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Neuronal plasticity in the brain specific locus in morphine-induced tolerance and dependence
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Opioid systems are present at multiple locations on analgesic and addiction pathways. The clinical utility of opioid analgesics is often overshadowed by the development of tolerance and dependence following chronic use. It has been proposed that some non-opioid neurons including anti-opioid neuron such as glutamate and N/OFQ neurons may cause a counter-adaptation to show such side effects. A major question is whether opioid neuronal plasticity by such anti-opioid system in morphine analgesic tolerance and dependence could be caused in specific loci or in the downstream of opioid neuron in the brain. To specify the brain locus, we performed the locus-specific rescue of gene into the brain of specific mutant mouse. We will discuss on the brain locus-specific plasticity of neuronal circuits in morphine tolerance and dependence.

S9-6

Effects of tumor necrosis factor-α and glial cell lined-neurotrophic factor on the toxicity-induced by methamphetamine in vivo and in vitro.
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We have found that the expressions of tumor necrosis factor-α (TNF-α) and glial cell lined-neurotrophic factor (GDNF) are increased in the brain of mice after repeated administration of methamphetamine. Drug dependence is one of most severe problems in all over the world, however, the mechanisms and related-genes have not been completely revealed. Here we would like to introduce tumor necrosis factor-α (TNF-α). Repeated treatment with methamphetamine induced an increase in TNF-α mRNA in the some brain regions. Exogenous TNF-α blocked the methamphetamine rewarding. TNF-α plays a neuroprotective role in methamphetamine drug dependence. These results suggest that TNF-α is one of key proteins. TNF-α itself might not be therapeutic tools, since it has immunological actions in physical conditions. Therefore, next, we found a stimulator, Leu·Ile, which enhances TNF-α synthesis in cultured neurons. Leu·Ile protected blocked the methamphetamine-induced rewarding effects. These results suggest that a stimulator of TNF-α synthesis may be one of therapeutic tools against drug dependence.