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Repeated administration of the dopaminergic agonist apomorphine: development of apomorphine aggressiveness and changes in the interaction between dopamine D_2 receptors and G-proteins

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Abstract:
The repeated administration of dopamine receptor agonists produces a progressive increase in the acute behavioral effects of these drugs, known as behavioral sensitization. These includes the development of impulsive aggressive behavior after repeated small doses of apomorphine. The aim of this investigation was to study the behavioral specificity of the apomorphine-induced aggressiveness model and its possible relationship with changes in the D_2 receptor-G-protein interaction. Apomorphine (1 mg/kg, *sc*) was administered daily for three weeks to two groups of male Wistar rats. One of the groups was repeatedly tested for the development of aggressiveness. Apomorphine aggressiveness developed stepwise with repeated behavioral testing. Neither apomorphine-treated group displayed any behavioral change in the open field test, forced swimming test, or quipazine-induced wet-dog shake response test. Three weeks of apomorphine administration in the home cage increased the GDP binding affinity and reduced the [^{35}S]GTPγS binding in striatal membranes, but this effect was not present in apomorphine-treated rats that had developed aggressiveness. In conclusion, sensitization to apomorphine, as measured by the expression of aggressiveness, developed only with accumulating apomorphine-induced fighting, was behaviorally specific, and appeared to be dependent on the D_2 receptor-G-protein interaction. The absence of sensitization to the dopaminergic stimulation may be mediated by the downregulation of D_2 receptor sensitivity *via* changes in the GDP affinity of G-proteins.

Key words:
apomorphine-induced aggressiveness, quipazine-induced wet-dog shakes, forced swimming test, open field test, [^{35}S]GTPγS binding

Introduction

The repeated administration of direct or indirect dopamine receptor agonists produces a progressive increase in the acute behavioral effects of drugs, an effect known as behavioral sensitization [15, 20]. Behavioral sensitization can be manifested in a number of ways, including complex behaviors such as the expression of aggressiveness, which is induced by repeated small doses of apomorphine. Although the phenomenon of apomorphine-induced aggressive behavior in rats has been known for over two decades, its neurobiology is still unclear. Evidence indicates the involvement of the mesocorticolimbic dopamine system [15]. Rowlett et al. [34, 35] reported that basal dopamine synthesis was enhanced and that changes in dopamine metabolism were induced by repeated apomorphine treatment. Another obvious mechanism in the development of sensitization to dopamine agonists is dopamine receptor stimulation [16, 19, 27], suggesting that repeated treatment with agonists results in persistent changes at the dopamine receptor level. In addition, Mattingly et al. [21, 23] demonstrated that the development of behavioral sensitization to apomorphine appears to require repeated stimulation of D_1 receptors. However, the findings have been contradictory with regards to the D_2 receptors. The repeated administration of cocaine leads to the marked subsensitivity of D_2 autoreceptors [11, 18] and an increase of the basal activity of the ventral tegmental area dopamine neuron population [11]. Matto and Allikmets [24] reported that apomorphine-induced aggressive male rats have higher [^{3}H]raclopride-binding to dopamine D_2 receptors in the striatum. However, in other works, the repeated administration of dopamine agonists did not change the parameters of striatal dopamine D_2 receptors in mice and rats [13, 17, 30]. Furthemore, repeated apomorphine treatment has been found to cause behavioral supersensitivity in association with reduced dopamine D_2 receptor binding in striatum as measured by [^{3}H]haloperidol [5]. G-protein coupling has been proposed to play an important role in the development of dopamine supersensitivity [38], but its role in apomorphine aggressiveness is not known.

Herein, we studied whether the repeated administration of small doses of apomorphine and the development of apomorphine aggressiveness are associated with changes in D_2 receptor-mediated signal transduction. We also investigated whether behavioral changes after repeated apomorphine treatment are associated with differences in locomotor activity.

Therefore, the aim of present study was to characterize the apomorphine-induced aggressiveness model with other behavioral measures to investigate its behavioral specificity.

