Pharmacology Biochemistry & Behavior, Vol. 12, pp. 53–59. Printed in the U.S.A.

Differential Behavioral Responses of Spontaneously Hypertensive (SHR) and Normotensive (WKY) Rats to d-Amphetamine[1]

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Received 24 August 1979

McCARTY, R., C. C. CHIUEH AND I. J. KOPIN. *Differential behavioral responses of spontaneously hypertensive (SHR) and normotensive (WKY) rats to d-amphetamine.* PHARMAC. BIOCHEM. BEHAV. 12(1) 53–59, 1980.—A comparison was made in the behavioral responses of spontaneously hypertensive (SHR) and Wistar-Kyoto (WKY) normotensive rats to d-amphetamine. Animals were tested at a young age (6 weeks) to minimize the effects of elevated blood pressure on drug responsiveness. SHR rats were more active than WKY rats after injections of 1.0, 2.0, and 4.0 mg/kg d-amphetamine. A significant strain difference in stereotypy was also noted; rearing occurred in SHR rats while lateral or vertical head movements (head waving) occurred in WKY rats. The lack of significant strain differences in the behavioral responses of rats to apomorphine, a direct acting dopamine agonist, suggested that the differential behavioral responses to d-amphetamine were not a result of differences between strains in receptor sensitivity. Pretreatment of rats with reserpine eliminated the strain differences in behavioral responses to d-amphetamine. Pretreatment of rats with alpha-methyl-p-tyrosine prior to administration of d-amphetamine eliminated the strain differences in stereotyped behavior; however, WKY rats remained less active than SHR rats. Pretreatment of SHR rats with parachlorophenylalanine had no effect on the behavioral responses to d-amphetamine. In contrast, pretreatment of WKY rats with parachlorophenylalanine resulted in an increase in rearing and a decrease in head waving following an injection of d-amphetamine. These findings suggest that the differences in responses to d-amphetamine of SHR and WKY rats are due in part to variations in the activities of central catecholaminergic and serotonergic neurons.

d-Amphetamine Apomorphine Catecholamines Serotonin SHR rat WKY rat Stereotypy Experimental hypertension

NUMEROUS reports have suggested a direct involvement of central monoamine-containing neurons in the development and maintenance of elevated blood pressure in several animal models of human hypertension [7, 8, 11, 16]. The relationship between changes in central adrenergic neurons and increases in arterial blood pressure has been studied intensively in the spontaneously hypertensive (SHR) rat [30, 33, 37, 39, 45, 49].

SHR rats were developed through selective inbreeding by Okamoto and coworkers from normotensive Wistar rats of a Kyoto strain (WKY) which are usually used as the most suitable control for the hypertensive strain [31,32]. The availability of SHR rats has stimulated an impressive volume of research into the pathophysiological alterations which attend the increases in arterial blood pressure with age. This strain is considered by many to be the best available animal model of human essential hypertension [15,54].

In addition to the physiological and metabolic changes which occur in SHR rats during the development and establishment of hypertension, several studies have noted significant differences in the behavior of SHR and WKY rats of various ages. For example, SHR rats are more active than WKY rats when placed into an open field arena [28,52] or a strange cage [27]. SHR rats are also more reactive to inescapable footshock [24] and to the anticipation of footshock [25]. Behavioral differences between SHR and WKY rats have been reported also for avoidance conditioning [46] and operant conditioning paradigms [40,41]. In several instances, the strain differences in behavior are evident prior to, as well as after, the establishment of hypertension. This finding suggests that factors influencing behavior are expressed independently of those regulating blood pressure in the SHR and WKY strains [12, 27, 40].

