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No Major Differences in Locomotor Responses to Dexamphetamine in High and Low Responders to Novelty: A Study in Wistar Rats

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GINGRAS, M. A. AND, A. R. COOLS. *No major differences in locomotor responses to dexamphetamine in high and low responders to novelty: A study in Wistar rats.* PHARMACOL. BIOCHEM. BEHAV. **57**(4) 857–862, 1997.—The aim of the study was to compare locomotor responses to acute and sub-chronic dexamphetamine in two distinct types of Wistar rats, namely the Nijmegen high responders to novelty (HR) and Nijmegen low responders to novelty (LR). HR and LR were chosen because they differ in neurochemical processes relevant to the control of the locomotor effects of dexamphetamine, such as the dopaminergic and adrenergic activity in the nucleus accumbens. In experiment 1, a dexamphetamine dose-response curve (0.0–2.0 mg/kg/IP) was established using standard activity boxes. The dose-response curve slightly, but significantly, differed between HR and LR: especially the increase elicited by 1.5 mg/kg dexamphetamine was significantly greater in HR than in LR. In experiment 2, locomotor effects of sub-chronic administration of dexamphetamine (1.0 mg/kg/IP) were analyzed in HR and LR for 5 consecutive days. HR showed a higher locomotor response to dexamphetamine than LR; however, the two groups did not differ in their sensitization rate. It is concluded that there are neither major HR-LR differences in the locomotor response to acute administration of various doses of dexamphetamine nor HR-LR differences in the rate of sensitization of this locomotor response to sub-chronic administration of dexamphetamine. Type-specific differences in the mutual interaction between corticosteroids and dexamphetamine as well as the nature of the chosen dependent variable, namely locomotor activity, are hypothesized to underlie the results of the present study. © 1997 Elsevier Science Inc.

Dexamphetamine Individual differences Rats Catecholamines Sensitization Locomotor activity

A LARGE body of evidence suggests that the locomotor stimulating effect of the psychostimulant dexamphetamine can be contributed to changes in the activity of catecholamines. In particular, an increase in the release of catecholamines is thought to mediate the locomotor effect of dexamphetamine.

Weissman and co-workers (64) were among the first to show that inhibition of catecholamine synthesis abolishes the behavioral effect of this drug. Later on, it has been shown that the two major catecholamines, noradrenaline and dopamine, are both involved in mediating the locomotor effect of dexamphetamine. Dexamphetamine increases adrenergic activity (38,62), and dexamphetamine-induced locomotor activity can be blocked by decreasing adrenergic activity or inhibiting α-receptors (18,51). The nucleus accumbens appears to play an important role in this respect (9). Dexamphetamine also induces an increase in the release of dopamine (3,31,35), and dopamine antagonists or lesions of dopaminergic neurons are effective blockers of dexamphetamine-induced locomotor activity (1,4,16); in this case too the nucleus accumbens seems to play an important role (49).

Large individual differences in the behavioral effects of dexamphetamine have been established. In addition, it has been shown that differences in spontaneous drug-independent behaviors can predict differences in the response to dexamphetamine and other psychostimulants (25,32,33,45,46,47,59). The individual locomotor activity in response to a novel environment, for instance, seems to be a good predictor of the degree of self-administration of dexamphetamine (45,46). In general, rats with the highest locomotor response to novelty have been reported to show the highest locomotor response to dexamphetamine (25,32,33).

The possibility to predict individual differences in the locomotor effect of dexamphetamine on the basis of drug-independent behavior suggest that differences in the biological make-

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up of the subjects may be a very important factor in determining their sensitivity to drugs. However, the neurochemical mechanisms determining these individual-specific differences in response to dexamphetamine are largely unknown. Therefore, we investigated the locomotor response to the acute and the repeated injection of dexamphetamine in two fundamentally distinct types of rat that have well characterized differences in their neurochemical make-up. These two distinct types of rat are normally present in unselected, outbred populations of Wistar rats. These rats are labeled Nijmegen high responders to novelty (HR) and Nijmegen low responders to novelty (LR), when they are selected with the help of a special open field procedure from the outbred population of Nijmegen Wistar rats (7,12,13). HR and LR are not tails of the population, but each group (HR and LR) represents a major part (40%–45%) of our outbred strain of rats; the remaining 10%–20% of rats form a heterogeneous group showing a mixture of HR and LR features, of which no details about the behavioral, neurochemical and neuroendocrinological features are known.