Materials and Methods

Animals

Adult male Wistar rats (from Kuopio National Animal Center, Kuopio, Finland) weighing 400–500 g were used in all of the experiments. At the time of the behavioral tests, the animals were about 8 months old (± 2 weeks). Animals were single-housed under standard laboratory conditions (water and food were available *ad libitum*, temperature 20 ± 2°C and lights on from 8:00–20:00 h). There were 10–12 animals in the drug treatment group, and 4 rats used for the binding studies. The experimental protocol was approved by the Ethics Committee of the University of Tartu.

Drugs

Apomorphine (1 mg/kg) (Reakhim, Krasnoyarsk, Russian Federation) was dissolved in distilled water containing 0.01% L-ascorbic acid and stored as a stock solution at +4°C. Immediately before an experiment, the apomorphine stock solution was diluted with distilled water and injected (1 mg/kg *sc*, once daily). Quipazine maleate (2.5 mg/kg *ip*) was from RBI Chemicals, Natick, MA, USA. Guanosine-5'-(γ-thio)-triphosphate ([^{35}S]GTPγS) was purchased from Perkin Elmer Life Sciences, USA, and guanosine diphosphate sodium salt (GDP), (+)-butaclamol hydrochloride and 3-hydroxytyramine hydrochloride (dopamine) were from Sigma-Aldrich Fine Chemicals, USA.

Apomorphine-induced aggressiveness test

The apomorphine-induced aggressiveness study was performed as described previously [29]. Experimentally naive (n = 33) animals were singly placed into standard polycarbonate, semitransparent cages held in stainless steel racks, and on the next day the apomorphine treatment was started. After an injection, the animals were either immediately tested for aggres-

siveness as described below or returned to the home cage. The same animal pairs were used throughout the experiment and were always picked from neighboring cages. The apomorphine treatment lasted for three weeks during which the aggressiveness was scored four times.

The aggressive behavior was measured in cages (35 × 35 × 55 cm, length × width × height) with transparent plastic sidewalls and a stainless steel floor, which was covered with wood shavings. Immediately after apomorphine injection, rats were placed pairwise in the test cage and observed from the time of the latency to the first aggressive posture or the first attack. The intensity of the aggressiveness was also monitored. The animals were observed for 15 min, and the intensity of aggressiveness was scored on a 0–3 point scale (modified from [1]): 0 – no aggressive manifestations; 1 – intermittent mild aggressive posture or attack of the other rat, no vocalizations; 2 – intermittent intensive upright aggressive posture or attack or boxing with the other rat, vocalizations, but no biting or continuous fighting; 3 – continuous fighting or attempts to bite the opponent rat, loud vocalizations. When the rats developed of the highest level of aggressiveness, the test was immediately terminated to avoid injuries.

To compare the effect of the chronic apomorphine treatment, the animals were divided into three groups. The effect of the repeated vehicle (1 ml/kg) and apomorphine treatment on the development of aggressiveness was measured on the 3rd, 6th, 9th, and 12th days. To assess the apomorphine treatment in the home cage group, aggressive behavior was measured once on the 12th day.

The other behavioral measures were recorded 24 h after the end of the apomorphine-induced aggressiveness tests, and there was one test per day (on the 13th, 14th, 15th, and 16th days). Apomorphine was administered after the behavioral test. The same animals were used to study the behavioral measures as in the apomorphine-induced aggressiveness test.

Open field test

The open field was a 50 × 100 cm metal quadrate arena with 40 cm sidewalls. The surface of the floor was divided into eight squares of equal size. Rats were placed into the center of the arena and observed for four minutes for (1) horizontal (number of line crossings) and (2) vertical activity (number of rears).

Forced swimming test

The forced swimming procedure [28] was carried out as previously described [12]. Briefly, rats (10–12 per group) were placed individually in a vertical glass cylinder (∅ 20 cm; height 40 cm) containing water (25 ± 2°C) with a level high enough to prevent the rats from supporting themselves by their hind legs or tail. In the first session, the rats were forced to swim for 15 min. After this, the rats were dried with laboratory tissues, and the apomorphine groups received their treatment. In the second session, which was 24 h later, the rats were re-exposed to the forced swimming for 5 min. The behavior in the forced swimming test on both days was recorded on videotape. Furthemore, the duration of immobility, swimming and climbing was measured during the first 5 min of the test on both days, based on behavioral categories as described by Page et al. [26] and Detke et al. [9]. A rat was judged to be immobile whenever it remained floating passively in the water in a slightly hunched but upright position, with its head just above the surface. The rat was described to be climbing when it was making active movements with its forepaws in and out of the water, usually directed against the wall. The time spent swimming was recorded when the rat was making active swimming motions that were more than necessary to merely maintain its head above the water (e.g., moving around the cylinder).

