

Effects of Apomorphine on the Expression of Learned Helplessness Behavior

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Abstract

Dopaminergic system and its D1 as well as D2 receptors are involved in the modulation of emotional behavior. This experiment investigated the role of dopaminergic activity in the inescapable stress-induced learned helplessness, a widely used depression animal model, by using the pharmacological manipulation through the apomorphine (APO), an agonist for D1 and D2 receptors, and sulpiride (SUL), a selective D2 antagonist. Male Sprague Dawley rats were used and tested in a shuttle box. In the day-1 session, the rats received a 10-trial (1 min/trial) inescapable stressor: a 3 sec conditioned stimulus (CS; 75 db sound and 250 lux red light) followed by a 10 sec unconditioned stimulus (UCS; electrical foot shock, 0.5 mA). In the day-2 session, a 15-trial active avoidance test, 3 sec CS followed by UCS, was performed 30 min after the administration of APO (0, 0.05, 0.5, 1, and 5 mg/kg, i.p.). The number of failures was counted and the UCS was stopped when the rats did not escape after 15 sec UCS. The results showed that APO at the dosage of 0.5 mg/kg had a tendency to enhance the avoidance behavior. In contrast, the treatment of higher dose of APO, 1 and 5 mg/kg, reduced the number of escape but increased the number of failure. Pretreatment of SUL (5 mg/kg, i.p.), 10 min before 1 mg/kg of APO, significantly enhanced the failure behavior. The present data suggest that the activity of D2 receptor may be associated with the adaptive or protective role in the prevention of escape deficits after exposure to inescapable stress. However, the excessive stimulation of D1 receptor may participate in the failure of coping behavior leading to learned helplessness and therefore in the pathophysiological mechanisms underling the development of depression.

Key Words: dopaminergic system, learned helplessness, apomorphine, avoidance test

Introduction

Depression is an affective disorder with an especially high prevalence among all emotional illnesses. Both the serotonergic and noradrenergic systems have been reported to be involved (26, 28). Previous observation indicates that psychological stress participates in the affective disorders (31). For example, over 84% of patients seeking treatment for depression

experienced severe stress in the preceding years (6). Evidence from animal studies has demonstrated that inescapable foot shock in learned helplessness model of depression caused a deficit in escape behavior. Such behavioral despair was reversed after enhancing the monoaminergic activity (24). Because the central dopaminergic system regulates the emotional and motivational behavior, the dysfunction of this system may also underlie the development of affective disorders.

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Received: March 1, 2006; Revised (Finally): September 11, 2006; Accepted: September 13, 2006.

R(-)-apomorphine hydrochloride (APO) is an agonist for the dopaminergic D1 and D2 receptors (21, 22). The stimulation of human growth hormone released by APO was used to test the sensitivity of dopaminergic receptor in psychiatric patients. In such test, the major depressive patients showed a significantly reduced growth hormone response to APO as compared to normal controls (30, 32), suggesting the malfunction of dopaminergic system in depressive patients. In addition, stressful experiences can trigger attacks of depression in already depressed individuals, but it is not yet clear how the dopaminergic system influences the outcome after inescapable stress. When animals face an avoidable stress, for example an electrical foot shock, they try to actively cope with it by performing an appropriate response, leading to avoid or escape from the aversive stimulus. However, chronic inescapable stress causes the learned helplessness, that is, animals express the passive despair or helplessness behavior when they encounter the stress that they had met before. Because these behavioral changes are compatible with the psychological dynamics seen in the depressive disorders, the learned helplessness paradigm is used as a depression animal model (1).

This study aimed to examine the influence of dopaminergic mechanisms on adaptive response of animals in learned helplessness paradigm. Male Sprague Dawley (SD) rats were initially tested in an open field, for detecting their general motor function, and then in the learned helplessness paradigm that was taken in a 2-day session by using a two-way shuttle box. Animals received inescapable foot shock on day-1 session and escapable shock, active avoidance test, on day-2 session. Pharmacological manipulations by using the APO and (\pm)-sulpiride (SUL), a selective antagonist of D2 receptor (25), were conducted before the active avoidance test. The avoidance, escape, and failure responses to the foot shock were recorded (1).

