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以制約場地偏好行為模式探討藥癮復發的行為神經機制

Investigation of neurobehavioral mechanisms of drug relapse by the use of conditioned place preference model

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I. Background

Accumulative evidence supports the idea that the addicted drugs act as reinforcers of drug-taking and drug-seeking behaviors. In other words, those drugs produce rewarding effects can then be characterized with abuse potential, such as psychostimulant drugs (e.g. amphetamine, cocaine) and opioid compounds (e.g. morphine, heroine). From the past, it is argued that the mesolimbic dopamine (DA) systems play a major role of the underlying neural mechanisms for drug reward. The use of traditional operant conditioning paradigm on self-administration and self-stimulation highlights that the release of dopamine in the brain serves as the reinforcement contingency for establishing the drug addictive behavior. However, the dopamine hypothesis for drug reward and addiction behavior has been continuously debated since the last decade. The dopaminergic mechanisms mediating the drug reward and/or addiction are more complicated than what were thought in the past. Similarly, as the challenge appeared on investigating neural mechanisms, there is a bottleneck to reveal the behavioral mechanisms for a sophisticated delineation of drug addiction. Despite the aforementioned progress made on in psychopharmacology of drug reward, it is still in obscure about the efficient anecdote or medical treatment for drug abuse. One of the critical concerns on behavioral characteristics of this syndrome is regarding to the resumption of drug seeking or drug consumption after a protracted abstinence, so-called relapse in clinical. Therefore, this project aims to investigate the neurobehavioral mechanisms of drug relapse. The project was approved to conduct those essential experiments over two years. In the first year, the main theme is to establish an animal behavior model of drug relapse by the use of psychostimulant drug (amphetamine) induced conditioned place preference (CPP). In the second year, experiments with pharmacological and intracranial manipulations will be conducted to study the neural substrates for the

drug relapse on aforementioned place conditioned behavior.

II. Data Accumulated

1. In the first year of this project, the procedures of amphetamine induced CPP established in this lab has been tried to be extended into the extinction sessions. There were several controls for the extinction procedure being tested. One of the controls was to stay in the home cage over the extinction sessions (10 days). The other was simply putting the subject into the conditioned compartments in alternate over 10 days, and without any injection of amphetamine or saline. Moreover, the third control group was treated with saline in the compartment where the subjects were previously given with amphetamine. Although the results showed that all three type of extinction (or withdrawal) treatments did impair the appearance of CPP, the statistical tests did not confirm the effect of extinction. It could be due to the relative large variation. And, this negative result might be attributed to the inadequate length of extinction sessions (10 days in this case). A new batch of subject is currently under going to be testes with the longer extinction, 20 days as set. This part of experiment is very critical for the rest of entire project, which procedures must be ensured to serve as a baseline for conducting further experiments in pharmacology and brain manipulation. The reason for slowing down in this part of experiment is due to the lack of automated CPP measures. Currently, all the CPP tests are conducted by manual recording, which is a high cost of man power. To encounter this shortage, this lab has been trying to set up additional CPP apparatus that can be recorded in automated. Most importantly, it can run four sets of CPP test at the same time. The progress of collect data for the extinction part is expected to speed up with this newly set automated CPP apparatus.

2. Besides running the aforementioned experiment, this lab has been continuing to collect data to deal with the animal model of place conditioning. Two experiments were done and presented below with title and abstract for each (labeled by 2.1 & 2.2).

2.1 Dose effects of Dopamine Receptor Antagonists on Stressor Induced Conditioned Place Preference in Rats

An immediate and robust release of dopamine appears in several brain regions under acute stressor, but it remains uncertain about how this enhancement of dopamine is involved in behavioral process of learning and memory. Conditioned place preference (CPP) is a behavioral task based on classical conditioning paradigm, which has been frequently used to measure the motivation and its relevant learning. Accordingly, this study manipulated the after-effect of elevated platform or restraint stressor was used as unconditioned stimulus (US) to be associated with a specific context. A place conditioning test given 24 h later, CPP was determined if subjects significantly showed conditioned approach behavior toward the stressor paired chamber more than the other one (non-stressor-paired). Such CPP effect was significantly induced by two types of stressor from placing the subject on an elevated platform and a restraint holder. Additional experiments were conducted to test the involvement of dopamine in this type of CPP by administering selective dopamine D1 and D2 receptor antagonist, SCH23390 (0.025 and 0.05 mg/kg) and raclopride (0.05 and 0.1mg/kg) respectively, before each stressor manipulation. The results showed that both dopamine receptor antagonists attenuated the formation of stressor induced CPP. Together, the stressor can serve as a valid US to facilitate the conditioned approach response to form a CPP, and such behavior is dopamine dependent.

2.2 Adenosine receptor agonists infused into striatal subareas blocking the

expression of conditioned place preference induced by amphetamine

Adenosine has been suggested to play a pivotal role in modulating central reward functions. A growing body of evidence indicates that adenosine receptors in different brain regions can affect the releasing level of several major neurotransmitters. Previous work showed that systemic injection of adenosine agonists influences the rewarding effects of psychostimulant drugs. However, the central mechanism of these interactions between the adenosine agonists and the psychostimulants are still unclear. It is presumed that different subtypes of adenosine receptors exert heterogeneous behavioral functions. The present study was designed to examine the role of adenosine subtype receptors in amphetamine (AMP) induced conditioned place preference (CPP) which is a widely used animal model to testify the drug addiction. Selective adenosine A1 and A2 receptor agonists, CPA and CGS21680 respectively, were locally infused into the lateral striatum and nucleus accumbens (NAC) on the expression of AMP CPP. Male Wistar rats with chronic cannulae implanted in the lateral striatum or NAC were subjected to CPP protocol with 3 AMP and 3 saline pairing trials in alternate. To induce CPP, the subjects were intraperitoneal injected either AMP (1.0 mg/kg) or saline shortly before conditioning sessions. The test session was conducted after 24 hrs after the last conditioning trial. On the post-conditioning test day, the subject was infused a dose of adenosine agonist or saline 20 min prior to the test session. The results showed that AMP significantly elicited CPP at the present dose tested. In which, the subject spent more time in the AMP paired context than the saline paired one on the post-conditioned test. Microinjections of both CPA and CGS21680 into lateral striatum suppressed the expression of AMP CPP at all doses tested. Similar results were revealed from the treatments of CPA and CGS21680 infused into NAC. These results show that local

infusion of selective adenosine A1 or A2 agonists into either lateral striatum or NAC attenuates the expression of CPP induced by AMP. It suggests that activation of adenosine A1 and A2 subtype receptors in the striatal areas is involvement in blocking the rewarding properties of AMP.

III. Summary

Some data collected in the first year had been submitted to an international journal for publication and currently under review (experiment shown in 2.1), while the other part of data have been submitted to present in the 2009 conference of Society for Neuroscience in Oct 17-21 in Chicago, Illinois, USA. Several other studies proposed for this grant project are currently either undergoing or ready to initialize. The progress of this project is under well controlled.