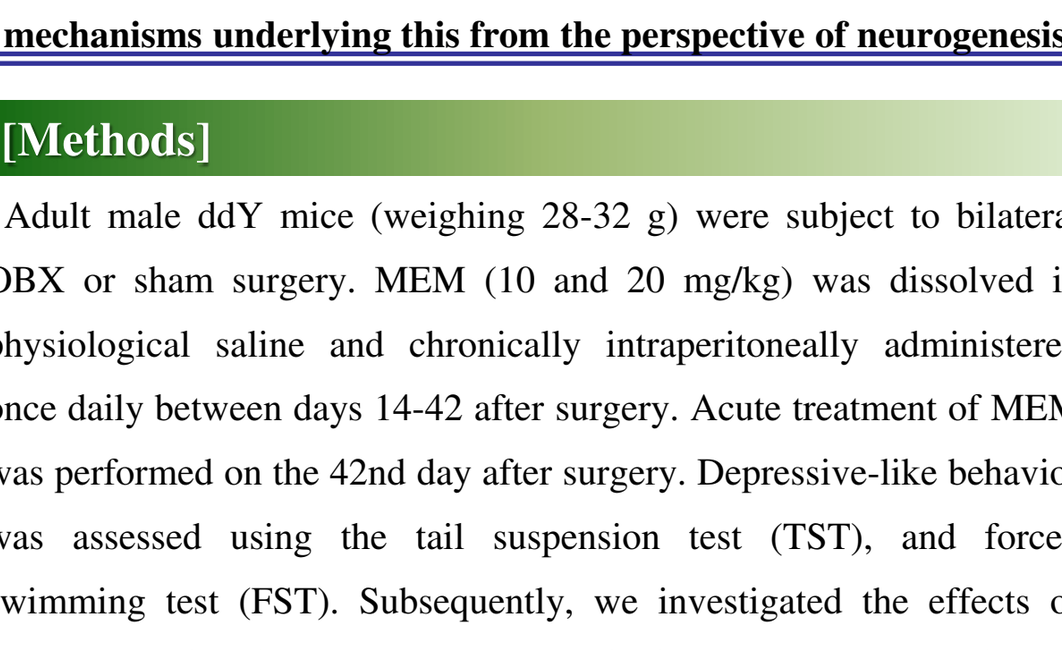
[Background]

Olfactory bulbectomized (OBX) mice have been found to be a useful experimental animal model for depression, since the OBX mice express abnormal behaviors, physiological and neurochemical changes similar to those of clinical depression. OBX-induced abnormal behaviors are reported to improve with chronic, but not acute, administration of antidepressant drugs. Indeed, OBX has been reported to decrease hippocampal neurogenesis, a putative pathogenic mechanism in depression. Our previous study suggested that a non-competitive N-methyl-D-aspartate receptor antagonist memantine (MEM) inhibits the reuptake and turnover of dopamine (DA) by inhibiting brain monoamine oxidase. Clinical studies have reported that MEM may improve depressive symptoms including emotional behavior; however, the specific detail mechanisms underlying this effect are unclear.

Therefore, we examined whether MEM improves OBX-induced depressive-like behaviors and investigated the molecular mechanisms underlying this from the perspective of neurogenesis.

[Methods]

Adult male ddY mice (weighing 28-32 g) were subject to bilateral OBX or sham surgery. MEM (10 and 20 mg/kg) was dissolved in physiological saline and chronically intraperitoneally administered once daily between days 14-42 after surgery. Acute treatment of MEM was performed on the 42nd day after surgery. Depressive-like behavior was assessed using the tail suspension test (TST), and forced swimming test (FST). Subsequently, we investigated the effects of MEM on distribution of tyrosine hydroxylase (TH) and cell proliferation in the hippocampus with immunohistochemistry. We also investigated MEM effects on the levels of norepinephrine (NE), DA, and their metabolites with high performance liquid chromatography, and of brain-derived neurotrophic factor (BDNF), and the downstream molecules in the hippocampus with western blotting.