The influence of monoamine neurotransmission on a variety of behavioral states has been emphasized in several recent reviews [2, 13, 18]. We were interested in examining

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0091-3057/80/010053-07$01.20/0

TABLE 1

A BRIEF DESCRIPTION OF BEHAVIORS NOTED DURING OBSERVATIONS OF SHR AND WKY RATS

Behavior	Description
1. Sleeping-resting	1. Animal in a resting posture with eyes opened or closed
2. Walking-running	2. Animal moving about cage with no evidence of stereotyped activity
3. Rearing	3. Animal standing on hind legs, usually in center of cage
4. Head waving	4. Animal remains stationary with rapid stereotyped movements of the head in a horizontal or vertical plane
5. Sniffing	5. Animal displays rhythmic sniffing of air or objects in cage, usually while stationary
6. Circling	6. Locomotor activity by the animal in a circular pattern
7. Burrowing	7. Coordinated digging of bedding material by the animal
8. Grooming	8. Animal grooms the pelage with the mouth or paws

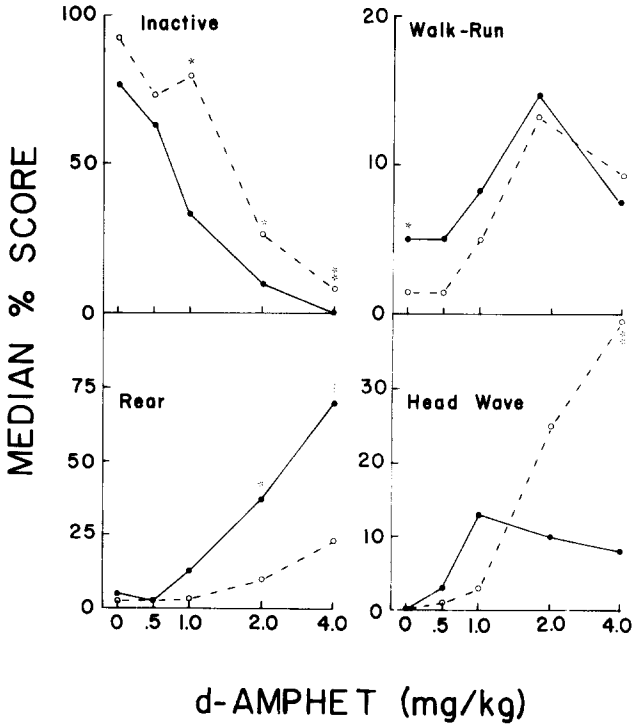

FIG. 1. Effects of various doses of d-amphetamine (d-AMPHET) on the behaviors of SHR (closed circles) and WKY rats (open circles). Values are median percent scores based on a total of 60 observations with 6 animals per group. $*p<0.05$, $**p<0.01$ (Kruskal-Wallis H test) for interstrain comparisons.

the behavioral responses to the central stimulants, d-amphetamine and apormorphine, in SHR and WKY rats. To minimize the influence of hypertension on the behavioral responses to various drugs, we restricted our studies to SHR and WKY rats that were 6 weeks old. At this age, strain differences in blood pressure are less dramatic than in animals several weeks older [26,29].

EXPERIMENT 1

In the first experiment, we examined the behavioral responses of SHR and WKY rats to several doses of d-amphetamine and apomorphine. Using this approach, we compared the dose-response relationships of the two strains to an indirect acting sympathomimetic agent, d-amphetamine [3, 9, 55], and a direct acting dopamine receptor agonist, apomorphine [10].

METHOD

Animals

Spontaneously hypertensive (SHR) and Wistar-Kyoto normotensive (SKY) male rats were obtained from Taconic Farms, Germantown, New York at 5 weeks of age. In our laboratory, animals were housed 4–5 per cage, with food and water available ad lib. The colony room was maintained on a 12-hr light-dark cycle (lights on at 0600) at a room temperature of 23 ± 1°C.

One week after arrival, rats were weighed and returned to their home cages. Each animal then received an intraperitoneal (IP) injection of saline, d-amphetamine sulfate (Smith, Kline and French) or apomorphine hydrochloride (Merck Chemical Company) in a total volume of 2 ml/kg and was placed into a clear plastic cage (24×25×16 cm) that contained a layer of fresh bedding material, food and water. Doses of each drug are expressed as the salt. Mean body weights for SHR and WKY rats at 6 weeks of age were 120 ± 2 g and 122 ± 2 g, respectively.