HR and LR were chosen because they differ in neurochemical processes relevant to the control of the locomotor effect of dexamphetamine, such as the dopaminergic and adrenergic activities in the nucleus accumbens (7,13,14). Thus, unchallenged HR have a low adrenergic and high dopaminergic activity in the nucleus accumbens, whereas unchallenged LR show the mirror image (14). HR are far more sensitive to pharmacological challenges which stimulate either α-adrenergic or dopaminergic receptors, than LR (8,21). Given the above-mentioned facts, it was therefore of interest to compare Nijmegen HR and LR for their locomotor response to dexamphetamine.

METHODS

Subjects

Eighty-five male Wistar rats, bred and reared in the Central Animal Laboratory of the University of Nijmegen, were selected with the help of the open field procedure described below. Animals were individually housed in standard plastic boxes (40 × 20 cm) and maintained on a 12 h day and night cycle (lights on: 0700-1900). Standard lab chow and water was continuously available.

Selection Procedure

Apparatus. A 160 × 160 cm horizontal flat glass table, 95 cm high and surrounded by a neutral white background, served as open field. Behavior was recorded with a computerized and automated tracking system described by Cools et. al. (7).

Selection procedure. Animals were placed on the open field for a period of 30 min. Ambulation was defined as the overall distance travelled (in cm/30 min); exploratory behavior was defined as the portion of the ambulation behavior which began after the rat was placed on the open field and ended when locomotor activity stopped for a period of 1.5 min. Distance travelled and habituation time were used as criteria to select the two types of rats (7,12). Rats which habituated in less than 480 s and covered less than 4800 cm/30 min were labeled LR. Rats which habituated after a period of 840 s and covered more than 6000 cm/30 min were labeled HR (12). Both variables which have been found to fully correlate in the Nijmegen Wistar rats (7), were used, since early postnatal handling has been found to disrupt this correlation (unpublished data; see also:53).

Each animal was individually housed during three consecutive days prior to the start of the selection period. Animals were transported to the open field room 30 min prior to testing in order to allow for environmental acclimatization. All testing was conducted between 0900–1700 h. The selection procedure produced 42 HR rats [distance, mean ± SEM (cm/30 min): 8856 ± 534; habituation time, mean ± SEM (min): 22 ± 2.48] and 43 LR rats [distance, mean ± SEM (cm/30 min): 2733 ± 382; habituation time, mean ± SEM (min): 4 ± 0.34].

Experiment 1: Acute Dose-Response Curve for HR and LR

Seventy rats (35 HR, 35 LR), weighing between 210–220 grams, were randomly assigned to five treatment groups. Each animal was individually housed for 3 days following the selection period. *d*-Amphetamine-sulphate obtained from RBI (Natick, USA) was diluted in distilled water (0.0, 0.5, 1.0, 1.5, 2.0 mg/kg/IP), and fresh solutions were made for each test session. Prior to dexamphetamine administration, each animal was placed in a locomotor box (36 × 24 × 25 cm) equipped with photocell beams for a period of 15 min. Following an injection of dexamphetamine (0.0: HR, $n = 7$ and LR, $n = 7$; 0.5: HR, $n = 7$ and LR, $n = 7$; 1.0: HR, $n = 7$ and LR, $n = 7$; 1.5: HR, $n = 7$ and LR, $n = 7$; 2.0: HR, $n = 7$ and LR, $n = 7$ mg/kg/IP) each animal was returned to the locomotor box for a period of 45 min. Each animal received one dose. Locomotor activity was assessed through beam interruptions and recorded by means of a computer according to previously described procedures (time bin = 2 min, 6).

