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BIOLOGICAL PSYCHIATRY - SHORT COMMUNICATION

Amphetamine Selectively Enhances Avoidance Responding to a Less Salient Stimulus in Rats

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Abstract This preclinical study examined the *psychological* processes affected by amphetamine that contribute to human psychosis. Using a novel avoidance conditioning paradigm involving two conditioned stimuli (CS) with varied salience, we found that acute amphetamine (1.5 mg/ kg, i.p.) selectively enhanced avoidance responding to a less salient stimulus, but not to a salient one. These findings suggest that elevated dopaminergic activity selectively enhances the attributions of motivational salience to a less salient stimulus, a process that may bear relevance to the development of human delusional thoughts.

Keywords: Amphetamine, Avoidance conditioning, Incentive salience, Rat

Introduction

It is well documented that repeated amphetamine exposure can produce the schizophrenia-like symptoms in non-psychotic individuals and exacerbate existing symptoms in schizophrenic patients. Amphetamine has thus been extensively used in the preclinical studies of neurobiological mechanisms and behavioral characteristics of schizophrenia (Castner *et al.* 2005; Robinson and Becker 1986). Recent approaches to modeling psychosis have been focusing on the information processing deficits that are thought to underlie the development of psychotic symptoms (Norman and Cassaday 2003; O'Tuathaigh *et al.* 2003; Swerdlow *et al.* 2000; Weiner 2003). Current research has emphasized the deficits in the attention domain (Buchanan *et al.* 2005). Although many studies have clearly demonstrated that amphetamine-induced attention deficits are useful in capturing some aspects of cognitive deficits of schizophrenia, it is still not clear how these deficits give rise to positive symptoms, such as delusional thoughts and hallucinations.

While in an acute psychotic state, schizophrenic patients seem to have a heightened ability to process information coming from trivial stimuli in their internal or external environment and show stronger cognitive and motivational responses toward them, of which normal people would not notice (Gray 1998; Hemsley 1993; Jones *et al.* 1991; Kapur 2003). This enhanced ability to respond to less salient environmental stimuli has been argued cogently as one important mechanism underlying psychosis (Beninger 2006; Kapur 2003). In the present study, we attempted to directly model this psychological process (*e.g.*, enhanced associative conditioning to a less salient stimulus) and investigated how repeated amphetamine treatment would impact this process in rats. We used a modified two-way (shuttle) avoidance-conditioning task involving two types of conditioned stimuli (CS1 and CS2) that varied in their salience and ability to predict the occurrence of the unconditioned stsimulus (US, foot-shock). We found that amphetamine (1.5 mg/kg, i.p.) selectively enhanced avoidance responding to the less salient CS2. Interestingly, amphetamine did not enhance avoidance responding to the more salient CS1. This effect of amphetamine may explain the psychological mechanisms underlying amphetamine psychosis and psychosis in schizophrenia.

Materials and methods

All procedures were approved by the Institutional Animal Care and Use Committee at the University of Nebraska-Lincoln. Twenty-eight male Sprague-Dawley rats (226- 250 g upon arrival, Charles River, Potage, MI, USA) were used. After 2 days of shuttle box habituation [see Li *et al.* (2007) for detailed description of the boxes custom built by Med Associates, St. Albans, VT, USA], all rats were tested every other day for a total of five sessions over a 10-day period. Fifteen minutes before the start of each session, amphetamine (AMPH, 1.5 mg/kg, i.p.) or saline (SAL) was injected to the subjects (n = 14 for each treatment). Two CAR testing conditions were used. Both conditions consisted of 30 training trials involving two types of CSs. In the 50% condition, ten trials used the onset of two houselights (CS1, 10 s "Lights ON") as the CS, and another ten trials used a pure tone (CS2, 10 s, 2,800 kHz, 85 dB, "Pure Tone"). The remaining ten trials used the compound of houselights and tone (CS1 + CS2). Only the 20 trials involving CS1 (*e.g.*, CS1 and CS1 + CS2, collectively termed "CS1 trials") were followed by a scrambled foot- shock (5 s maximum, 0.8 mA, US) if the rats did not run from one compartment into the other during the CS. The ten CS2 trials were never followed by the shock even if the rats did not run. Thus the CS2 signaled the occurrence of the shock in 50% of trials. In the 0% condition, there were 20 CS1 trials (with shock) and ten CS2 trials (without shock), thus the CS2 had 0% prediction to the shock. Every trial started by presenting the CS (CS1, CS1 + CS2, or CS2) for 10 s; its offset was immediately followed or not followed by the shock. If a subject moved from one compartment into the other during the CS, the CS was terminated and this response was recorded as avoidance(*e.g.*, avoidances to the CS1 or CS2). A crossing response during the shock terminated the shock and registered as an escape response. The motor activity of each subject was also recorded as the number of photobeam breaks. Based on the treatment (AMPH vs. SAL), and testing conditions (50 vs. 0%), rats were further randomly assigned into four experimental groups: AMPH, 50% (n = 8); AMPH, 0% (n = 6); SAL, 50% (n = 8); and SAL, 0% (n = 6).

