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Differential Effects of Selected Dopaminergic Agents on Locomotor Activity in Normotensive and Spontaneously Hypertensive Rats

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HYNES, M. D., D. H. LANGER, D. L. HYMSON, D. V. PEARSON AND R. W. FULLER. *Differential effects of selected dopaminergic agents on locomotor activity in normotensive and spontaneously hypertensive rats.* PHARMACOL BIOCHEM BEHAV **23**(3) 445–448, 1985.—Spontaneously hypertensive rats (SHR) exhibit a significantly higher level of spontaneous locomotor activity than age-matched normotensive controls (WKY). The direct-acting dopamine agonists, apomorphine and pergolide, produced a biphasic effect on locomotor activity levels in normotensive controls. Low doses of these agonists decreased activity levels, while higher doses of these agonists dramatically stimulated activity. In marked contrast to these results was the effect observed in the SHR, in which these agonists at all doses tested decreased activity. Amphetamine, a dopamine releaser, stimulated activity levels in both the WKY and SHR; however, the magnitude of the increase was somewhat attenuated in the SHR.

Spontaneously hypertensive rats (SHR) Apomorphine Pergolide Amphetamine Locomotor activity Dopamine agonists

SPONTANEOUSLY hypertensive rats (SHR) are extensively utilized in the study of hypertension and its pharmacological treatment. In addition to the hypertension exhibited by these rats, which makes them a useful resource for cardiovascular research, they also show a number of behavioral abnormalities. The SHR exhibit a higher level of spontaneous locomotor activity than age-matched Wistar Kyoto control rats (WKY) [4, 7, 8, 11, 12, 13, 14, 15]. Deficits in conditioned suppression of motor activity [18] and conditioned emotional responses [19] are also observed in the SHR but not the WKY. Abnormal behavior is also observed in SHR in operant tasks [5,19].

In addition to these behavioral differences, a variation in the responses to several drugs has been reported between SHR and WKY. For example, SHR are less susceptible to barbiturate anesthesia [21] and to hypermotility induced by a direct-acting D_2 dopamine agonist [4,7]. Additionally, the hypothermic response to apomorphine and L-dopa is more pronounced in the SHR than in WKY [10]. The present study was undertaken to investigate the responses to several direct-acting dopamine agonists with affinity for both D_1 and D_2 receptors in comparison to the responses elicited by amphetamine, a dopamine releaser.

METHOD

Spontaneously hypertensive rats (SHR) and their age-matched normotensive Wistar Kyoto control rats (WKY) were obtained from Taconic Farms (Germantown, NY). At the time of the study, the rats were 14 to 16 weeks of age and were housed in a controlled-light room with a 12-hour light/dark cycle for at least 24 hours prior to utilization in the experiments. These rats were dosed with vehicle or increasing concentrations of apomorphine, pergolide or amphetamine. Each rat was used only once. Immediately after injection, the rats were placed in activity monitors for a one-hour test period. Locomotor activity was measured by means of an electronic activity monitor (Stoelting Co., Chicago, IL). A radio frequency field was passed through the floor of the activity monitor. An activity count registered each time this radio frequency was interrupted.

The data are expressed as mean number of locomotor activity counts per hour ± the standard error of the mean for 6 to 18 SHR or WKY rats per group. The response to a given dose of test compound in the SHR and WKY rats was determined at the same time. Statistical comparisons between control and treated groups and between SHR and WKY rats were made using the Student's '*t*' test.

Drugs

Pergolide mesylate and apomorphine hydrochloride were provided by Eli Lilly and Company, Indianapolis, IN. Dextro-amphetamine sulfate was purchased from the Sigma Chemical Company, St. Louis, MO. All compounds were

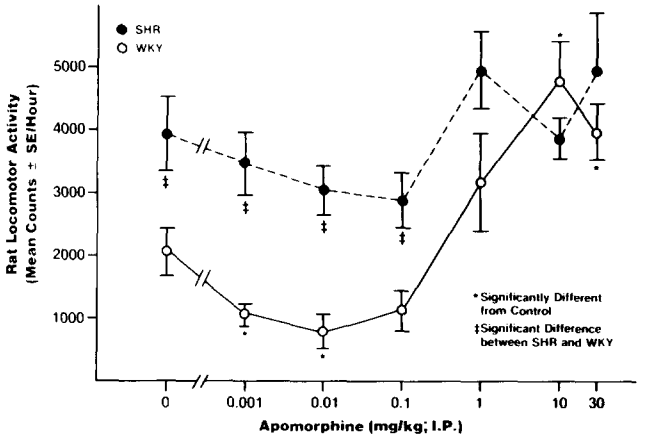

FIG. 1. Dose-dependent changes in locomotor activity after intraperitoneal administration of apomorphine in SHR and WKY.