Quipazine-induced wet-dog shake test

Head twitches were induced by quipazine, a mixed 5-$HT_{2A/3}$ receptor agonist [41]. Quipazine-induced wet-dog shakes were observed in individual polycarbonate cages (20 × 14 × 20 cm, floor covered with wood shavings). Immediately after the administration of quipazine (2.5 mg/kg, *ip*), the animals were placed into the individual test cage, and the number of wet-dog shakes was observed for 60 min. Latency to the first wet-dog shake was also recorded.

[^{35}S]GTPγS binding assay

Twenty-four hours after the last injection of apomorphine, the animals were decapitated, and the brains were quickly removed and prepared on an ice-cold plate. The brain samples were stored at –80°C until assayed.

For biochemical experiments, the rat striatal membranes were prepared as described previously [19].

Brain tissue samples were homogenized by sonication in 100 vol (ww/v) of ice-cold homogenization buffer (50 mM Tris-HCl, pH 7.4). The membranes were collected by centrifugation at 25,000×g for 20 min at 4°C and washed two times by homogenization and centrifugation. The final pellets were homogenized in 90 vol (ww/v) of the incubation buffer (20 mM K-Hepes, 7 mM $MgCl_2$, 100 mM NaCl, 1 mM EDTA, 1 mM DTT, pH 7.4) and were used directly for binding experiments. Binding of [^{35}S]GTPγS was carried out as previously described [31] with slight modifications. In brief, the membranes (500 μg per tube) were incubated with 0.2 nM [^{35}S]GTPγS and different concentrations of GDP (3 mM – 1 μM) in the presence of 100 μM dopamine or 10 μM butaclamol for 90 min at 30°C, and the reactions were terminated by rapid filtration through GF/B filters using a Brandel cell harvester with three washings of 5 ml of ice-cold washing buffer (20 mM NaK phosphate buffer, 100 mM NaCl, pH 7.4).The radioactivity content of the filters was counted in 5 ml of OptiPhase HiSafe®3 (Wallac Perkin Elmer Life Sciences, Cambridge, UK) scintillation cocktail by a Beckman LS 1800 scintillation counter.

Statistical analysis

All binding data were analyzed by nonlinear least-squares regression analysis using Graph Pad PRISM 4.03 (GraphPad Software, San Diego, USA). The data were subjected to an analysis of variance (ANOVA) and to a Student's *t*-test with data from the development of apomorphine aggressiveness. When a significant drug treatment effect or a pretreatment × drug treatment effect was found, data were further analyzed using a Fisher's LSD test. Probability levels $p < 0.05$ were considered statistically significant.

Results

Development of apomorphine-induced aggressive behavior

The repeated apomorphine treatment gradually induced aggressive behavior as evidenced by the day-by-day shortened time of latency and increased intensity of aggressiveness (Fig. 1). In contrast, aggressive behavior was completely absent in rats that had received apomorphine in their home cage.

Effect of apomorphine treatment on forced swimming and open field behavior

Repeated administration of apomorphine, irrespective of whether aggressiveness developed or not, did not affect either the open field activity or any behaviors in the forced swimming test (data not shown).

Effect of apomorphine treatment on quipazine-induced wet dog shakes

The number of head shakes reached a plateau during the 60 min of observation. Neither of the apomorphine-treated groups differed from the vehicle group (data not shown).