Experiment 2: Sub-Chronic Administration of Dexamphetamine in HR and LR

Fifteen rats (7 HR, 8 LR) weighing between 210–220 grams were used. In order to allow for habituation animals were placed into the locomotor boxes during 30 min for 2 consecutive days prior to the start of the sub-chronic treatment. Animals were repeatedly exposed to the test environment in order to reduce locomotor activity as much as possible at the start of the sensitization procedure so that sensitization could occur. HR and LR were given daily activity tests during a period of 45 min following dexamphetamine injections (1.0 mg/kg/IP) for five consecutive days. The animals were replaced in their home cages at the end of each test. The locomotor boxes and method of assessment were the same as in experiment 1.

Statistics

Data were evaluated with analysis of variance (ANOVA). In the first experiment, a two-way ANOVA with dose and group as factors was used, followed by a post hoc *t*-test to detect the source of the difference. In the second experiment, a two-way ANOVA for repeated measurements with days and group as factors was used. A probability level of $p < 0.05$ was taken as statistically significant for all experiments.

RESULTS

Experiment 1: Acute Dose-Response Curve for HR and LR

The dose-response curve slightly, but significantly, differed between HR and LR [2-way ANOVA: Overall $F(9, 77) = 15.49$; $p < 0.0001$; Fig. 1]. Dexamphetamine induced a dose-dependent increase in locomotor activity in both types of rats [2-way ANOVA: $F(4, 77) = 33.79$; $p < 0.0001$]. Moreover, HR and LR differed in their response to dexamphetamine [2-way ANOVA: $F(1, 77) = 3.87$; $p < 0.05$]: post hoc compari-

sons revealed that this difference was primarily due to the effects of 1.5 mg/kg dexamphetamine [post hoc *t*-test: $t(13.56) = -2.41$; $p < 0.05$].

Experiment 2: Sub-Chronic Administration of Dexamphetamine in HR and LR

The overall ANOVA showed a slight, but significant, difference between HR and LR [2-way ANOVA: Overall $F(9, 65) = 5.70$; $p < 0.0001$; Fig. 2]. Locomotor activity significantly increased over days [2-way ANOVA: Days effect $F(4, 65) = 9.72$; $p < 0.0001$]. HR and LR animals also differed significantly in their response to dexamphetamine over the 5 days of testing [2-way ANOVA: Group effect $F(1, 65) = 10.55$; $p < 0.002$]. However, these differences did not change over days [ANOVA Group × Day interaction $F(4, 65) = 0.46$; $p > 0.75$].