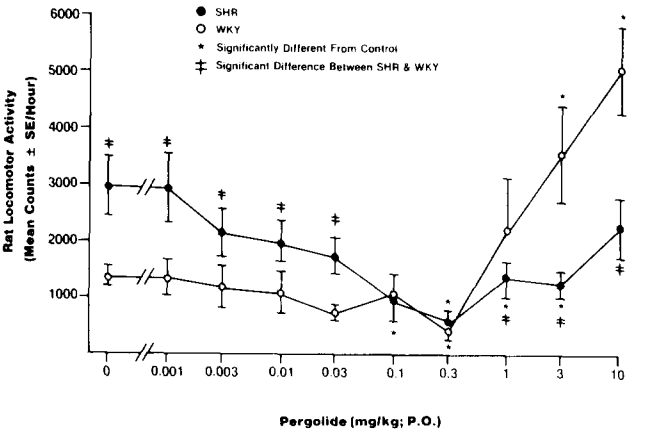

FIG. 2. Dose-dependent changes in locomotor activity after oral administration of pergolide in SHR and WKY.

dissolved in distilled water. Apomorphine was administered by the intraperitoneal route, while pergolide and amphetamine were given orally.

RESULTS

The effect of apomorphine injected intraperitoneally on the level of spontaneous locomotor activity in the SHR and WKY is depicted in Fig. 1. The SHR had a significantly higher level of spontaneous locomotor activity than did age-matched WKY controls. Low doses of apomorphine, 0.001 and 0.1 mg/kg, decreased activity in the WKY. Apomorphine doses greater than 1 mg/kg produced a marked stimulatory effect. In direct contrast to the effects of apomorphine on activity levels in the WKY was the lack of such an increase in the SHR. No significant increase in activity was observed with apomorphine doses as high as 30 mg/kg in SHR.

The data summarized in Fig. 2 show changes in locomotor activity in SHR and WKY following administration of increasing oral doses of pergolide. In the WKY, pergolide significantly decreased activity at 0.3 mg/kg and significantly increased activity at 3 and 10 mg/kg. However in the SHR, pergolide only decreased activity. Significantly reduced activity was observed following 0.1, 0.3, 1 and 3 mg/kg doses of pergolide. Doses as high as 10 mg/kg did not stimulate activity in these hypertensive rats.

The effects of orally administered amphetamine in doses from 0.001 to 10 mg/kg on locomotor activity levels in SHR and WKY are shown in Fig. 3. In the WKY, there was a slight but nonsignificant decrease in activity levels following administration of amphetamine at 0.003 and 0.01 mg/kg. Administration of amphetamine doses in excess of 0.3 mg/kg resulted in a significant increase in activity. The effect of amphetamine in the hyperactive SHR closely paralleled that observed in the WKY. Significant elevations in activity levels were observed when amphetamine was administered in doses of 1, 3 and 10 mg/kg. However, the effect of the 10 mg/kg dose in the SHR was significantly less than observed in the WKY controls.

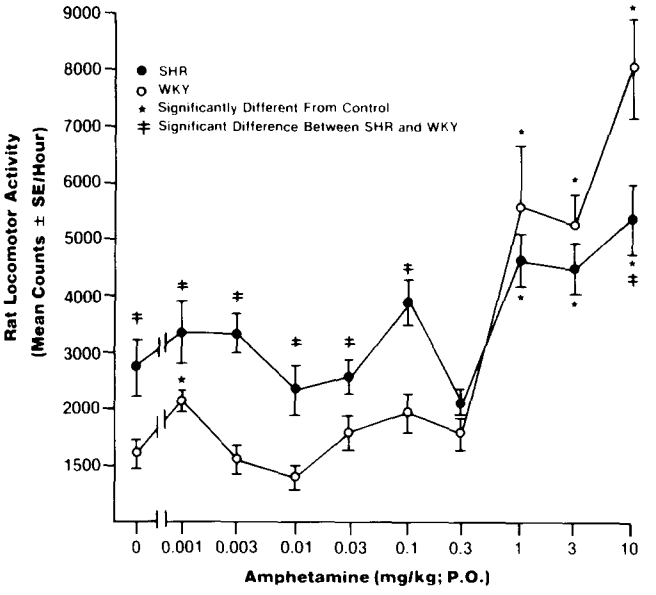

FIG. 3. Dose-dependent changes on locomotor activity after oral administration of amphetamine to SHR and WKY.