Materials and Methods

Animals

Male Sprague-Dawley rats (National Laboratory Animal Center, ROC; 417 ± 7 g) were used and housed in groups of five rats in acrylic cages ($35 \times 56 \times 19$ cm) in an animal room with a 12-h light-dark cycle (lights on at 07:00 a.m.) with food and water provided *ad libitum*. One day prior to the experiment, each animal was handled (10 min) twice, in the morning and afternoon, respectively to reduce the defensive behavior to the experimenter. All experimental procedures were approved by the Animal Care Committee of the Chung Shan Medical University.

General Procedure

The behavioral tests were performed in the following order: an open field test on the first day and a 2-day session of learned helplessness paradigm on the following days. The day-1 session was inescapable foot shock; the day-2 session was active avoidance test. All behavioral tests were taken between 10:00 and 16:00. First, the animals were weighed in the animal room. Then, they were placed individually in a clean cage ($25 \times 41 \times 19$ cm) and transported to a dim observation room (28 lux) for behavioral testing. The pieces of test equipment were thoroughly cleaned by using 20% alcohol followed by thorough drying before each rat was tested. The behavioral parameters were analyzed by an automated computer program. The drugs, APO and SUL (Sigma, St. Louis, MO, USA), were dissolved in ddH₂O and dilute aqueous acid, respectively, immediately before usage and administered by intraperitoneal injection (i.p.) in a volume of 1 ml/kg of body weight before the day-2 session of the learned helplessness test. APO (0, 0.05, 0.5, 1, and 5 mg/kg) was injected 30 min before the test. SUL (5 mg/kg) was administered 10 min before the APO (1 mg/kg), in the case of co-administration. The n value was 6-9 for each group.

Behavioral Tests

Open Field

Since the dosages of APO and SUL used in this study have been documented to increase rather than decrease the spontaneous locomotion in rats, we did not detect the motor effects of these drugs in this experiment. To control the basal motor activity of animals and to avoid the possible disturbance on learned helplessness paradigm, the open field test was taken before the pharmacological manipulations. The open field consisted of an acrylic box ($40 \times 40 \times 54$ cm) that was monitored by an automated activity monitoring system (Digiscan-16 Animal Activity Monitor System; model RXYZCM, Omnitech Electronics Columbus, OH, USA) (16). The following measures were obtained by an automated computer program in a 5-min observation: [1] locomotor distance, [2] movement time, and [3] rearing time.

Learned Helplessness

This test was conducted in a commercial shuttle box (25×60 cm wide, 25 cm high; AccuScan Instruments, Columbus, OH, USA). The apparatus is divided into two equal compartments by a central barrier that has a hole (10 cm diameter) with a grid floor. The floor consisted of 2 mm diameter stainless-steel rods spaced

Table 1. Motor activity of rats in the open field test

	Vehicle (n = 8)	APO : 0.05 mg/kg (n = 6)	APO : 0.5 mg/kg (n = 7)	APO : 1 mg/kg (n = 8)	APO : 5 mg/kg (n = 7)	APO : 1 mg/kg + SUL : 5 mg/kg (n = 7)
Movement distance (cm)	1166.5 ± 83.4	1069.3 ± 86.4	1118.4 ± 88.2	1053.1 ± 89.4	1239.9 ± 75.9	1089.0 ± 142.3
Movement time (sec)	115.6 ± 7.8	119.3 ± 6.4	119.4 ± 5.5	98.3 ± 9.3	114.7 ± 9.5	97.1 ± 8.0
Rearing time (sec)	85.3 ± 5.1	81.5 ± 10.8	95.0 ± 5.6	76.4 ± 11.4	94.4 ± 9.1	84.9 ± 11.5

Open field test is taken for 5 min. APO: apomorphine, SUL: sulphiride. Data are expressed as mean ± SEM.

1.7 cm apart center-to-center. Scrambled shock was delivered to the floor. Two speakers and two light bulbs were mounted in the center of the top of each compartment for delivery of sound and illumination stimuli.

Day-1 session, inescapable foot shock: The animals were placed into the shuttle box and allowed to explore the entire apparatus for 1 min. Then, the hole of the central barrier was closed. The rats were administered 10-trial inescapable foot shocks, consisting of 3-sec conditioned auditory (75 db) and illumination (250 lux) stimuli immediately followed by 10-sec 0.5-mA shocks delivered on a random-interval (range 42-57 sec). On the next day, a 15-trial escapable foot shocks, active avoidance test, were taken.