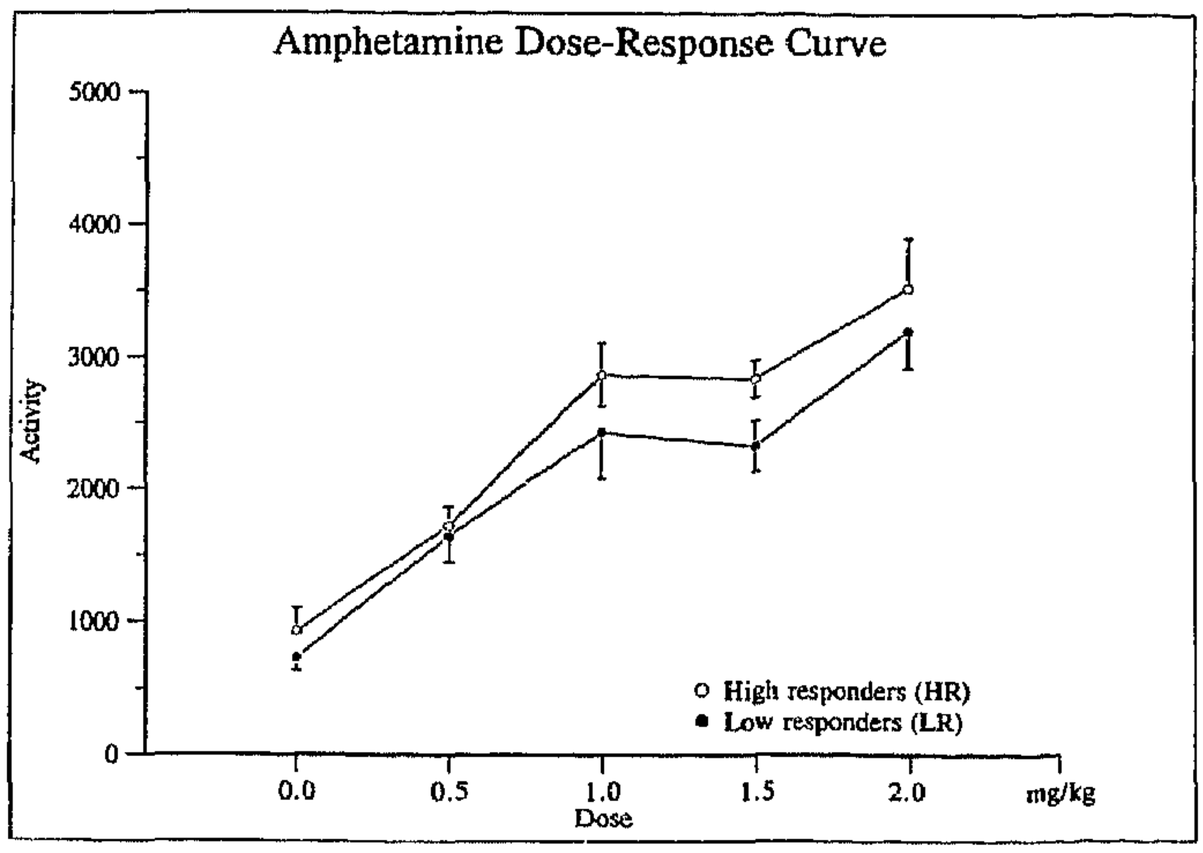

FIG. 1. Acute administration of dexamphetamine on locomotor activity in Nijmegen high (HR) and low (LR) responders. Post hoc tests revealed that only 1.5 mg/kg caused a significant difference between HR and LR ($p < 0.05$). The vertical bars represent the standard error of the mean.

DISCUSSION

This study shows that the experimental set-up used produced no major type-specific differences in locomotor response to dexamphetamine after acute or sub-chronic treatment. In fact, the first experiment shows that the type-specific difference in the locomotor response to dexamphetamine was limited to the effect of 1.5 mg/kg, whereas the apparent type-specific difference in the sensitization to dexamphetamine (experiment 2) was simply the result of a type-specific difference in baseline activity on day 1. Thus, it is concluded that there are no major differences in the locomotor response to dexamphetamine between HR and LR. This conclusion appears to be at variance with that of other authors (25,32,33,45). Still, the outcome of the first experiment fully fits in with the data reported by them. Piazza et al. (45) and Exner and Clark (25) have also found that HR show a greater response to 1.5 mg/kg (IP) dexamphetamine than LR do, but they did not test any additional dose, preventing them to generalize their finding to other doses. In contrast, the present study in which an extended dose-response curve was made, shows that the type-specific difference seen at dose 1.5 mg/kg disappeared, when lower or higher doses were tested. Remarkably, Hooks et al. (32) have done a similar observation in HR and LR: among the various doses tested, only 0.5 mg/kg (IP) dexamphetamine resulted in a type-specific difference following its acute administration to naive animals. Since the effects of dexamphetamine are known to vary according to the differences in baseline activity (17,34,60), it is not surprising that Hooks et al. (32) have found an effective dose that differs from the effective dose found in the present study: for, our rats were habituated for a short period of 15 min, whereas the rats of Hooks et al. (32) were habituated for a period of 90 min and, accordingly, must have had a far lower baseline activity than our rats.

