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Evidence that a Behavioral Augmentation Following Repeated Amphetamine Administration Does Not Involve Peripheral Mechanisms[1]

R. KUCZENSKI,[2] D. S. SEGAL, S. B. WEINBERGER AND R. G. BROWNE[3]

Department of Psychiatry, School of Medicine
University of California at San Diego, La Jolla, CA 92093

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KUCZENSKI, R., D. S. SEGAL, S. B. WEINBERGER AND R. G. BROWNE. *Evidence that a behavioral augmentation following repeated amphetamine administration does not involve peripheral mechanisms.* PHARMAC. BIOCHEM. BEHAV. 17(3) 547–553, 1982.—Repeated administration of amphetamine (AMPH) to rats results in an augmentation of the drug-induced locomotion and stereotypy. The studies reported below were directed at examining the potential role for some dispositional and peripheral sympathomimetic factors in mediating the enhanced stereotypy response. These included three factors associated with repeated AMPH administration: (1) the possible accumulation of AMPH in a peripheral mobilizable pool; (2) repeated sympathetic activation; and (3) AMPH metabolite-induced depletion of peripheral stores of norepinephrine. The approach utilized was to selectively reduce or mimic the peripheral actions of AMPH through the use of non-pharmacological or pharmacological manipulations which are relatively lacking in AMPH-like central stimulant effects. The results indicate that these factors cannot account for the augmentation of the behavioral response to AMPH and suggest that these behavioral alterations reflect changes in the responsiveness of brain mechanisms which mediate the behavioral effects of the drug.

Amphetamine Sympathomimetics Repeated administration Stereotypy Disposition Locomotor activity Behavioral augmentation

ADMINISTRATION of amphetamine (AMPH) to rats produces a constellation of physiological and behavioral effects mediated by peripheral sympathomimetic actions of the drug and activation of central catecholaminergic (CA) systems. Repeated administration of AMPH results in the development of tolerance to some of these effects including anorexia [13,15] and hyperthermia [10] as well as its discriminative stimulus properties [3] and its facilitation of self-stimulation behavior [12]. In contrast, AMPH-induced locomotion and stereotypy are progressively augmented with long-term administration [21]. Drug dispositional factors may contribute to the development of tolerance and/or augmentation. For example, in rats d-AMPH is metabolized primarily to *p*-hydroxyamphetamine (POA) [2] which is subsequently converted to the false neurotransmitter p-hydroxynorephedrine (PONE) [8]. These metabolites may be involved in the development of tolerance to the hyperthermic and anorexigenic actions of AMPH [4,14] and in the mechanisms underlying the behavioral augmentation [20]. It has also been suggested that the behavioral augmentation may result from the accumulation of a pool of AMPH in fat stores which is mobilized by the sympathetic activation produced by subsequent administration of AMPH [23]. Such a mechanism would be consistent with the recent observations of Kuhn and Schanberg [11] that repeated injections of relatively high doses of AMPH results in enhanced brain levels of the drug with subsequent AMPH administration.

It is also important to consider possible competitive interactions between various effects of AMPH in assessing potential mechanisms underlying changes in the response with repeated administration of the drug. Thus, for example, the apparent enhanced stereotypy may reflect an unmasking of this effect as a consequence of tolerance development to sympathomimetic actions of AMPH which interfere with the

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[2]These studies were performed while on leave from the Pharmacology Department, Vanderbilt University, Nashville, TN 37217.

[3]Present address: Pharmacology Department, Chas. Pfizer Inc., Groton, CT 06340.

expression of various components of the behavioral response.

The purpose of the present studies was to examine the potential role for some dispositional and peripheral sympathomimetic factors in mediating the enhanced stereotypy which results from repeated administration of AMPH. Our results indicate that these factors are not significantly involved in the behavioral augmentation effect.

METHOD

Male Wistar rats (300–350 g) obtained from Hilltop Laboratories, were housed for at least one week under standard laboratory conditions. Subsequently, animals were placed individually into sound-attenuated activity chambers 24 hr prior to the initial drug injection. The animals remained in the behavioral chambers for the duration of the experiment. All drugs were administered in saline subcutaneously, unless otherwise specified, in a volume of 1 ml/kg. Drug doses refer to the free base.

The behavioral chambers and data recording system have been described in detail elsewhere [20]. Briefly, food and water were available on a continuous basis and lighting was maintained on a 12-hr bright-light (6 a.m.–6 p.m.) and 12-hr dim-light cycle. The rats were injected at about 10 a.m. each day during which time the chambers were serviced. This entire process required about 2 min per chamber and represented the only time during the day that the animals were disturbed. Movements from one quadrant to another (crossovers) were automatically counted by means of contacts in the floor of each chamber. Rearings were recorded by contact with touchplates set approximately 13 cm above the floor. Both measures of locomotion were monitored continuously by a NOVA 1200 computer. Stereotypy, including continuous sniffing, licking, chewing, and gnawing, and repetitive movements, concurrent with the absence of forward locomotion was characterized by regular observations through a viewing lens in the door of each chamber and by detailed analysis of videotapes made of representative animals.

Animals subjected to foot-shock were removed from the activity chamber 24 hr after the last pretreatment drug injection and placed in a chamber containing a floor of stainless steel rods to which was connected a shock generator/scrambler. A shock of 2 mA for 1.0 sec, on the average of one shock per min was delivered for 15 min. Animals were then immediately returned to the activity chambers, and after 24 hr were challenged with AMPH. Control animals were placed in the shock chamber for the same length of time, but did not receive shock.

