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Apomorphine produced more yawning in Sprague-Dawley rats than in F344 rats: a pharmacological study

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Abstract

Apomorphine induced yawning in both Sprague-Dawley and F344 rats in the same dose range, but F344 rats emitted only about 1/4 as many yawns as did Sprague-Dawley rats. At higher doses, rats of both strains exhibited stereotypic behavior with a comparable intensity. Pretreatment with either SCH 23390 [*R*(+)-8-chloro-2,3,4,5-tetrahydro-3-methyl-5-phenyl-1*H*-3-benzazepine-7-ol] or pindolol increased apomorphine-induced yawning further in Sprague-Dawley rats, but had little effect on the low yawning score produced by apomorphine in F344 rats. The low yawning response to apomorphine in F344 rats is, therefore, not due to a high baseline dopaminergic or adrenergic activity. Apomorphine-induced yawning in F344 rats was increased after an acute injection of physostigmine, or 24 h after an injection of reserpine. It is postulated that a low baseline cholinergic activity in F344 rats may be responsible, in part, for their lower yawning response to dopaminergic receptor stimulation.

Keywords: Yawning; Sprague-Dawley rat; F344 rat; Dopamine

1. Introduction

The in-bred Fischer 344 (F344) rats have a number of biochemical, neuroendocrine and behavioral differences from other rat strains. Compared to 5 other in-bred strains and the out-bred Sprague-Dawley rats, F344 rats were least active in spontaneous locomotor activity, but had the highest level of tyrosine hydroxylase activity in the midbrain and striatum (Segal et al., 1972). Blaker et al. (1983) reported that F344 rats performed better than four other strains of rats in a shuttlebox conditioned avoidance task. They also found inter-strain differences in acetylcholine concentration and turnover rate in several regions of the brain; but the neurochemical differences did not correlate with the behavioral performance. Several studies compared dopaminergic differences between F344 rats and the Buffalo strain of rats. Apomorphine produced more intense stereotypy in F344 than in Buffalo rats. The former strain also have more dopamine D_2 receptors in the striatum and the olfactory tubercle, and more α_2-adrenoceptors in the frontal cortex than the latter strain (Helmeste et al., 1981). Kerr et al. (1988) also found a higher dopamine D_2 receptor density in the forebrain of F344 than Buffalo rats, but a similar number of dopamine D_1 receptors. Based on brain dopamine receptors and responses to amphetamine, Helmeste and Seeman (1983) suggested that the F344 rat may serve as a model for childhood attention deficit disorder with hyperactivity.

The response of F344 rats to acute and chronic stress has been compared to other rat strains. F344 rats are much more sensitive than Sprague-Dawley rats to foot-shock stress by several neurochemical and behavioral endpoints (Rosecrans et al., 1986). The greater responsiveness of the hypothalamic-pituitary-adrenal axis in the F344 rats was thought to be responsible for their greater resistance to experimentally induced inflammation (Sternberg et al., 1992). To our knowledge, the dopaminergic responses to acute stress in F344 rats have not been specifically compared to other strains.

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In the course of a study on the dopaminergic-induced yawning in rats, we noticed that F344 rats emitted less yawning after a variety of dopamine agonists. Since the yawning response in rats is subject to dopaminergic and cholinergic influences (Yamada and Furukawa, 1980; Urba-Holmgren et al., 1993), this study investigated the pharmacological difference in the yawning response to apomorphine for F344 and Sprague-Dawley rats. Stereotypic chewing and licking were scored for each animal simultaneously.

2. Materials and methods

2.1. Animals

Male rats of the Sprague-Dawley (Hsd:Sprague-Dawley) and Fischer 344 (F344/NHsd) strains were supplied by Harlan Sprague-Dawley, Indianapolis, IN. Each animal weighed between 180–220 g (46–49 days old) upon arrival in the laboratory, and were housed in group cages 1–2 weeks before use in experiments. The ambient lighting in the room was regulated on a 6 a.m.–6 p.m. cycle, and food and water were available at all times. Tests were carried out between 9 a.m. and 3 p.m.