Procedure

For each replicate of this experiment, a group of 20–24 rats was observed, with equal numbers of each strain and dose of vehicle or drug represented. Behavioral observations began immediately after the last animal of a replicate was injected (less than 10 min). One of us (RM) then recorded the occurrance of 8 different behaviors using a scan sampling technique [1]. A description of each behavior is presented in Table 1. Every 2 min and continuing for 50 min (apomorphine) or 120 min (d-amphetamine), each rat was observed and its behavior at that instant was noted on a check sheet. With few exceptions, the 8 behaviors were mutually exclusive and rarely was an animal observed engaging in more than one of the behaviors simultaneously. All observations were begun between 0900–1400 hrs to minimize diurnal fluctuations in behavior and in drug responsiveness.

Mean arterial blood pressure (MAP, mm Hg) and heart rate (HR, beats/min.) were measured directly in naive SHR and WKY male rats at 6 weeks of age [26]. Briefly, rats were anesthetized with pentobarbital (40–50 mg/kg) and the ventral caudal artery was exposed, dissected free, and cannulated with PE-50 tubing that was filled with heparinized saline (500 U/ml). The end of the tubing was connected to a

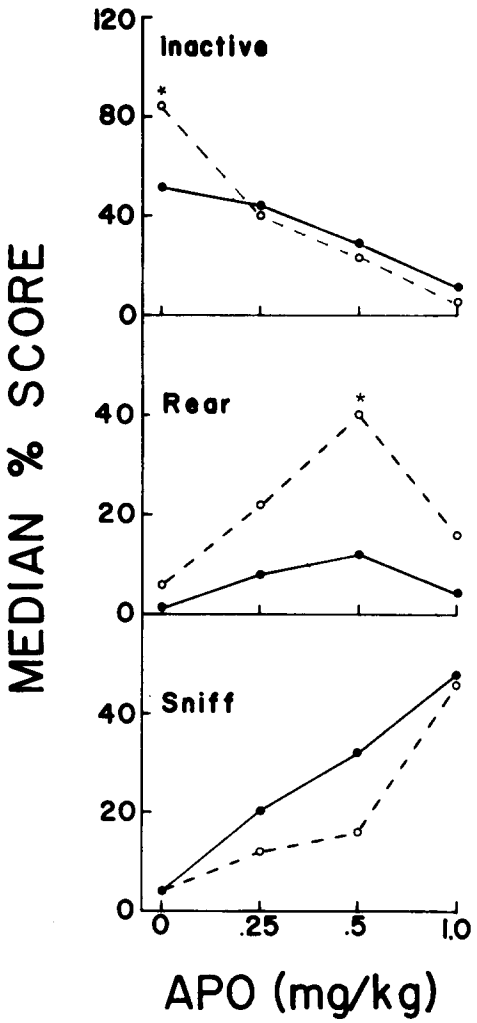

FIG. 2. Effects of various doses of apomorphine (APO) on the behaviors of SHR (closed circles) and WKY rats (open circles). Values are median percent scores based on a total of 25 observations with 6 animals per group. *$p<0.05$ (Kruskal-Wallis H test) for interstrain comparisons.

Statham pressure transducer with tracings made on a Grass polygraph.

The occurrance of each behavior was summed for each animal across all observations and expressed as a percentage of the total number of observations. Median percent scores were then calculated according to a non-parametric Kruskal-Wallis H test [53]. Strain differences in MAP and HR were determined by Student's "t" test.

RESULTS

In a 2-hr observation period following a single injection of d-amphetamine, there was a dose-related decrease in the time spent sleeping or resting by rats of both strains (Fig. 1). SHR rats were more active than WKY rats after injections of 1.0, 2.0, or 4.0 mg/kg d-amphetamine. Basal locomotor activity was greater in SHR rats; however, no strain differences in locomotor activity were observed following an injection of d-amphetamine.

TABLE 2

MEAN ARTERIAL BLOOD PRESSURES (MAP) AND HEART RATES (HR) OF PENTOBARBITAL-ANESTHETIZED SHR AND WKY MALE RATS AT SIX WEEKS OF AGE

	Strain	
	WKY	SHR
MAP (mmHg)	92 ± 3	131 ± 3*
HR (bests/min)	388 ± 9	408 ± 11

Values are means ± SEM for groups of 10 animals.
*$p<0.01$ (two-tailed "t" test).