Day-2 session, active avoidance test: The animals were placed into the shuttle box and allowed to explore the entire apparatus for 1 min. Then, they received 15 shuttle trials, where they were allowed to terminate a shock by crossing the adjoining compartment. Each trial began with a 75 db tone and 250 lux illumination, lasted 3 sec, and followed by a 0.5-mA scrambled foot shock. If the animal crossed the barrier during the conditioned stimuli, these stimuli were terminated, that is, no shock would be delivered, an avoidance response being recorded. If the animal crossed the barrier during shock delivery, an escape response would be recorded. If the rat failed to cross, the shock would be terminated after 15 sec, and a failure response would be recorded. After an interval ranging from 42 to 57 sec, the next trial was initiated. The latency to avoid or escape, and the number of avoidance, escape, and failure were recorded.

Data analysis: The comparison of drug effects was carried out by one-way analysis of variance (ANOVA), followed by least-significant (LSD) tests. All results were expressed as mean ± SEM. The level of significance was defined as $P < 0.05$.

Results

In the 5-min open field test, the movement distance,

movement time, and rearing time of all the rats were 1123.4 ± 38.5 cm, 110.4 ± 3.4 sec, and 81.6 ± 3.7 sec, respectively. No between-group difference was observed (Table 1). One day after the 10-trial of inescapable stress, the number of avoidance (0.6 ± 0.5), escape (12.4 ± 0.8), and failure (1.9 ± 0.7) in the 15-trial active avoidance test in the control group were recorded. The administration of APO at dosage of 0.05 mg/kg 30 min before the active avoidance test didn't affect the rats' performance. Whereas, APO at the dosage of 0.5 mg/kg had a trend of enhancement on the avoidance behavior (2.1 ± 0.5), $P = 0.09$ compared to the control group. However, when the dose used was higher, 1 and 5 mg/kg, APO aggravated the behavioral performance, attenuating the escape behavior but facilitating the failure behavior ($P < 0.01$) in the escapable environment. The pretreatment of SUL (5 mg/kg), 10 min before 1 mg/kg of APO, facilitated the failure behavior, $P < 0.05$ compared to the control group (Fig. 1).

Discussion

Behavioral test following the pharmacological manipulation provides data to evaluate the function of dopaminergic system in affective disorders because this system modulates the motivational and emotional behavior. General motor function in novel environment of rats used in the present study was not different between groups. The administration of APO at 0.5 mg/kg had the trend to increase the avoidance behavior of rats that had been subjected to an inescapable stress when encountered an escapable stress. However, when the dose used was higher, 1 and 5 mg/kg, APO aggravated the behavioral performance, attenuating the escape but facilitating the failure behavior in the escapable environment. Pretreatment of SUL, at the dosage of 5 mg/kg, significantly exaggerated the behavioral effects of APO (1 mg/kg). This was similar to the result found after the highest dose of APO.

The dosage of drugs used in this study has been reported to increase rather than decrease the locomotor