2.2. Experimental procedure

After an s.c. injection of apomorphine, each rat was placed individually in transparent cubicles (15 cm × 15 cm × 15 cm) and observed continuously for the next 30 min. The floor of the cubicle was covered with a piece of corrugated paper. Stereotypic chewing and licking on the floor or wall was scored every 5 min: 2 = continuous licking or chewing, 1 = intermittent licking or chewing, 0 = no licking or chewing. The six observations gave a maximum total score of 12. In addition, the number of yawns was recorded for each 10-min period. Six rats were used for each treatment group, including a control group receiving saline injection. Statistical significance between treatments was estimated using one-way analysis of variance followed by pair-wise comparisons of means (Dunnett's t-test).

2.3. Test drugs

The following compounds (source in parenthesis) were used in this study: apomorphine HCl and physostigmine salicylate (Sigma Chemical Co.), (+)SCH 23390 HCl, (±)-pindolol, and reserpine (Research Biochemicals International). Apomorphine, SCH 23390, and physostigmine were dissolved in saline and injected s.c., while pindolol and reserpine were suspended in 0.25% methylcellulose and injected i.p. The volume of injection was always 1 ml/kg body weight.

3. Results

3.1. Yawning and stereotypy produced by apomorphine in Sprague-Dawley and F344 rats

Apomorphine injected s.c. at doses between 0.01 and 0.1 mg/kg induced yawning in both F344 and Sprague-Dawley rats with an inverted U-shaped dose-response relationship (Fig. 1). At doses higher than 0.1 mg/kg, there was an increasing intensity of chewing and licking. The dose-response relationships for yawning and stereotypy were similar for the two strains of rats, except that the maximum instance of yawning in the F344 rats was only about 1/4 of that in the Sprague-Dawley rats.

3.2. Antagonism of stereotypy by SCH 23390 in both Sprague-Dawley and F344 rats; and potentiation of yawning in Sprague-Dawley rats only

Since the dopamine D_1 receptor agonist, SKF 38393, suppressed apomorphine-induced yawning in Sprague-Dawley rats (data not shown), the dopamine D_1-selective antagonist, SCH 23390, was tested for enhancement of yawning in both strains of rat. A low dose (0.01 mg/kg) of SCH 23390 partially antagonized stereotypy, and more than doubled the number of yawns in the

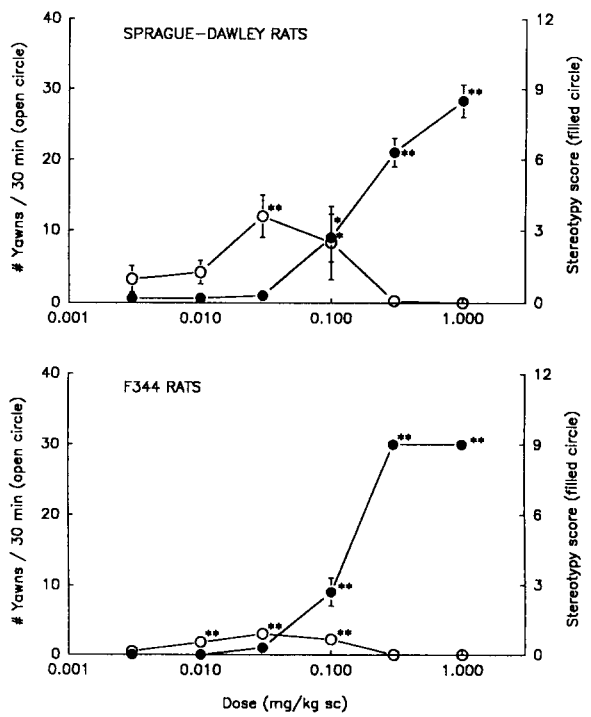

Fig. 1. Yawning and stereotypy produced by apomorphine in Sprague-Dawley and F344 rats. Means (±S.E.M.) are represented for six rats per dose group. $^{**}P < 0.01$; $^{*}P < 0.05$; as compared to a parallel saline-treated control group, which has an average yawning or stereotypy score of less than 1.0 (data not shown).