TABLE 3

BEHAVIORAL RESPONSES TO d-AMPHETAMINE (2 mg/kg) IN SHR AND WKY RATS PRETREATED WITH RESERPINE (2 mg/kg) OR SALINE 16 HR PRIOR TO OBSERVATIONS

Strain	SHR		WKY	
Pretreatment	Saline	Reserpine	Saline	Reserpine
Behavior				
Sleep-rest	0	7*	3	10
Walk-run	5	22†	10	18
Rearing	77	37†	27	40
Sniffing	8	12†	3	12†
Head Waving	8	0†	40	0*

Values are median % scores for 45 observations with n=6 rats per group.
*$p<0.05$, †$p<0.01$ Kruskal-Wallis H test when compared to saline-injected rats of the same strain.

There was a marked strain difference in the pattern of stereotyped behavior following the injection of d-amphetamine. For SHR rats, there was a dose-related increase in the frequency of rearing. For example, rearing was noted for 70% of the observations of SHR rats receiving 4.0 mg/ kg d-amphetamine. In contrast, the frequency of rearing for WKY rats never exceeded 25% of the observations in the 2-hr period after administration of d-amphetamine (Fig. 1).

The most frequent form of stereotypy of WKY rats was head waving, which occurred during 35% of the observations of animals receiving 4.0 mg/kg d-amphetamine. For SHR rats, the frequency of head waving remained below 15% of observations for all doses of the drug (Fig. 1). There were no differences between strains in the responses to d-amphetamine for the following behaviors: burrowing, circling, sniffing, and grooming.

For SHR and WKY rats, there was a dose-related decrease in the time spent inactive following an injection of apomorphine (Fig. 2). In addition, basal levels of activity were greater for SHR rats ($p<0.05$). Thus the increment in activity following apomorphine was greater in WKY rats because their basal level of activity was less than for SHR rats.

In rats of both strains, treatment with apomorphine resulted in increased frequencies of rearing and sniffing with little effects of locomotor activity (Fig. 2). WKY rats reared more than SHR rats at each dose of apomorphine, with the difference at 0.50 mg/kg attaining significance ($p<0.05$).

The MAP of 6 week old SHR rats was significantly higher

TABLE 4

BEHAVIORAL RESPONSES TO d-AMPHETAMINE (2 mg/kg) in SHR AND WKY RATS PRETREATED WITH AMPT-ME (100 mg/kg) OR SALINE 2 HR PRIOR TO OBSERVATIONS

Strain	SHR		WKY	
Pretreatment	Saline	AMPT-ME	SALINE	AMPT-ME
Behavior				
Sleep-rest	4	53*	16	89*
Walk-run	13	7	4	0
Rearing	58	11*	11	2*
Sniffing	9	7	27	4*
Head waving	13	0*	38	0*

Values are median < scores for 45 observations with n=6 rats per group.

*$p<0.01$ Kruskal-Wallis H test when compared to saline-injected rats of the same strain.

TABLE 5

BEHAVIORAL RESPONSES TO d-AMPHETAMINE (2 mg/kg) IN SHR AND WKY RATS PRETREATED WITH PCPA-ME (150 mg/kg) OR SALINE 48 HR AND 24 HR PRIOR TO OBSERVATIONS

Strain	SHR		WKY	
Pretreatment	Saline	PCPA-ME	Saline	PCPA-ME
Behavior				
Sleep-rest	3	3	3	2
Walk-run	3	3	5	10
Rearing	82	92	34	51
Sniffing	3	2	0	10*
Head waving	7	2	57	15*

Values are median < scores for 30 observations with n=6 rats per group.

*$p<0.05$ (Kruskal-Wallis) H test when compared to saline-injected rats of the same strain.

than for age-matched WKY rats as measured directly in anesthetized animals ($p<0.01$). There were no strain differences in heart rate (Table 2).