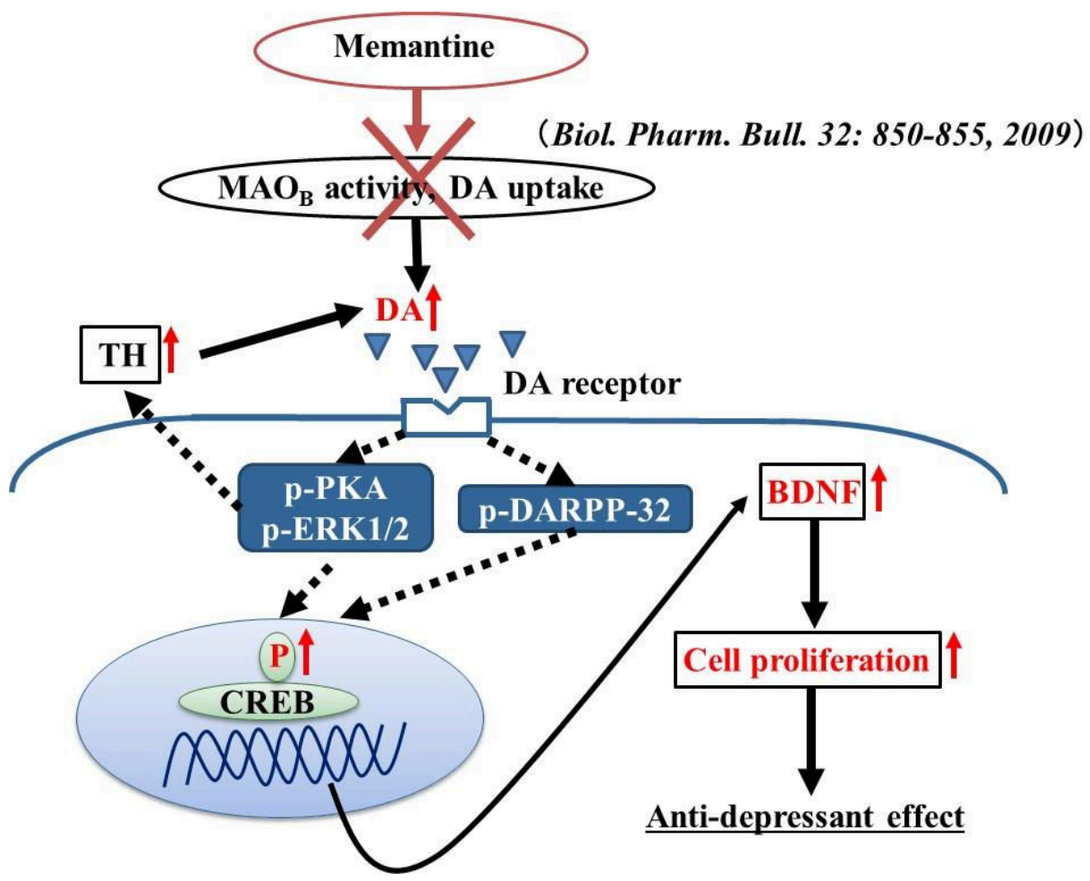


[Results]

Forty-two days after surgery, OBX mice showed depressive-like behaviors, as well as decreased levels of monoamines, reduced cell proliferation, and lower levels of TH, p-TH (ser31 and ser40), p-protein kinase A (PKA), p-dopamine- and c-AMP-regulated phosphoprotein 32 (DARPP-32), p- extracellular signal-regulated kinases ½ (ERK1/2), p- cAMP response element binding protein (CREB), doublecortin, NeuN levels. These changes (except for those in NE) were reversed with chronic administration of MEM (20 mg/kg).

[Conclusions]

These results suggest that MEM-induced antidepressant effects are associated with enhanced hippocampal cell proliferation via the PKA-ERK-CREB-BDNF pathway and increased DA levels. Our results provide the basis for the development of MEM strategies not only towards treating dementia, but also depression.



Hypothesis of MEM antidepressant mechanism.

Acknowledgements and conflict of interest disclosure

This study was supported in part by JSPS KAKENHI (Grant Number: JP26460102 and 18K06687) and Matching Fund Subsidy for Private Universities (Grant Number: S1511001L) from the Ministry of Education, Culture, Sports, Science and Technology of Japan. The authors would like to thank Ms. Yurika Yamamoto, Mr. Kazuya Sano, Mr. Jinichi Isono, Mr. Shogo Kadota and Mr. Kotaro Yabuki of Tohoku Medical and Pharmaceutical University for their technical assistance. The authors have no conflict of interest to declare.

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