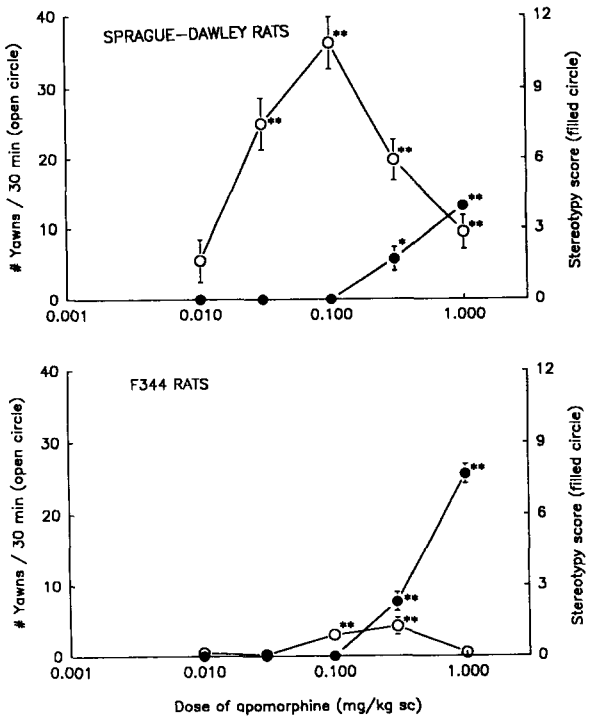

Fig. 2. Pretreatment with a low dose (0.01 mg/kg s.c.) of SCH 23390 30 min before injections of apomrophine reduced stereotypy in both Sprague-Dawley and F344 rats and potentiated yawning in Sprague-Dawley rats. $^{**}P < 0.01$; $^{*}P < 0.05$; compared to saline control group.

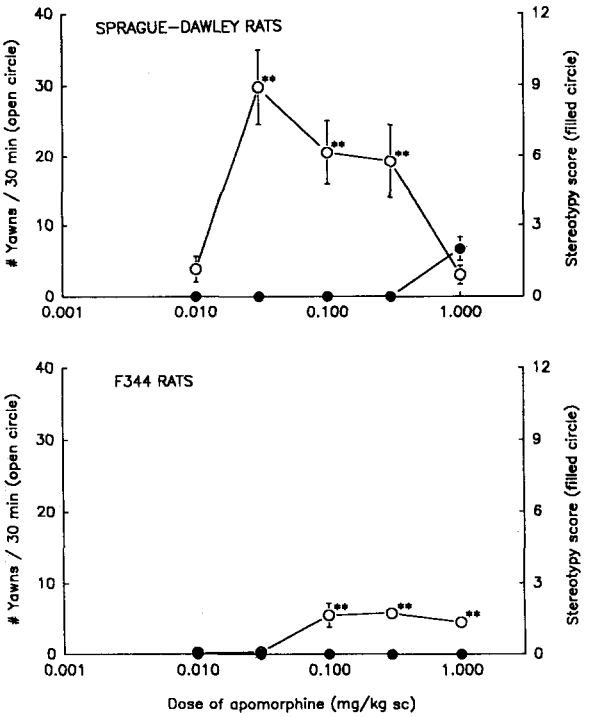

Fig. 3. Pretreatment with a high dose (0.1 mg/kg s.c.) of SCH 23390 30 min before injections of apomorphine abolished stereotypy in both Sprague-Dawley and F344 rats and potentiated yawning only in Sprague-Dawley rats. $^{**}P < 0.01$; $^{*}P < 0.05$; compared to saline control group.

Sprague-Dawley rats (Fig. 2). The optimal dose for yawning was shifted from 0.03 to 0.1 mg/kg. In the F344 rats, there was also a shift of the optimal dose to the right, but the maximum response was not changed. With a higher dose (0.1 mg/kg) of SCH 23390, apomorphine-induced stereotypy was almost completely abolished in both strains (Fig. 3). With this pretreatment, the potentiation of apomorphine-induced yawning persisted in the Sprague-Dawley rats, while there was still no significant increase of maximum yawning in F344 rats.

