S47-1 Neuronal mechanisms underlying improvement of cognitive impairment and depressive behaviors in novel therapeutics of Alzheimer's disease

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We investigated effects of oral chronic administration of ZSET1446, which is a novel Alzheimer's disease therapeutics stimulating acetylcholine (ACh) release in the brain, on cognitive and depressive behaviors in the olfactory bulbectomized (OBX) mice. The cognitive enhancement by ZSET1446 was closely associated with CaMKII and PKC activation underlying LTP induction in the hippocampal CA1 region. Furthermore, we confirmed that an enhanced acetylcholine release impaired in OBX hippocampus likely accounts for the cognitive improvement. Notably, OBX mice decreased the number of newborn cells in the dentate gyrus (DG) by immunohistochemical analysis of 5-bromo-2-deoxyuridine (BrdU) incorporation. The impaired neurogenesis and depressive behaviors observed in OBX mice were improved by the chronic treatment with ZSET1446. We confirmed the treatment with mecamylamine, a nicotinic acetylcholine receptor antagonist, inhibits the ZSET1446-enhanced neurogenesis in the DG. Furthermore, ZSET1446 treatment restored decreased phosphorylation of Akt and extracellular signal-regulated kinase (ERK) in DG of OBX mice. Taken together, the chronic administration of ZSET1446 restores cognitive function through CaMKII and PKC activation in the hippocampal CA1 region and improves depressive behaviors through enhanced neurogenesis in the DG.