EXPERIMENT 2

In this experiment, we examined in SHR and WKY rats the contributions of the neurotransmitters, dopamine, norepinephrine, and serotonin to the strain differences in response to d-amphetamine. On the basis of our previous findings, we selected a dose of d-amphetamine (2 mg/kg) which produced a consistent difference between strains in activity and stereotypy.

METHOD

Animals

SHR and WKY rats were obtained and housed as described in Experiment 1. All rats were 6 weeks old at the time of testing.

Procedure

Three drugs which alter the metabolism of brain dopamine, norepinephrine and serotonin were examined for their effects on the behavioral responses of SHR and WKY rats to d-amphetamine. In the first study, rats were pretreated with saline or reserpine (2.0 mg/kg, SC, Sigma) 16 hrs. prior to receiving an injection of d-amphetamine sulfate (2 mg/kg, IP). Behavioral observations were made as described above for 90 min. following an injection of d-amphetamine. In the second study, rats were injected with alpha-methyl-p-tyrosine-methyl ester (AMPT-ME, 100 mg/kg, IP, Sigma), an inhibitor of tyrosine hydroxylase [35], 2 hr prior to receiving an injection of d-amphetamine sulfate (2 mg/kg, IP). Behavioral observations continued for 90 min following the injection. In the final study, rats were pretreated with saline or p-chlorophenylalanine-methyl ester (PCPA-ME, 150 mg/kg, IP, Sigma), an inhibitor of trytophan hydroxylase [20], 48 hr and 24 hr prior to an injection of d-amphetamine (2 mg/kg, IP). Behavioral observations continued for 60 minutes after the injection. Doses of each drug are expressed as the salt.

RESULTS

Pretreatment of rats with reserpine modified several of the components of the behavioral response to an amphetamine challenge, with SHR rats affected to a greater degree than WKY rats (Table 3). In reserpinized SHR rats, after d-amphetamine there was an increased incidence of sleeping-resting, locomotor activity and sniffing and a decreased incidence of stereotyped behaviors (rearing and head waving). Pretreatment of WKY rats with reserpine resulted in an increase in sniffing and complete elimination of head waving elicited by d-amphetamine. In addition, there was an increase in the frequency of rearing in WKY rats pretreated with reserpine: however, the change did not attain statistical significant (Table 3).

In rats pretreated with AMPT-ME, there was also a significant alteration in the behavioral responses to d-amphetamine. SHR and WKY rats pretreated with AMPT-ME spent more time sleeping and resting and less time in stereotyped behaviors (i.e., rearing, sniffing, head waving) following d-amphetamine (Table 4).

There was a significant strain difference in the effects of pretreatment of rats with PCPA-ME on the behavioral responses to d-amphetamine. Pretreatment of SHR rats with PCPA-ME had no effect on the behavior responses to d-amphetamine. In contrast, pretreatment of WKY rats with PCPA-ME resulted in an increase in sniffing and a decrease in head waving in response to d-amphetamine. In addition, there was an increase in rearing in WKY rats which approached, but did not attain statistical significance (Table 5).

DISCUSSION

In the present experiments, we have compared the behavioral responses of SHR and WKY rats to several centrally acting drugs. To minimize the possible interactions between high blood pressure and responsiveness to the various drugs, we chose to restrict our sample to animals 6 weeks of age. In spite of this precaution, we observed that the MAP of 6 week old SHR rats was approximately 40 mmHg higher than age-matched WKY rats. Indeed, there is a significant difference between strains in MAP as early as 3–4 weeks of age [14,29]. It may be argued, however, that the possibility of changes in drug responsiveness attending elevations in arterial pressure

would be greater in animals tested at older ages. In addition, several drugs used in the present study (e.g., reserpine) may indirectly influence the behavioral responses of SHR and WKY rats to d-amphetamine by their actions on the cardiovascular system.