3.3. Potentiation of yawning by pindolol in Sprague-Dawley rats only

Yamada et al. (1989) reported that β-adrenoceptor antagonists potentiated yawning induced by dopaminergic or cholinergic agonists. Pretreatment with (±)-pindolol (20 mg/kg) potentiated yawning in Sprague-Dawley rats, with no change in the stereotypic behavior (Fig. 4). The potentiation is, therefore, different from that with SCH 23390. On the other hand, a similar pretreatment with pindolol had absolutely no effect on either yawning or stereotypy in the F344 rats.

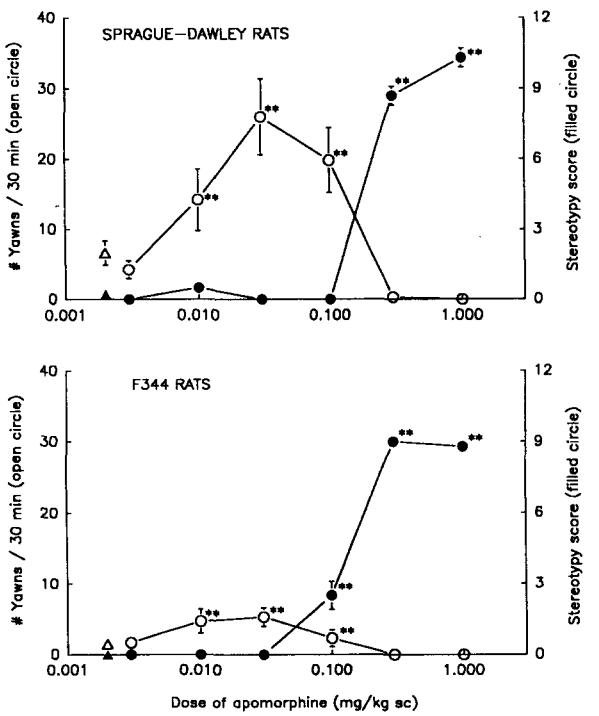

Fig. 4. Pretreatment with pindolol (20 mg/kg i.p.) 30 min before injections of apomorphine potentiated yawning in Sprague-Dawley rats, with no change in stereotypy. Open and filled triangles represent animals with pindolol pretreatment only. $^{**}P < 0.01$; $^{*}P < 0.05$; compared to saline control group.

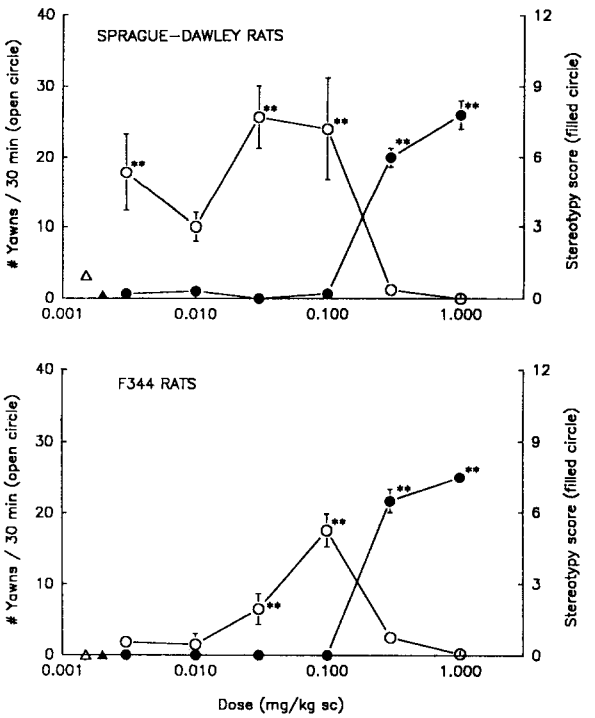

Fig. 5. Pretreatment with reserpine (5 mg/kg i.p., −24 h) potentiated apomorphine-induced yawning in F344 rats. Open and filled trianalges represent animals treated with reserpine only. $^{**}P < 0.01$; $^{*}P < 0.05$; compared to the saline control group.

