行政院國家科學委員會專題研究計畫成果報告

安非它命的濫用：
以動物模式研究其生理與心理的機制
(整合型計畫)

探討長期安非它命引發操作式學習行爲
時效耐藥性之神經行爲機制(三)
(子計畫)
Neurobehavioral Mechanisms for Contingent Tolerance
of Chronic Amphetamine on Operant Behavior (III)

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中文摘要

安非它命在過去的研究中被認爲對行爲功能具有深層的影響力，尤以長期使用安非它命者的影響更鉅，因爲其長期藥物經歷過程中的行爲變項更爲複雜。操作式學習行爲模式因具有較優之行爲量化性及行爲歷程的實驗操控性，本研究計劃採此行爲模式加上'事先/事後'注射方式，對安非它命的行爲神經機制進行探討。從這個計畫的第三年執行中，結果發現長期注射安非他命的處理對維持在 FR20 增強條件的受試較 FR5 者敏感。就這種長期注射安非他命引發的行爲耐藥性而言，它是可以被一些注射歷程（包括注射時間及地點）所改變。這種實驗操弄可以使事前組的耐藥性效果漸弱，而相對的使事後組的行爲壓抑反應趨向一種類似「致敏化」的效果。另外，個體在戒斷階段的行爲反應趨勢，會取決於其先前在長期注射安非他命階段的表現。經過長期注射安非他命的事前及事後組受試，其行爲消除反應並無不一致。綜合整個三年計畫之實驗結果而言，操作式行爲的耐藥性出現與否取決於行爲反應與藥物作用之交互作用，這是可以由心理藥理學的實驗操弄所驗證。長期性之安非它命注射對操作式學習行爲影響效果，亦與度巴胺神經系統功能之調適有關。

關鍵詞：操作式行爲，安非它命，行爲耐藥性，度巴胺，大白鼠。

abstract

Numerous studies indicate that amphetamine (AMP) can have profound effects on the behavioral function, especially for chronic treatment. Operant behavioral paradigm provides the advantages of behavioral quantifiability and conditional manipulability in experimental level, which has been applied to the examination of drug induced behavioral effects. The present study investigated the neurobehavioral mechanisms of chronic AMP by employing operant behavioral model along with the Before/After design of drug administration. For the third year of this project, the results first present the dose effects of chronic AMP were more sensitive for the subjects maintained on FR20 than on FR5. Further, the effects of chronic AMP on FR-typed behavior could be shifted by different parameters of drug administration as the injection time and context manipulated. While the contingence tolerance diminished in the Before group, a sensitization-like effect of response suppression was developed in the After group. The operant performance on FR behavior during the withdrawal was dependent on the preceding outcomes of chronic AMP treatment. Also, the extinction effects of FR5 behavior after chronic AMP was similar for both Before and After groups. All together, including the data collected from previous two years, it is clear that appearance of contingent tolerance to AMP on FR behavioral subtly relied upon the interaction between behavioral performance and drug action, which can be manipulated in terms of psychopharmacology. Chronic effects of AMP on operant behavior are also relevant to a potential neural adaptation in the dopamine systems.

KeyWords: operant behavior, amphetamine, behavioral tolerance, dopamine, rat

I. Introducrion

Behavioral effects of drugs can provide valuable insights into the drugs' actions. Drugs can have profound, long-lasting effects on behavior that alter neuronal processes in quantifiable ways. Continuous drug treatment can result in a pattern of behavioral changes. It is now known that drug abuse has its origins in both psychological and biological factors. Focus on the interaction between drug and behavior has been the center for the study of drug abuse (Stolerman, 1992). In terms of amphetamine (AMP), it is not only to modify ongoing behavior but also enter into critical behavioral processes. The intend of this project was to examine the potential behavioral factors based on the operant paradigm in affecting the AMP effects. Using operant task to manipulate the potential behavioral factors, experimenter can arrange the schedule of reinforcement (Ferster & Skinner, 1957). Different types of operant behaviors, derived from schedules of reinforcement are believed to characterize distinctive behavior profiles. Operant techniques are widely used for assessing drug effects on the schedule controlled behavior (review see Sanger, 1989).