Our findings demonstrate that SHR rats differ significantly from WKY rats in their behavioral responses to d-amphetamine. This strain difference was most dramatic in SHR rats whereas lateral and vertical head movements (head waving) were observed in WKY rats. In contrast, no strain differences in behavior were observed following administration of apomorphine, a direct acting dopamine receptor agonist. These results are consistent with the report of Shimamoto and Nagaoka [43], who noted that the behavioral excitement caused by methamphetamine was greater in SHR rats than in control Wistar rats with regard to peak effect and duration of action of the drug. In addition, SHR rats did not differ from normotensive controls in apomorphine-induced locomotion or stereotypy [23,43].

It was further noted that pretreatment of rats with AMPT-ME, an inhibitor of tyrosine hydroxylase, blocks effectively the locomotor and stereotyped behaviors in response to d-amphetamine. This finding is consistent with other reports which have documented the importance of catecholamine synthesis to the behavioral effects of amphetamine [9,50].

The central actions of d-amphetamine are dependent upon the release of catecholamines from a presynaptic pool [42,50]. Several studies suggest that the release of dopamine is essential for the induction of locomotor activity and stereotypy by d-amphetamine [17, 34, 44]. However, other studies have demonstrated that the behavioral effects of amphetamine result from the release of norepinephrine as well as dopamine [6, 19, 36].

In contrast to the indirect actions of d-amphetamine, apomorphine is a direct acting dopamine receptor agonist [10]. From this information we conclude that the strain differences in behavior following d-amphetamine as reported in Experiment 1 result from a differential effect of the drug on the release of catecholamines from a presynaptic pool. There was no evidence to suggest a difference between SHR and WKY rats in the sensitivity of postsynaptic dopamine receptors.

Differences between SHR and WKY rats in the central metabolism of catecholamines and serotonin may contribute to the differential behavioral responses to d-amphetamine. For example, levels of dopamine-β-hydroxylase and norepinephrine are lower in discrete hypothalamic nuclei of 4 and 14 week old SHR rats when compared to age-matched WKYs [38,39]. In contrast, levels of dopamine in areas of the cortex and brainstem are higher in adult SHR rats than in WKY controls [48]. Furthermore, PNMT activity and epinephrine content of several hypothalamic and brainstem nuclei are elevated in young but not adult SHR rats in comparison to WKYs [37, 39, 51]

In contrast to the extensive studies of brain catecholamine content in SHR rats, relatively less effort has been directed toward examination of the serotonin system in this model of essential hypertension. It was reported that tryptophan hydroxylase activity is elevated in the hypothalamus but not in the thalamus and pons-medulla of SHR rats [30]. Similarly, Takaori *et al.* [47] reported that serotonin concentrations in the telencephalon and brainstem of adults SHRs were greater than in WKY rats and that treatment of rats with PCPA resulted in an increase in blood pressure which persisted for up to 5 days. In addition, there was a decrease in blood pressure with an injection of 5-hydroxytryptophan and this effect was more pronounced in SHRs.

Serotonin has been reported to exert an inhibitory action on the central stimulant effects of amphetamine [4, 5, 21, 22]. In this study, we observed a significant difference between strains in the effect of serotonin depletion by PCPA-ME on the behavioral response to d-amphetamine. Pretreatment with PCPA had no effect on the responses of SHR rats to amphetamine whereas, in WKY rats, there was an increase in sniffing, a decrease in head-waving and a slight increase in rearing and locomotor activity. We conclude from these findings that the brain serotonin system of SHR rats is hypofunctional with regard to its modulation of the central effects of amphetamine.

Recently, a number of studies have reported significant differences in the behavior of SHR and WKY rats. Specifically, SHR rats are behaviorally hyperresponsive to a variety of test procedures, including placement in a novel environment [27] or an open field arena [52], exposure to inescapable footshock [26], instrumental conditioning [41], and avoidance conditioning [46]. The differences between strains in behavior do not appear to be causally linked to factors regulating blood pressure.

In summary, we have demonstrated a greater behavioral response to d-amphetamine in 6 week old SHR rats than WKY rats. This response is influenced by the effects of amphetamine on central catecholaminergic as well as serotonergic neurons. The possible relationship between the central neurochemical alterations attending amphetamine administration and neuronal influences on the cardiovascular system remain to be elucidated.

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