<table>
<thead>
<tr>
<th><strong>Title</strong></th>
<th>Ketamine abuse and apoptosis in the cortex in monkeys and mice</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Author(s)</strong></td>
<td>Li, Q; Wai, SP; Lam, WP; Yew, DT; McAlonan, G</td>
</tr>
<tr>
<td><strong>Citation</strong></td>
<td>The 26th CINP Congress, Munich, Germany, 13-17 July 2008.</td>
</tr>
<tr>
<td><strong>Issued Date</strong></td>
<td>2008</td>
</tr>
<tr>
<td><strong>URL</strong></td>
<td><a href="http://hdl.handle.net/10722/126822">http://hdl.handle.net/10722/126822</a></td>
</tr>
<tr>
<td><strong>Rights</strong></td>
<td>This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License.; International Journal of Neuropsychopharmacology. Copyright © Cambridge University Press.</td>
</tr>
</tbody>
</table>
Implication of dopamine D1A and D2 receptors in hippocampus in the conditioning of the rewarding effect of cocaine

T. Tanaka, N. Hironaka. JST Shimojyo Project, Kanagawa, Japan

Objective: The hippocampus is important for contextual conditioning. The conditioned place preference (CPP) to drugs of abuse is a form of associative process, this can be assumed to reflect hippocampal-dependent processes. Dopamine is the one that has been more extensively implicated in the mechanism of drug addiction. However, little if any is known about the functional and direct implication of hippocampal dopamine receptors in the development of a cocaine-induced rewarding effect. In the present study, we investigated whether dopamine D1A and D2 receptors in hippocampus are implicated in the development of cocaine-induced rewarding effect using a CPP paradigm in rats.

Methods: Rats were divided into four groups by session frequency: Group 0 underwent no conditioning session, pre- and post-test only; Group 1 underwent pre-test, one pair of conditioning session (1 day for cocaine at 15 mg/kg, s.c., and 1 day for saline) and post-test; Group 2 underwent two pairs of conditioning sessions once a day and Group 3 underwent three pairs of conditioning sessions between pre- and post-test.

Results: Preference levels for the cocaine-associated box were frequency-dependently increased. The mRNA of dopamine D1A and D2 receptors significantly increased in the hippocampus of Group 2 only.

Conclusion: These results indicate that dopamine D1A and D2 receptors in the hippocampus may be one of the critical mediators of the neuronal changes necessary for the induction of this cocaine-induced rewarding effect. The dynamic synaptic events regulated by neurotransmitters and their cognate receptors underlie long-lasting changes that contribute to the intensity and persistence of the drug in memory.
significantly increases in the cortex of the ketamine abused mice, however, there is no difference of caspase-6 expression in the cortex in the ketamine abused mice.

Figures 1,2. fMRI studies of the cortex in monkeys. In this study, we moved the monkeys' right legs up and down 5 times during the stimulation periods under fMRI. The white arrow indicates the sensation area of the cortex for the response of leg movements; figure 1: monkeys administered vehicle for 14 days; figure 2: monkeys administered 1 mg/kg ketamine for 14 days.

**Conclusion:** Administration of ketamine for long time could decrease neuronal activities. Caspase-dependent apoptosis in central nervous system (CNS) may involve in this alteration. But further relations between caspases-dependent apoptosis and neuronal activities in ketamine abuse models need to be investigated.

**Methods:** Wistar rats were injected intraperitoneally within 4 days in elevated doses with: 1) physiological saline (control; 0.1−0.2−0.4−0.8 ml/rat), 2) amphetamine (0.5−1.0−2.0−4.0 mg/kg), 3) fentanyl (0.00625−0.0125−0.025−0.05 mg/kg), 4) ethanol 40% solution (0.5−1.0−2.0−4.0 g/kg), 5) sodium ethaminal (2.5−5.10−20 mg/kg) or 6) dexta-methasone (0.5−1.0−2.0−4.0 mg/kg). The forced regimen of drug administration led to gradual load of the organism and prevented drug tolerance. This method was actively used for formation of drug dependence (or its features) from different narcotics.

**Results:** The biggest mRNA expression for corticosterin was registered in amygdala after administration of dexamethasone (0.46 units compared with β-actin), and the minimal one was after sodium ethaminal (0.07) and fentanyl (0.037). In hypothalamus, sodium ethaminal produced the elevated mRNA expression (0.8 unit), then were ethanol (0.37) and fentanyl (0.039). Amphetamine did not activate mRNA expression for corticosterin nor in hypothalamus, nor in amygdala for all of the drugs studied. The mRNA expression for vasopressin did not register for all drugs both in hypothalamus and amygdala.

**Conclusion:** Therefore, the reinforcing system of hypothalamus supports the typical reaction on narcotics administration, where as the extended amygdala includes both the proper reinforcement and stress reaction elements.

**Methods:** The clonic seizure threshold was tested in separate groups of male NMRI mice following injection of vehicle, the cannabinoid selective agonist arachidonyl-2-chloroethylamide (ACEA) and ultra-low doses of the opioid receptor antagonist naltrexone and a combination of ACEA and naltrexone doses in a model of clonic seizure induced by pentylenetetrazole (PTZ).