One explanation for the apparent discrepancy between the various studies might be that Nijmegen HR and LR are not comparable to HR and LR that are studied in other laboratories. Apart from the fact that there are actually no real differences between the various studies, this is highly unlikely in view of the following. The bimodal variation in responses to novelty in Nijmegen Wistar rats is consistently coupled to a bimodal variation in a great variety of features. This individual consistency in behavior and physiology is known to occur in rodents across laboratories (2,13,26,36,56,63). In 1985 we have started a breeding program to get insight into various type-specific differences. Since the gnawing response to apomorphine is used in this breeding program, HR and LR are labeled as apomorphine-susceptible (APO-SUS) and apomorphine-unsusceptible (APO-UNSUS) rats, respectively (11,13,14). These studies have shown that HR (APO-SUS) and LR (APO-UNSUS) show a bimodal variation in various anatomical, neurochemical, endocrinological, immunological, pharmacological and behavioral features (5,7,10,11,12,13,14,21,23, 27,28,29,42,43,52,53,54,55,61). Given the fact that the HR and LR selected on the basis of their response to novelty in Bordeaux, for instance, show type-specific differences in their endocrinological response to novelty that are identical to those found in the Nijmegen HR and LR (48), it can be excluded that one is dealing with fully different groups of HR and LR. Still, future research is required to provide direct evidence in favor of this suggestion.

The fact that the key structures that are involved in the locomotor response to aminergic drugs (nucleus accumbens and neostriatum) differ from the key structures that are involved in exploratory behavior and response to stress (e.g. hippocampus) cannot explain the absence of major type-specific differences in the locomotor response to dexamphetamine. For, the bimodal variation in the aminergic make-up of the nucleus accumbens and neostriatum of HR and LR is consistently coupled to the bimodal variation in the neurochemical make-up of the hippocampus of HR and LR (11).

The finding that the type-specific difference in the locomotor response to dexamphetamine is limited to a particular dose (present study, 32) is highly surprising in view of the facts mentioned in the Introduction: (a) dexamphetamine enhances the activities of dopamine and noradrenaline in the nucleus accumbens; (b) the dopaminergic and adrenergic activities in the nucleus accumbens significantly differ between HR and LR; and (c) dexamphetamine exerts its effect on locomotor activity at least partly by changing the dopaminergic and adrenergic activities in the nucleus accumbens. Factors that might have contributed to the relative lack of type-specific differences in the locomotor response to dexamphetamine are discussed below. First, it is relevant to note that there exists a mutual interaction between dexamphetamine and corticosteroids: dexamphetamine is able to enhance the release of corti-

costeroids (37), whereas corticosteroids, in turn, are known to influence the locomotor response to dexamphetamine (8,50). Furthermore, it is known that both the baseline plasma level of corticosteroids and the increase in corticosteroids in response to environmental of pharmacological challenges significantly differ between HR and LR (53,54,55). In view of the finding that the type-specific difference in locomotor response to dexamphetamine varies according to the dose of dexamphetamine administered, it is therefore hypothesized that the type-specific difference in reactivity of the hypothalamic-pituitary-adrenal axis together with the type-specific difference in vulnerability to dexamphetamine (present study, 15,25,32,33,45,46,47,48,59) determine the degree in which the mutual interaction between dexamphetamine and corticosteroids results in dose- and type-specific differences in the locomotor response to dexamphetamine. Future research is necessary to (in)validate this hypothesis.

An additional factor that might have contributed to the outcome of the present study is that the analysis was restricted to the assessment of changes in locomotor activity in a rather restricted environment. For, it is known that dexamphetamine not just increases locomotor activity, but actually alters the whole spatio-temporal programming of behavior (19,20,22,39, 40,41,44,57,58), of which the nature varies according to the physical aspects of the environment (6,24,30). Follow-up studies in our laboratory in which we have analyzed dexamphetamine-induced effects in terms of changes in the sequence of paths and places of stopping on a large open field, have indeed shown that HR are significantly and dose-dependently more vulnerable to dexamphetamine than LR (15). In view of the latter findings, it is therefore suggested that the absence of major type-specific differences in the response to dexamphetamine is at least partly due to the fact that the analysis was limited to the plain assessment of locomotor activity in a rather restricted environment.