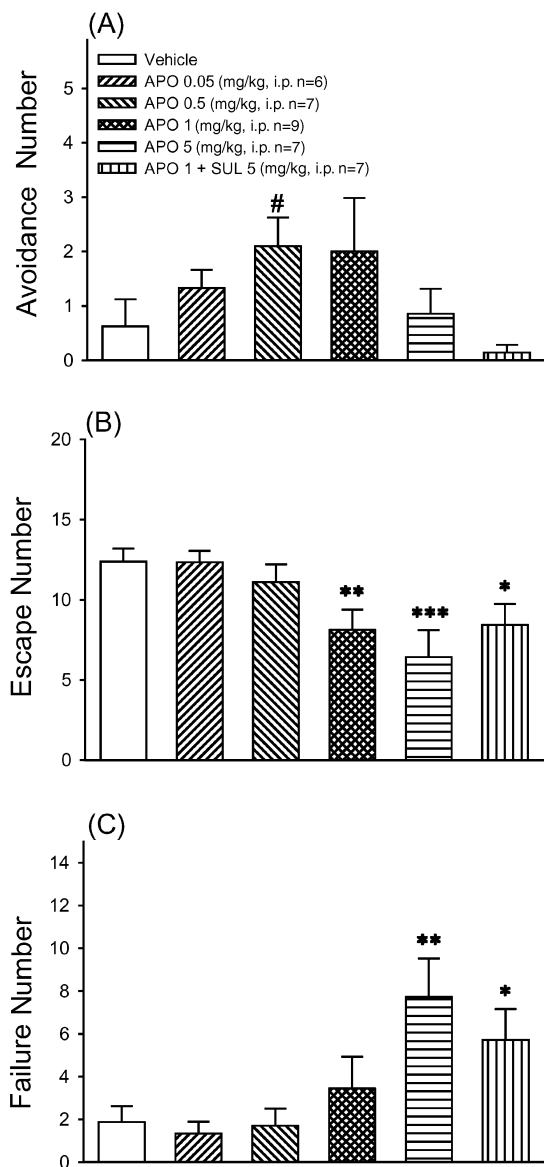


Fig. 1. Effects of apomorphine (APO) on the avoidance (A), escape (B), and failure behavior (C) in learned helplessness task. All the rats received a 10-trial inescapable foot shock stress, 0.5 mA, 10 sec, one day before the experiment. The APO (0, 0.05, 0.5, 1, and 5 mg/kg, i.p.) is administered 30 min before the 15-trial active avoidance test. The sulpiride (SUL; 5 mg/kg, i.p.) is pretreated 10 min before the APO, 1 mg/kg. APO causes a trend of enhancement on the avoidance behavior, at the dosage of 0.5 mg/kg, but attenuates the escape and facilitates the failure behavior at the dosages of 1 and 5 mg/kg. Pretreatment of SUL causes a result similar to that seen after the treatment of highest dose of APO (5 mg/kg). Data are expressed as mean \pm SEM. # $P = 0.09$, * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, compared to vehicle control.

activity of rats. The treatment of APO (0.25 mg/kg, SC) elevated locomotor activity of SD rats from baseline to maximum levels 10 min after the injection,

with the duration of this effect being 30 min (36). After the injection of a higher dose of APO, 1 and 5 mg/kg, similar results have also been observed, with the duration of locomotor stimulation being 45 and longer than 100 min, respectively (2, 27). In addition, when given along, SUL (5-40 mg/kg, i.p.) had no effect on locomotor and exploratory activity (8, 14). Therefore, the drug-induced behavioral changes in the present study could not be due to the impairment of motor function.

Active avoidance test is used to detect the learning acquisition (11). In typical active avoidance procedure, with no day-1 inescapable stress being administered, animals can escape from the aversive stimulus by crossing the adjoining compartment of the testing apparatus. After over a number of trials, the rats learned to make a shuttling response in order to avoid or escape from the electrical stimulation (12). Thus, the animals showed an increasing rate of responding in the presence of the conditioned stimulus and a decrease of the escape latency. Our previous experiment found that, in a 20-trial typical active avoidance test, rats showed successful avoidances upon exposure of the conditioned stimulus in about 40% of trials and escape behavior during shock delivery in about 60% of trials. That is, almost no failure behavior was observed. In addition, the escape latencies of rats decreased gradually across trials and reached an asymptotic level of about 3 sec, as short as the length of conditioned stimulus, indicating that the animals had learned to escape from foot shock (17). Therefore, the number of avoidance and the escape latency in an active avoidance test are suggested to be an index for learning performance. However, in the learned helplessness paradigm, the treatment of day-1 inescapable stress influenced the behavior of rats in the day-2 active avoidance test. Since the inescapable stress used in the present experiment, 10-trial 0.5 mA current, sustained for 10 sec, it was not as strong as what was used in other studies, 40-100 trials (18, 19) 0.8-1.0 mA current sustained for 10-15 sec (3, 4, 19, 23), the rats in the control group of the present study were still able to perform the escape behavior when encountered the aversive electrical stimuli again one day after the inescapable stress. Whereas the day-1 inescapable stress had impaired the coping behavior when the rats was challenged by the aversive stress again. The percentage of avoidance number, 4%, was lower but the percentage of failure number, 13%, was higher in the day-2 15-trial active avoidance test, compared with the results of our previous study using a typical active avoidance procedure (17). Interestingly, pretreatment of APO at the dose of 1 and 5 mg/kg impaired the rats to cope with the foot shock stress and caused the failure behavior in the day-2 session, although the central barrier of the shuttle box was open and the rats had explored the entire

apparatus. It has been reported that the emotional function but not the sensory threshold for electric shock is involved in the behavioral responses of rats in foot shock studies. Our previous study showed that the anxiety level affects the behavioral performance in active avoidance test (17). Borta and Schwarting reported that the emotional but not pain procession determine the behavior in the inhibitory avoidance test (5). The elongation of escape latency and the failure behavior seen after the drug treatment may not be correlated to the changes of the perception or pain threshold of rats because the intraperitoneal administration of APO, 1-10 mg/kg, has been demonstrated having no effect on tail-flick latency (13), and the struggling and vocalization of rats were observed during the foot shock.