**Results:** Systemic administration of ultra-low doses of naltrexone (1 mg/kg, i.p.) significantly potentiated the anticonvulsant effect of ACEA (1 mg/kg, i.p.). Moreover, the very low dose of naltrexone (0.5 mg/kg) unmasked a strong anticonvulsant effect for very low doses of ACEA (10 and 100 mg/kg). A similar potentiation by naltrexone (0.5 mg/kg) of anticonvulsant effects of non-effective dose of ACEA (1 mg/kg) was also observed in the generalized tonic-clonic model of seizure.

**Methods:** The effects of ascorbic acid on morphine withdrawal symptoms in rats

**Objective:** Recent studies indicate that the glutamatergic and Dopaminergic systems are also involved in morphine tolerance and dependence on morphine and in morphine withdrawal syndrome. Ascorbic acid (ascorbate) which is an antioxidant vitamin released from glutamatergic neurons and modulate the synaptic action of dopamine and glutamate as well as behavior. Since ascorbate modulate the synaptic action of dopamine and glutamate, in this study the effect of ascorbate on morphine withdrawal syndrome in rats has been investigated.

**Objective:** to determine the effects of Ascorbic acid on morphine withdrawal syndrome.

**Methods:** 30 Male rats (250−300g) were tested in this study in two groups. The first group as the control group received 3% sucrose in tap water(n=6) and the second group as the dependent group received morphine (0.1, 0.2, 0.3, 0.4 mg/ml each one for 48h, and 0.4 mg/ml remaining days to 21th days) and 3% sucrose in tap water (n = 24), this group divided in 4 sub groups: (1) morphine group, (2,3,4) morphine-Ascorbic acid groups which received AA (100, 500, 1000 mg/kg I.P) every 48 h and in the end (21th day) 30 min before naloxone administration for evaluation effects of AA on withdrawal signs.

**Results:** Our results show that: Ascorbates (100, 500, 1000 mg/kg I.P) can greatly attenuate most of morphine withdrawal syndrome (but not all) dose dependently.

**Methods:** Ultra-low dose opioid antagonist naltrexone potentiates cannabinoid anticonvulsant effects in the pentylenetetrazole-induced seizure in mice

**Objective:** It is widely accepted that cannabinoid compounds are anticonvulsant since they have inhibitory effects at micromolar doses, which are mediated by activated receptors coupling to G protein-proteins. Surprisingly, both the analgesic and anticonvulsant effects of opioids are enhanced by ultra-low doses (nanomolar to picomolar) of the opioid antagonist naltrexone and as opioid and cannabinoid systems interact, it has been shown that ultra-low dose naltrexone also enhances cannabinoid-induced antinociception. Concerning the seizure modulating properties of both classes of receptors, this study investigated whether the ultra-low dose opioid antagonist naltrexone influences cannabinoid anticonvulsant effects.

**Results:** Asimilar potentiation by naltrexone (0.5 ng/kg) of anticonvulsant effect of non-effective dose of ACEA (1 mg/kg) was also observed in the generalized tonic-clonic model of seizure.

**Conclusion:** The present data indicate that the interaction between opioid and cannabinoid systems extends to ultra-low dose levels and ultra-low doses of opioid receptor antagonist in conjunction with very low doses of cannabinoids may provide a potent strategy to modulate seizure susceptibility.

**Methods:** The effects of ascorbic acid on morphine withdrawal symptoms in rats

**Objective:** to determine the effects of Ascorbic acid on morphine withdrawal syndrome.

**Methods:** 30 Male rats (250−300g) were tested in this study in two groups. The first group as the control group received 3% sucrose in tap water(n=6) and the second group as the dependent group received morphine (0.1, 0.2, 0.3, 0.4 mg/ml each one for 48h, and 0.4 mg/ml remaining days to 21th days) and 3% sucrose in tap water (n = 24), this group divided in 4 sub groups: (1) morphine group, (2,3,4) morphine-Ascorbic acid groups which received AA (100, 500, 1000 mg/kg I.P) every 48 h and in the end (21th day) 30 min before naloxone administration for evaluation effects of AA on withdrawal signs.

**Results:** Our results show that: Ascorbates (100, 500, 1000 mg/kg I.P) can greatly attenuate most of morphine withdrawal syndrome (but not all) dose dependently.

**Methods:** Ultra-low dose opioid antagonist naltrexone potentiates cannabinoid anticonvulsant effects in the pentylenetetrazole-induced seizure in mice

**Objective:** It is widely accepted that cannabinoid compounds are anticonvulsant since they have inhibitory effects at micromolar doses, which are mediated by activated receptors coupling to G protein-proteins. Surprisingly, both the analgesic and anticonvulsant effects of opioids are enhanced by ultra-low doses (nanomolar to picomolar) of the opioid antagonist naltrexone and as opioid and cannabinoid systems interact, it has been shown that ultra-low dose naltrexone also enhances cannabinoid-induced antinociception. Concerning the seizure modulating properties of both classes of receptors, this study investigated whether the ultra-low dose opioid antagonist naltrexone influences cannabinoid anticonvulsant effects.