Taking the above-mentioned discussion together, it is concluded that there are neither major HR-LR differences in the locomotor response to various doses of dexamphetamine nor

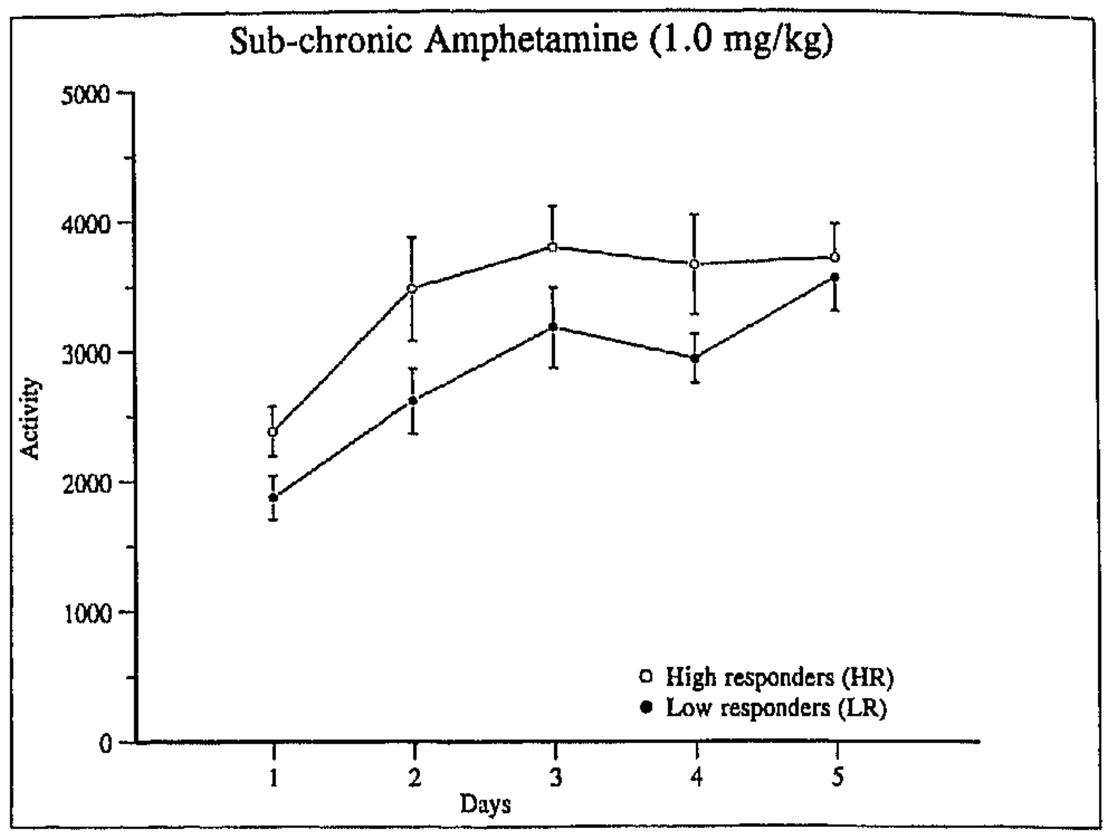

FIG. 2. Sub-chronic effects of 1.0 mg/kg dexamphetamine administration on locomotor activity in Nijmegen high (HR) and low (LR) responders on test days 1 through 5. The vertical bars represent the standard error of the mean.

HR-LR differences in the rate of sensitization to dexamphetamine. The possible involvement of two underlying factors is discussed: (a) the degree in which the mutual interaction between dexamphetamine and corticosteroids directs the locomotor response, varies according to the type-specific difference in reactivity of the hypothalamic-pituitary-adrenal axis and the type-specific difference in vulnerability to dexamphetamine; and (b) dexamphetamine-induced changes in locomotor activity are certainly not ideal for detecting subtle differences in type-specific differences in vulnerability to dexamphetamine.

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