Anxiolytics are able to increase the avoidance behavior (10). Our previous work found that the rats with low anxiety level learned to avoid the foot shock in the active avoidance test quicker than the high anxiety rats (17). This is consistent with the observation that anxiolytic manipulations can improve active avoidance performance (9, 29). Therefore, lowering the anxiety level may underlie the mechanisms by which the APO at low dose enhances the avoidance number, and vice versa. This view is supported by the finding that APO has anxiolytic action at low dose, but the dose-response curve was biphasic, inversely U-shaped, indicating an anxiogenic effect at higher dose (15).

APO activates both D1 and D2 receptor when administered at high dose but mainly stimulates the dopaminergic autoreceptor when given at low dose (21), causing an inhibition of dopaminergic functions. It may explain the biphasic effects of APO on learned helpless behavior displayed in the present study, which increased the avoidance at 0.5 mg/kg but facilitated the failure at higher dose. These results are consistent with a previous report in which the avoidance was enhanced at 0.5 mg/kg but no effect was found at 2 mg/kg (34). Pretreatment of SUL may block the autoreceptor action of low dose of APO and result in an augmentation of dopaminergic activity, hence causing the results similar to that observed after the high dose of APO. Furthermore, it has been reported that the density of D1 receptor is significantly higher in the nucleus accumbens and striatum of rats that did not become helpless after stress, compared to rats that developed learned helplessness (20). Because the up-regulation of D1 receptor may refer to the lower transmission of dopaminergic system, it suggests that lower activity of this system may be associated with adaptive or protective role in the prevention of escape deficits after exposure to inescapable stress. These results provide new insights into the possible role of dopaminergic activity in the coping behavior or learning ability in the stress.

Chronic inescapable stress is able to cause the learned helplessness, that is, the active avoidance behavior is reduced but the passive despair behavior is increased when the rat that had faced the chronic stress encounters the stress challenge again. Such behavioral changes are compatible with the psychological dynamics seen in the depressive disorders (35). Clinical studies have shown that stressful experiences can trigger attacks of depression in already depressed individuals. For example, Brown found that over 84% of a large sample of patients seeking treatment for depression had experienced severe stress in the preceding years (6). Neurological evidence demonstrates that inescapable stress-induced behavioral despair is reversed by anxiolytic treatment (24). In addition, inescapable stress decreases the density of D1 receptors in the limbic system where the motivation and emotional behaviors are mediated (20). This evidence indicates that the results from learned helplessness paradigm provide data to evaluate the dynamic changes of neuronal and behavioral function in affective disorders (1).

The dopaminergic system is suggested to be the neural substrate for defensive behavior. It may contribute to generation and elaboration of defensive behavior in response to threat or danger. The involvement of dopamine in the stress response has been evidenced by using the electrical stimulation of the inferior colliculus, a midbrain structure primarily integrating sensory information of aversive nature, at the escape threshold, producing a long-lasting increase in the levels of dopamine in the brain (7). As the above description, the intensity and duration of the inescapable stress used in the current study may not be strong enough to elicit the learned helplessness. However, when the dosage used was larger than 0.5 mg/kg, APO facilitated the failure but decreased the avoidance behavior. Pretreatment of SUL, at the dosage of 5 mg/kg that did not affect the locomotion of rats *per se* (14), significantly exaggerated the failure behavior, similar to the result found after the highest dose of APO. SUL is a selective blockade of D2 receptor (25). It can increase dopamine turnover, enhance the neural firing, dopamine synthesis and release in dopaminergic regions of the rat brain (33). Hence, it is suggested that excessive activation of D1 receptor by high dose of APO may involve in the learned helpless behavior after the inescapable stress. On the other hand, D2 receptor may play a role in the coping behavior, for example, avoidance, in the stress environment. Using the microinjection or microdialysis to deliver selective drugs into a specific brain region is helpful to further elucidate the role of dopaminergic system in the development of learned helplessness because APO affects several DA pathways, and the functions of both presynaptic and postsynaptic D2 receptors need to be considered.

Acknowledgements

This work was supported by grants from the National Science Council of the ROC (NSC 93-2320-B-040-015), the Chung Shan Medical University (CSMU 93-OM-B-001; CSMU 93-OM-A-011), and the Chang-Hua Christian Hospital (C950006).

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