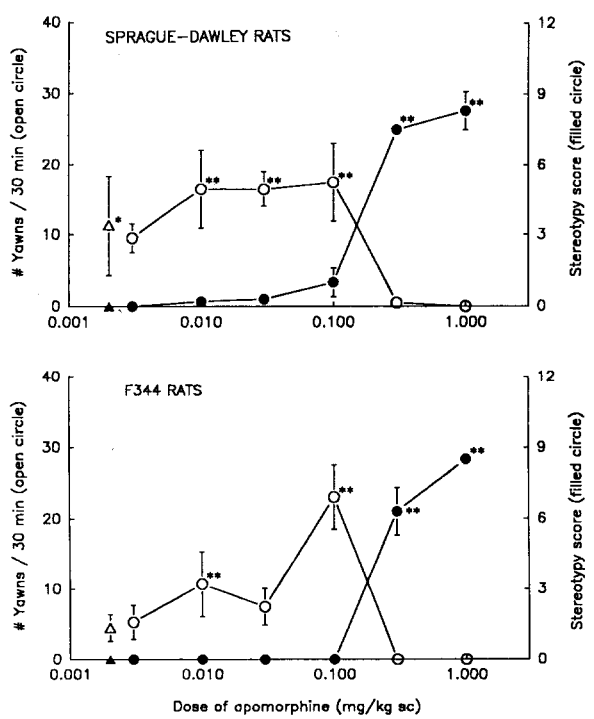

Fig. 6. An additional injection of physostigmine (0.2 mg/kg i.p.) at the time of apomorphine increased spontaneous yawning and potentiated the effects of apomorphine in F344 rats. Open and filled triangles represent animals with physostigmine injection only. $^{**}P < 0.01$; $^{*}P < 0.05$; compared to saline control group.

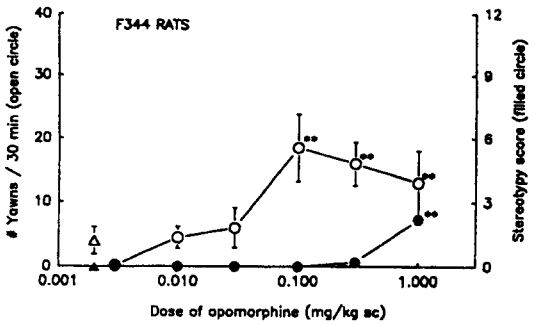

Fig. 7. Pretreatment with SCH 23390 (0.01 mg/kg s.c., −30 min) and physostigmine (0.2 mg/kg i.p.) antagonized stereotypy and potentiated yawning from apomorphine in F344 rats. Open and filled triangles represent animals treated with (SCH 23390 + physostigmine). $^{**}P < 0.01$; $^{*}P < 0.05$; compared to a saline-treated group.

3.4. Potentiation of yawning by 24-h reserpine pretreatment in F344 rats

Pretreatment of Sprague-Dawley rats with reserpine resulted in no spontaneous yawning 24 h later, but greatly potentiated the apomorphine-induced yawning (Fig. 5). Unlike pretreatment with SCH 23390, the potentiation was not accompanied by suppression of stereotypy. A similar reserpine treatment in F344 rats also did not affect apomorphine-induced stereotypy, but potentiated the yawning response.

3.5. Potentiation of yawning by physostigmine in F344 rats

An acute injection of physostigmine (0.2 mg/kg) induced significant yawning in the Sprague-Dawley rats (Fig. 6). The pretreatment had only a slight additive effect on apomorphine-induced yawning in this strain of rat. The same dose of physostigmine by itself did not produce yawning in F344 rats, but did potentiate apomorphine-induced yawning to an extent comparable to that in Sprague-Dawley rats and more than that from pretreatment with SCH 23390 or pindolol. We also tested the combined pretreatment of SCH 23390 and physostigmine in this strain. Although the addition of SCH 23390 blocked the apomorphine-induced stereotypy, maximum yawning was not further enhanced in the physostigmine-pretreated F344 rats (Fig. 7).

4. Discussion

Apomorphine induced yawning in rats with a inverted bell-shape dose-response relationship. In the male Sprague-Dawley rats, apomorphine at the optimal dose induced about 12 yawns during the 30 min post-injection period. This is similar to that reported by other investigators using this strain of rats (Serra et al.,

1987; Urba-Holmgren et al., 1993). In male Wistar rats, the best dose of apomorphine produced from 6 to 15 yawns (Yamada et al., 1989; Protais et al., 1983). Male F344 rats, in contrast, respond to apomorphine with about three yawns at the optimal dose. We are therefore interested in the biological differences involved with this dopaminergic response.

