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KNT-127, a selective delta-opioid receptor agonist, exhibits antidepressant effects through PI3K-Akt-mTOR signal transduction in the mice prefrontal cortex.

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Recently, it has been suggested that mammalian target of rapamycin (mTOR) signaling in the prefrontal cortex (PFC) plays key roles in the molecular mechanisms of antidepressant-like effects in rodents. We previously reported that a selective delta-opioid receptor (DOP) agonist, KNT-127 produced robust antidepressant-like effects in the forced swimming test (FST) in mice. However, the detailed mechanism of its effect has remained elusive. Therefore, we attempted to identify the molecular mechanism of the antidepressant-like effects of KNT-127 using the mouse FST. We firstly demonstrated that a selective mTOR inhibitor rapamycin (i.c.v.) significantly diminished the antidepressant-like effects of KNT-127 (s.c.) in the FST. In addition, a selective PI3 kinase inhibitor LY294002 (i.c. v.), which inhibits the upstream molecules of mTOR, also diminished the antidepressant-like effects of KNT-127. Furthermore, a protein immunoblotting assay revealed that KNT-127 (s.c.) increased the level of phosphorylation of Akt in the mouse PFC. Taken together, we proposed that KNT-127 produced the antidepressant-like effects in the FST via the activation of PI3K-Akt-mTOR signal transduction pathway in the PFC in mice. These results take the first step on the way to elucidate the mechanical functions of DOP agonists for antidepressants.