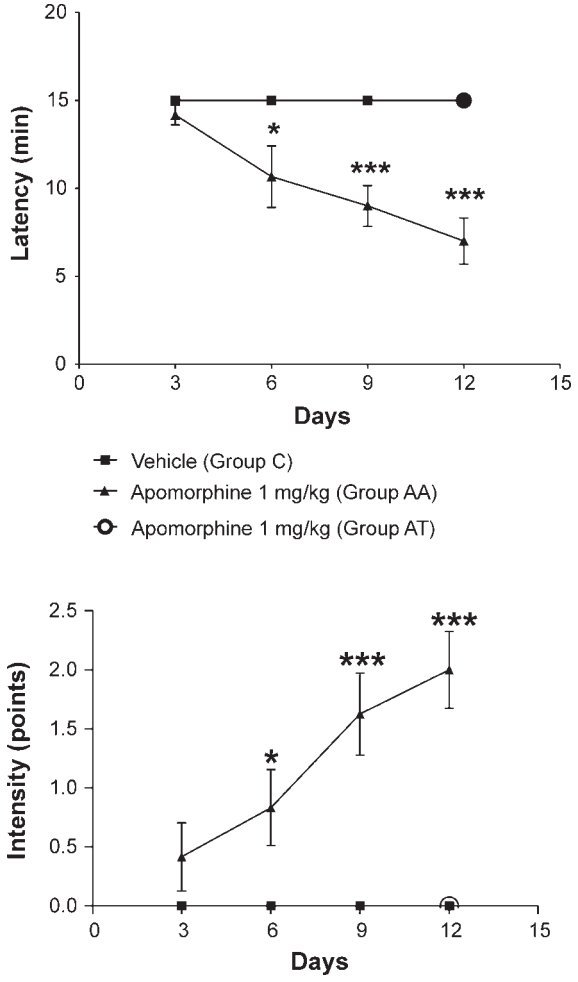

Fig. 1. Effect of repeated apomorphine administration on time of latency and intensity of aggressiveness. C – control animals (■); AT – apomorphine-treated animals (○), AA – apomorphine-aggressive animals (▲). Data expressed as the means ± SEM. * $p < 0.05$, *** $p < 0.001$ *vs.* control (Fischer's LSD test)

Effect of chronic apomorphine treatment on [^{35}S]GTPγS binding

Treatment with apomorphine had an effect on the GDP binding affinity to striatal membranes [$F(2, 10) = 21.6$, $p < 0.001$]. Thus, two weeks of apomorphine administration in the home cage increased the GDP binding affinity, but this effect was not present in apomorphine-treated rats, which had developed aggressiveness. These differences in GDP affinity were detected in the presence of 100 μM dopamine (activated receptors, $\Delta EC_{50} = 0.24$, $n = 4$, $p = 0.0004$) (Fig. 2A) as well as in the presence of 10 μM butaclamol (blocked receptors, $\Delta EC_{50} = 0.27$, $n = 4$, $p = 0.0002$, data not shown graphically). The effect of dopamine receptor activation on the GDP affinity was similar in all groups. In the presence of 100 μM dopamine and 40 μM GDP, lower levels of [^{35}S]GTPγS binding ($\Delta B = 3.5$ fmol/mg tissue, $n = 4$, $p = 0.012$) were found in the striatal membranes of apomorphine-treated rats that did not develop aggressiveness (Fig. 2B).

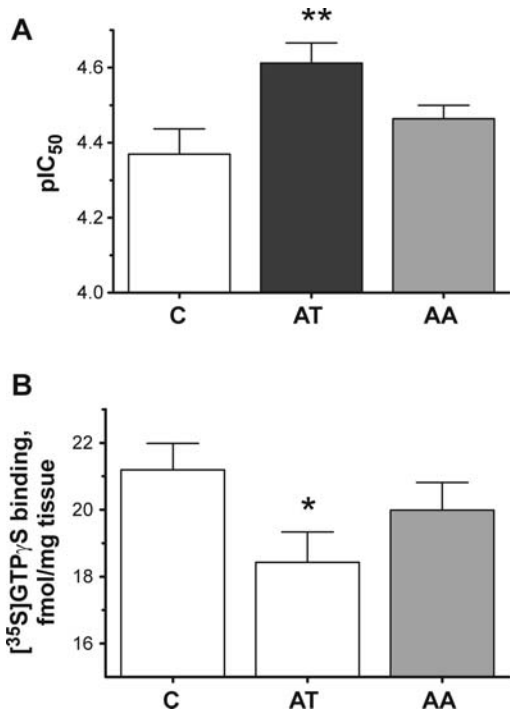

Fig. 2. Effect of chronic apomorphine treatment on the regulation of dopamine-dependent binding of nucleotides. The affinity of GDP **(A)** was measured by its ability to inhibit [^{35}S]GTPγS (0.2 nM) binding in the presence of dopamine (100 μM). The activation of [^{35}S]GTPγS binding at 40 μM GDP **(B)** was determined as the difference of [^{35}S]GTPγS binding in the presence of 100 μM dopamine and 10 μM butaclamol. C – control animals; AT – apomorphine-treated animals, AA – apomorphine-aggressive animals. Data expressed as the means ± SEM. * $p < 0.05$, ** $p < 0.01$ vs. control (Student's *t*-test)