DISCUSSION

The increased level of baseline locomotor activity observed in the SHR is in agreement with previous reports [4, 6, 7, 8, 12, 13, 14, 15]. In addition to their high level of spontaneous locomotor activity, these rats showed an altered response to the direct-acting dopamine agonists apomorphine and pergolide. These dopamine agonists produced a biphasic effect on activity levels in the WKY controls. Low doses of these agonists decreased activity levels, while higher doses produced a marked increase. The response of the SHR to apomorphine and pergolide were markedly different from those in WKY, in that at no dose of the agonists tested was an increase in locomotor activity observed. The results with these agonists are in close agreement with those observed after the administration of LY141865, a selective D_2 agonist [4]. In contrast to these findings with direct-acting dopamine agonists were those achieved with amphetamine, a releaser of dopamine. The amphetamine dose-response curve for activity stimulation in SHR was similar to that in WKY, although the magnitude of the response was somewhat attenuated in the SHR.

The reason that direct-acting dopamine agonists do not stimulate locomotor activity levels in the SHR as they do in the WKY is not known. In previous work with LY141865, a selective D_2 agonist which does not stimulate activity in the SHR [4,7], other dopaminergic responses to LY141865 occurred in the SHR as well as WKY. For example, LY141865 decreased striatal and mesolimbic concentrations of 3,4-dihydroxyphenylacetic acid and homovanillic acid, increased striatal and mesolimbic concentrations of acetylcholine, decreased hypothalamic concentrations of epinephrine, increased serum corticosterone concentrations and decreased serum prolactin concentrations in the SHR and WKY [4]. In view of the similarity in these dopamine receptor mediated responses to LY141865, the lack of activity stimulation in the SHR was postulated to be due to an abnormality in some synaptic mechanism beyond the activation of dopamine receptors but before the expression of behavioral hypermotility [4]. One potential location for this abnormality is the globus pallidus, where pharmacologic alterations have been found to modify the expression of hypermotility in response to dopaminergic stimulation in the nucleus accumbens [20]. A physiologic or pathologic change in some other "relay station" in the brain, in addition to or instead of the globus pallidus, is a possibility.

The finding that amphetamine stimulates activity in the SHR to a different extent than in the WKY also suggests an alteration in the brain neuronal systems involved in locomotor activity. This alteration does not appear to affect hypermotility induced by amphetamine to the same extent as that induced by direct-acting agonists. The reason for this difference might be related to the fact that amphetamine, in addition to acting on dopaminergic systems, also releases other neurotransmitters such as norepinephrine, which may stimulate activity levels through systems that do not rely on the "relay station" altered in the SHR.

Interestingly, the profile of activity in the SHR closely parallels that in hyperactive children. An increased level of locomotor activity is observed in hyperactive children [16] as it is in the SHR [4, 6, 7, 8, 12, 13, 14, 15] when they are compared to the age-matched controls. Additionally, they both exhibit the same change in motor activity in response to amphetamine. Normal and hyperactive boys both show a significant decrease in motor activity when dosed with amphetamine [17]. The extent of the decrease was greater in hyperactive than in normal boys. These results suggest that hyperactive children do not have a paradoxical response to amphetamine compared to normal children, nor do SHR compared to WKY controls.

Since the response to higher doses of dopamine agonists such as LY141865, apomorphine and pergolide differs between SHR and WKY, it is difficult to predict whether dopamine agonists would be efficacious in the treatment of hyperactive children. The only clinical studies on the treatment of hyperactive boys with a direct-acting dopamine agonist have utilized piribedil. This study found piribedil not effective in the treatment of hyperactive boys [1]. It is important to note that piribedil's lack of efficacy may be related to the fact that it is not a highly selective dopamine agonist and has effects on other neurotransmitter systems [2,3]. Clinical studies that have attempted to increase brain levels of dopamine by administration of its metabolic precursor, L-dopa, have met with limited success. L-Dopa was found mildly effective for inattention and classroom restlessness in hyperactive boys [9]. The fact that dopamine agonists cause a decrease in activity levels in both SHR and WKY suggests that they should be clinically evaluated in hyperkinetic children. A clinical study of this nature might result in the identification of a better pharmacotherapy for hyperactivity and would also ascertain the role of brain dopamine in this disorder.

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