Like other abused agents, AMP taken by addicted individuals is often administered repeatedly. Generally, a drug's effects diminished after repeated exposure is termed as tolerance. The categorization of tolerance as a procedure for assessing drug dependence potential is based on the observation that acquisition of tolerance is often associated with the development of withdrawal on discontinuation of drug treatment (Balster, 1985). Like other issues of drug abuse, tolerance involves a range of mechanisms of different levels of complexity (Goudie & Emmett-Oglesby, 1989). In contrast to dispositional tolerance, there is now good evidence showing that tolerance may also be derived from several different behavioral processes (Goudie & Griffiths, 1986). A so-called before/after design has been particularly useful for analyzing the potential role of behavioral learning in the formation of tolerance (Chen, 1968). Chen studied the effect of ethanol on the performances of rats trained to run in a circular maze. After meeting the stable daily performance on the baseline level, rats were divided into two groups. One (noted as the Before group) was received ethanol 10 min before the behavioral session, whereas the other (noted as the After group) was injected with ethanol 10 min after the behavioral session. The contingent tolerance was shown in the Before group, rather than the After group, 4 days later when both groups received ethanol injection prior to the behavioral test. Chen suggested that rats in the Before group showed tolerance due to that they had an opportunity to behave under the operant contingencies under the influence of the drug. Using operant paradigm, instead of reflexive type of behavioral measure, an early report of the present project showed that the tolerance was significantly developed in the operant behavior maintained under FR20 schedule of reinforcement. Moreover, chronic AMP had little effects on the FI60 responding, whereas it significantly shift the DRL30 performance (Liao, 1998).

In the third year of this project, this laboratory continuously investigated the neurobehavioral mechanisms of chronic AMP on the operant behaviors. This report covers that 1) the dose effects of chronic AMP on operant behavior under FR20 in comparing with those under FR5, 2) the effects of chronic AMP on FR-typed behavior with different parameters of drug administration, and 3) the operant performance on FR5 during the withdrawal from chronic AMP, and 4) the extinction effects of FR5 behavior after chronic AMP. The last part of this report presents a brief review for this three-year project.

II. Methods and Materials

Subjects The subjects were male Sprague-Dawley rats with body weights approximately in 300g at the beginning of experimentation. Subjects were individually housed in a temperature controlled colony with a 12 hr / 12 hr light-dark cycle. After 2 weeks of adaptation to the laboratory with food and water provided ad libitum, a water deprivation regimen was introduced permitting 5 min access to tap water in the home cage 1 hr after each daily experimental session. Subjects were monitored and kept at 85% of their pre-experimental body weight. Food pellets were freely provided in the home cage. Training and/or testing events were conducted in the same time period during the light portion of vivarium.

Drug Administration D-amphetamine sulfate (Sigma Chemical Co.) was dissolved in normal saline (0.9% NaCl w/v). The injection of AMP or its vehicle was given IP at a volume of 1.0 ml/kg of body weight. Doses of AMP are expressed as the salt.

Apparatus Operant responding was measured in multiple Skinnerian chambers (MED Associates Inc.) which was enclosed by the sound-attenuating wooden box. Each chamber (28cm x 21cm x 21cm) was equipt with a lever as the operant manipulandum, a house light to provided dim illumination, and a solenoid-operated liquid dispensor to deliver drips of tap water as the reinforcer. An electric fan ventilated each box and provide constant background noise. All chambers was simultaneously served and controlled by a microcomputer. Operant contingencies were programmed and modified from a commercial kit (MED State Notation, Med Associates Inc.). The numbers of lever presses and reinforcers were recorded as raw data.

Procedure In regarding the acquisition of operant behavior One week of adjustment to water deprivation was conducted before rats were trained in the operant chamber. All animals were manually shaped to press the operant manipulandum after one session of magazine training. Then, animals were placed upon a continuous reinforcement schedule (CRF) for two sessions. The acquisition of the responding under the CRF schedule was judged as the initiation of operant behavior. Rats were subsequently placed on a specific schedule by gradually increasing the parameter. The schedules of reinforcement employed in the present study were the fixed ratio type (FR) and differential reinforcement for lower rate of responding type (DRL). The baseline criterion was the less than 10 percent of variation on the response rate successively across daily sessions for each schedule. Each session of 15 min was conducted on a different day. The dripper flow time were 2 sec from shaping through the remainder of the experiment.