In rats, dopamine receptor agonist-induced yawning appears to be incompatible with stereotypic movements, with the former being suppressed when doses are sufficiently high to induce sniffing (Protais et al., 1983). Helmeste et al. (1981) reported that apomorphine produced slightly more stereotypy in F344 rats than the Buffalo strain of rat. In this study, we found little difference in the potency of apomorphine to induce stereotypy between F344 and Sprague-Dawley rats. Selective D_2-receptor agonists, such as quinpirole (unpublished observation), talipexole and SND 919 (Yamada et al., 1990), induced yawning in rats with a bell-shaped dose-response relationship similar to apomorphine, although no stereotypy was observed in high doses. It appears that factors other than stereotypy account for the low yawning response to apomorphine in F344 rats.

In the Sprague-Dawley rats, apomorphine-induced yawning was enhanced by blockade of dopamine D_1 receptors by SCH 23390. Our result is similar to that reported by Zarrindast and Poursoltan (1989), but opposite to that of Serra et al. (1987), who also used Sprague-Dawley rats in their study. It is noteworthy that blockade of stereotypy by SCH 23390 increased yawning scores without shifting the optimal dose to the left. The potentiation is, therefore, different from receptor supersensitivity which produces a leftward shift of the dose-response relationship. If D_1 receptor activation has a dampening effect on yawning, at least in our experiments with Sprague-Dawley rats, the lower yawning response to apomorphine in F344 rats could be due to a higher baseline D_1 activation. This did not seem to be the case as pretreatment with SCH 23390 did not release additional yawning in F344 rats as it did in Sprague-Dawley rats. However, the effective doses to elicit yawning in F344 rats extended to a higher level as stereotypy was antagonized by SCH 23390.

Yamada et al. (1989) reported that apomorphine-induced yawning in Wistar rats was potentiated by centrally active β-adrenoceptor blockers and inhibited by β-adrenoceptor agonists. We have confirmed the above finding in Sprague-Dawley rats that pindolol potentiated apomorphine-induced yawning with no effect on stereotypy. The same treatment with pindolol, however, did not potentiate apomorphine-induced yawning in F344 rats. The low yawning response in F344 rats is probably not due to a high tonic activity of central adrenergic mechanism.

A central muscarinic mechanism of yawning in rats has been proposed by Urba-Holmgren et al. (1977) in that physostigmine and pilocarpine induced yawning which was antagonized by scopolamine. Scopolamine also completely antagonized apomorphine-induced yawning (Yamada and Furukawa, 1980). We found that physostigmine potentiated yawning induced by apomorphine in F344 rats to a degree not seen with pretreatment with SCH 23390 or pindolol. Physostigmine induced some spontaneous yawning in Sprague-Dawley rats, with only a slight additive effect on apomorphine. The results are consistent with the existence of a cholinergic link in the dopamine agonist-induced yawning response for both strains of rats. A lower cholinergic tone in F344 rats may account for its normally lower yawning score produced by apomorphine. The potentiation of yawning after reserpine in F344 rats can also be interpreted in terms of increased cholinergic activities when central catecholamines are depleted. The potentiation of yawning after reserpine also did not change the optimal dose of apomorphine. A difference in cholinergic tone alone, however, cannot account for the low yawning response in F344 rats since a combined treatment of physostigmine, SCH 23390 and apomorphine in the F344 rats still did not elicit the maximal yawning as elicited in Sprague-Dawley rats after D_1-receptor blockade. Apomorphine-induced yawning can be powerfully influenced by sex and pituitary hormones (Berendsen and Nickolson, 1981; Serra et al., 1983). A difference in endocrine functions should be investigated.

In summary, the weaker yawning response to apomorphine in F344 rats appeared unrelated to a greater propensity for stereotypy. Increasing cholinergic tone can potentiate the apomorphine effect in F344 rats, but does not account for all the differences.

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