Discussion

The classic Pavlovian conditioning and environmental (contextual) cues seem to play important roles in the development of apomorphine-induced sensitization [4] elicited by a large dose of apomorphine. Apomorphine has been reported to be effective in inducing intraspecific aggression in rats, and the observed level of fighting behavior increased with repeated drug-fight experiences [10]. In the present experiment, repeated apomorphine treatment caused a step-by-step development of aggressiveness, which concurs with previous studies [17, 36, 37]. The apomorphine-induced aggressiveness developed with repeated apomorphine treatment only with fighting experience, which also agrees with prior results [10]. Locomotor sensitization has been demonstrated after repeated treatments with apomorphine [8, 20, 22, 40]. Dopamine receptor agonists enhanced the effects of antidepressants in the forced swimming test [14, 33], and several dopaminomimetic drugs induced the anti-immobility effect in the forced swimming test with a single treatment, which may be due to an increase in general motor activity [6, 39], or, possibly, impulsivity [12]. On the other hand, acute administration of apomorphine reduced the number of wet-dog shakes [3, 7]. In our experiment, repeated apomorphine treatment had no effect in the open field, quipazine-induced wet-dog shakes or forced swimming tests, irrespective of whether the animals had developed aggressiveness or not. In the study of Võikar et al. [42] they found, using the same Wistar rat line, that the changes in the stereotyped behavior as a consequence of repeated apomorphine treatment (0.5 mg/kg) do not correlate with increased locomotor activity. Because increased locomotor activity is one of the most important components, which may precipitate the development of aggressiveness, it should be kept in mind that the changes in the monoamine content found in our previous study [25] are valid only for the "hight apomorphine responders".

The sensitivity of the dopaminergic signal transduction system is also determined by the efficacy of receptors coupled to G-proteins. The affinity of GDP for G-proteins is a key parameter in signal transduction [32], and changes in this may affect the receptor sensitivity. For example, the 6-hydroxydopamine-induced unilateral lesions of the nigrostriatal system, which elicited a prolonged loss of dopamine nerve terminals, caused a decrease in the affinity of GDP for

the G-proteins. It is likely that when the affinity of GDP is lower, fewer receptors are required to activate the same number of G-proteins, thereby causing the higher sensitivity of the receptors [38]. In the present study, the increase in the affinity for GDP appears to reduce the dopamine receptor sensitivity, resulting in lower dopamine-stimulated [^{35}S]GTPγS binding (Fig. 2B). Thus, the chronic administration of the dopamine receptor agonist downregulated the D_2 receptor sensitivity by changing the GDP affinity of G-proteins. Interestingly, this downregulation of sensitivity was not present when the animals had the possibility to fight and had developed aggressiveness. This means that the development of apomorphine aggressiveness is related to the absence of desensitizaton of dopamine D_2 receptors due to the missing changes at the level of G-proteins. What limits the development of this alteration when the animals have the regular fighting experience remains to be elucidated. Interestingly, we observed a similar association in rats preselected on the basis of their exploratory activity and given low doses of amphetamine. In rats that did not develop locomotor sensitization to amphetamine, there was a decrease in D_2 receptor-dependent [^{35}S]GTPγS binding, whereas such a decrease did not occur in rats sensitized to amphetamine [2].

In conclusion, our experiments demonstrate that apomorphine-induced aggressiveness, which develops only with accumulating experience of apomorphine-induced fighting, is unrelated to the sensitivity of 5-HT_2 receptors and is not probably related to a non-specific increase in behavioral reactivity to environmental stimuli. In addition, apomorphine-induced fighting, appears to be dependent on the D_2 receptor-G-protein interaction, and the absence of sensitization to dopaminergic stimulation may be mediated by a downregulation of D_2 receptor sensitivity by changes in the GDP affinity of G-proteins.

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