The Before/After design was used to determine the behavioral tolerance of AMP. Rats trained on a specific schedule of reinforcement were divided into two halves. Half of them noted as the Before group were injected with AMP 10 min before the daily session, whereas the other half called as the After group were injected with AMP 10 min after the daily session. The Before/After injections was conducted for varied sessions. The challenge of AMP doses (0.5 - 2.0 mg/kg)was conducted to test the potential tolerance under FR20 operant behavior. Behavioral tolerance was determined by comparing the differences between the Before and the After groups. Two parameters for FR-typed behavior (FR20 and FR5) were examined under chronic AMP in order to test whether the reinforcement density would be involved in this paradigm. In another set of experiments, using FR20, the effects of chronic AMP were evaluated with different parameters of drug administration. The injection times

before and after session were manipulated by 10 min and 30 min. The context following the completion of the before injection was also manipulated by placing the subject in either the colony or the test room. The operant performance on FR5 during the withdrawal from chronic AMP was investigated by running the subjects in both Before and After groups across 7 operant sessions without any injection. In addition, these subjects were all entered into 3 daily sessions for the extinction, in which the omission of reinforcer was conducted under FR5.

Statistics Data collected from all experiments were analyzed by proper types of ANOVA and the follow-up comparison of means.

III. Results

The contingent tolerance has been shown in the Before group as compared to the After group during the chronic treatment of AMP. The inhibitory effects of FR20 responding was gradually diminished for the subjects of the Before group as the injection days progressed. Although the subjects in the After gradually decreased their responses across the chronic stage, this trend was not statistically significant. In contrast to these previous findings on FR20 behavior, the contingent tolerance was not revealed from the Before group when the drug administration was shifted. These manipulations included to shorten the injection times before and after the session as well as to place subject in the test room when conducting the priori and posterior injections. When the injection time was 10 min before and after the session, the operant responding was completely disrupted during the chronic phase for the subjects in the Before group. By contrast, the operant deficits of response suppression for the subjects in the After group were magnified as the chronic sessions went by. For either FR20 or FR5, these effects, including the lack of contingent tolerance in the Before group and the magnified operant deficit in the After group, were also presented by those subjects with the injection conducted in the operant test room but not in their home cage. The only difference between FR20 and FR5 on this pattern of operant responding was a higher sensitivity for the drug to induce operant changes in the former condition. As the withdrawal test conducted on FR5, different patterns of operant responding were demonstrated between the Before and the After group. The subjects in the Before group appeared to perform as well as the baseline level across a 5-day withdrawal test, whereas those in the After group produced a significant deficit of response suppression during the withdrawal. In terms of extinction, it was found that both groups completely diminished operant responding in three days.

IV. Discussion

Following the work down in previous two years with finding the contingent tolerance of AMP on FR20 behavior, the present study (of the third year) mainly focused on the investigation of mechanisms for this effect. It was found that the contingent tolerance of AMP on FR20 behavior was subtle as relied upon the drug administration and its relevant factors. The lack of contingent tolerance to AMP in the Before group appeared to experimental condition manipulated by either shortening the injection times before and after session to 10 min from 30 min or placing the subject in the operant test room rather than the colony as the injection conducted. Along with this phenomenon, the subjects in the After group showed a sensitization-like effect of drug-induced response suppression across the chronic phase. The observation in the After group was a major findings in the present work, which has not been reported in the past. Despite the present manipulation, behavioral effects to AMP in the After

group have been known to be negligible (Chen, 1968, Wolgin, 1989). However, the previous work from other laboratory almost all employed the reflexive type of behavioral tasks (ie., tread-mill locomotion, milk consumption), while the present study used operant conditioned behavior. Performance on the latter required a lot more integrated components than just a sensory-motor reflex. More work has to be done before a proper explanation for addressing this issue. This may also be related to the After group under withdrawal. The After group seemed to have a carry-over effect following chronic AMP treatment in comparing to the Before group.

In conclusion for this three-year project, using before/after design, the contingent tolerance to AMP can be subtly obtained from operant behavior. In comparing with FI behavior, operant behaviors maintained on FR or DRL schedule of reinforcement were more sensitively affected by chronic AMP. It was indicated the tolerance to AMP on DRL behavior was dopamine dependent, especially relevant to D2 receptor subtypes. Appearance of contingent tolerance to AMP on FR behavioral subtly relied upon the interaction between behavioral performance and drug action, which can be manipulated in terms of psychopharmacology. Together, these data indicate that chronic effects of AMP on operant behavior are dependent on the schedule of reinforcement, administration of drug dose, and a potential neural adaptation involved.

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