Data were expressed as mean values ± SEM and were analyzed using a factorial repeated measures analysis of variance (ANOVA) with the between-subjects factors being treatment ("Treatment," *e.g.*, AMPH vs. SAL), and test conditions ("Condition,", 50 vs. 0%), and the within-subject factor being the test sessions ("Session," *e.g.*, day 1 test, day 2 test, *etc.*). On the second avoidance conditioning test, data from six rats were missing due to the mechanical malfunction (two rats in the 0% SAL condition, one rat in the 50% SAL condition, and two rats in the 0% AMPH condition, and one rat in the 50% AMPH condition). Their data were replaced with estimates computed using a linear interpolation method. A conventional two-tailed level of significance at the 5% level was required.

Results

Figure 1 shows the effects of acute amphetamine administration on avoidance responding to the CS1 and CS2 in the rats tested under the 50 or 0% conditions over the five test sessions. All rats improved in their avoidance responses to the CS1 progressively across the sessions ($F_{(4, 96)}$ = 15.347, $p < 0.001$). Acute amphetamine treatment seems to have an enhancing effect on the acquisition of avoidances to CS1, however, this effect was not significant (the main effect of "Treatment," $F_{(1, 24)}$ = 3.969, p = 0.058). In contrast, amphetamine did enhance avoidance responding to the CS2, as confirmed by a highly significant main effect of "Treatment" ($F_{(1, 24)}$ = 19.614, $p < 0.001$).

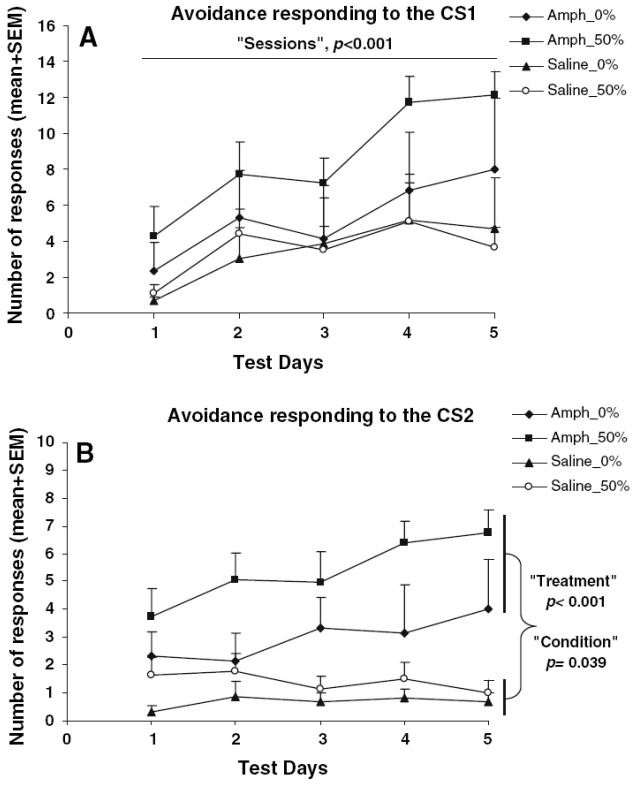

Fig. 1 Effects of acute amphetamine administration on avoidance responding to the *CS1* (**a**) and *CS2* (**b**) in the rats tested under 50 or 0% conditions over the five avoidance testing sessions. Amphetamine significantly enhanced avoidance responding to the *CS2* ($F_{(1, 24)}$ = 19.614, $p < 0.001$), but not to the *CS1* ($F_{(1, 24)}$ = 3.969, p = 0.058). The CAR test conditions also influenced this measure as the rats testing in the 50% condition exhibited more avoidance responses to the *CS2* than those in the 0% condition ($F_{(1, 24)}$ = 4.786, p = 0.039)

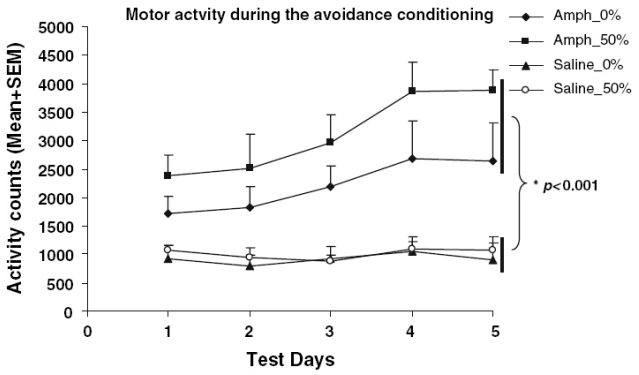

Fig. 2 Motor activity during the five avoidance testing sessions in rats that were treated with either amphetamine (AMPH) or saline (SAL) and tested under the 50% condition or 0% condition. Amphetamine-treated rats showed a much higher level of motor activity than the saline rats during the five CAR test sessions ($F_{(1,\ 24)} = 32.609$, $p < 0.001$), and this effect was progressively enhanced across the sessions ($F_{(4,\ 96)} = 6.145$, $p < 0.001$)

Figure 2 displays the motor activity of rats during the CAR test sessions. It is evident that amphetamine-treated rats showed a much higher level of motor activity than the saline rats, and this effect was progressively enhanced with each subsequent amphetamine administration, indicating a strong behavioral sensitization effect ("Treatment": $F_{(1,\ 24)} = 32.609$, $p < 0.001$; "Session": $F_{(4,\ 96)} = 6.145$, $p < 0.001$; and "Treatment" 9 "Session" interaction: $F_{(4,\ 96)} = 4.379$, $p = 0.003$).

The enhanced avoidance responding to the CS2 by amphetamine was unlikely accounted for by amphetamine's motor stimulating effect. We calculated the partial correlation coefficients for the 50 and 0% amphetamine groups separately using the partial correlations procedure. This procedure allows the identification of the linear relationship between the motor activity and avoidance responses to the CS2 while controlling for the effects of avoidance responses to the CS1 on the motor activity. Results show that in the 0% condition, there was no single significant association between the motor activity and the CS2 avoidances (the p values ranges from 0.256 to 0.715), while in the 50% condition, significant correlations were only found on the day 1 ($p = 0.009$) and day 3 ($p = 0.035$), but not on other days (the p values ranges from 0.275 to 0.530). Overall, this finding suggests that the amphetamine's unconditional effect on motor functions was an unlikely factor responsible for the enhanced avoidance responses to the CS2.

Discussion

The present study directly investigated the psychological mechanisms underlying amphetamine-induced psychosis, and possibly schizophrenic psychosis. Using a novel two-way avoidance conditioning paradigm, we tested rats repeatedly administered with amphetamine (1.5 mg/kg, i.p.) or saline and found that amphetamine acutely enhanced avoidance responding to a less salient and less informative CS in a dose-dependent fashion (*e.g.*, a stronger effect in the 50% condition than the 0% condition). This effect was highly specific as it did not enhance avoidance responding to the CS1 (a highly salient stimulus). Also, this selective effect could not be accounted for by the general motor-stimulating effect of amphetamine because there was no significant and consistent correlation between the motor activity and the CS2 avoidances. These results indicate that amphetamine may preferentially enhance conditioned response to a relatively less salient stimulus, but not to a highly salient stimulus (*e.g.*, CS1), and this effect is dissociable from its motoric effect.

This heightened conditioned response to a less salient stimulus as a result of amphetamine treatment is consistent with a large body of evidence showing that amphetamine, by enhancing dopaminergic function, is capable of facilitating reward-based learning in both appetitive (Wyvell and Berridge 2001) and aversive situations (Killcross *et al.* 1994). What is unique about the present study is that we not only confirmed that elevation of dopaminergic activity by amphetamine can enhance several psychological processes involved in reward-based learning (Berridge and Robinson 1998; Wise 2004), but also showed that it does so more selectively. It appears that amphetamine has a preference to enhance associative conditioning to a less salient stimulus over to a more salient stimulus. This particular finding is similar to that of Norman and Cassaday (2003), who showed that amphetamine selectively enhanced associative processing of less salient stimuli (trace CS, contextual cues, *etc.*) in a Pavlovian fear conditioning paradigm. Our results extended Norman and Cassaday's finding to an instrumental conditioning situation. Furthermore, we carefully manipulated the stimulus salience by pre-arranging the relations between the CS2 and US in the 0 and 50% conditions, and showed a graded effect of amphetamine in this regard: As the putative salience of the CS2 increased, so did the effect of amphetamine.

Kapur (2003) postulates that psychosis is a disorder of an aberrant salience due to the hyperdopaminergic function in schizophrenic patients. Specifically, they tend to perceive and conceive an irrelevant stimulus, which just happens to be occasionally associated with a high significant stimulus, as a powerful behavior-controlling force and react to it and over-generalize their abnormal associations to other circumstances. Our results are consistent with this idea.

In conclusion, the present study demonstrated that el-

evated dopaminergic activity through repeated amphetamine injections selectively enhanced an aversively conditioned response to a less salient stimulus in a dose-dependent fashion, and this effect may reveal an important psychological process that underlies the genesis of psychotic symptoms in schizophrenia. These findings support previous evidence for a basic role of dopamine in reward-based learning and motivated behaviors and underscore the importance of attention selection and motivational salience attributions in the development of psychosis. In contrast, it is suggested that elevated dopaminergic activity is less likely to cause behavioral changes (*e.g.*, social interaction and memory) that resemble the negative symptoms of schizophrenia.

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