All data, including crossover and rearing counts, as well as stereotypy scores were analyzed for statistical significance using either a Mann-Whitney U- or a Kruskal-Wallis test where appropriate [22].

RESULTS

Experiment 1: Mobilizable Pool of AMPH

If the behavioral augmentation associated with the repeated administration of AMPH is mediated by the release of accumulated drug from a sympathetically mobilizable pool, then reduction of this pool prior to challenge with AMPH should decrease the more rapid onset and intensification of stereotypy. This hypothesis was tested with the use of two

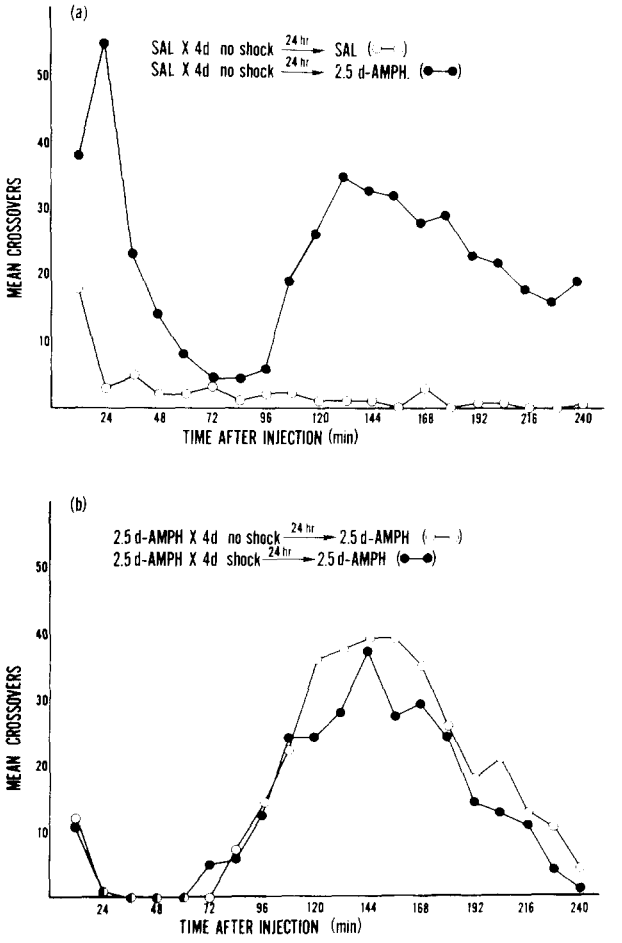

FIG. 1. The effects of foot-shock on the locomotor response to d-AMPH (2.5 mg/kg) following four pretreatment injections of saline or AMPH. (a) Mean crossovers during successive 12-min intervals following an acute injection of AMPH or saline. The response of animals subjected to footshock 24 hr prior to AMPH (data not shown) was identical to the non-shock controls. (b) Mean crossovers following the fifth injection of AMPH. Animals were subjected to foot-shock or control manipulation 24 hr after the fourth pretreatment injection, and 24 hr later were tested with AMPH. Foot-shock did not alter the more rapid onset of and enhanced intensity of stereotypy. N=8 in each group.

experimental manipulations which would be expected to mobilize such a pool.

Foot-shock. Sparber *et al.* [23] reported that AMPH administration resulted in an accumulation of drug in adipose tissue. This accumulation was increased by 60% after six daily injections of AMPH, and foot-shock was found to mobilize this pool. To determine if such a pool is implicated in the behavioral augmentation, rats received four daily injections of 2.5 mg/kg AMPH or saline. Twenty-four hr after the last injection, the animals were subjected to mild foot-shock, as described in Methods, to mobilize and presumably reduce the amount of residual drug. After an additional 24 hr, a challenge dose of 2.5 mg/kg AMPH was administered and the behavioral response was monitored. A single injection of 2.5 mg/kg AMPH produced the characteristic multiphasic response pattern [20], consisting of an initial period of en-

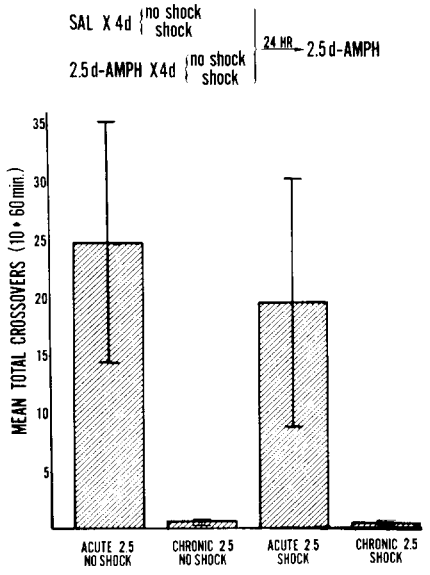

FIG. 2. The effects of foot-shock on mean total crossovers (±SEM) during the 10–60 min interval following a first or fifth injection of 2.5 mg/kg d-AMPH. Activity during the first 10 min was not included to eliminate the post-injection increase apparent in saline treated animals (see Fig. 1a). The more rapid onset of and enhancement of stereotypy following the fifth injection of AMPH is evident in the significant ($p<0.01$) decrease in crossovers relative to an acute injection of the drug. Foot-shock did not alter the locomotor response to either the first or fifth injection. N=8 in each group.

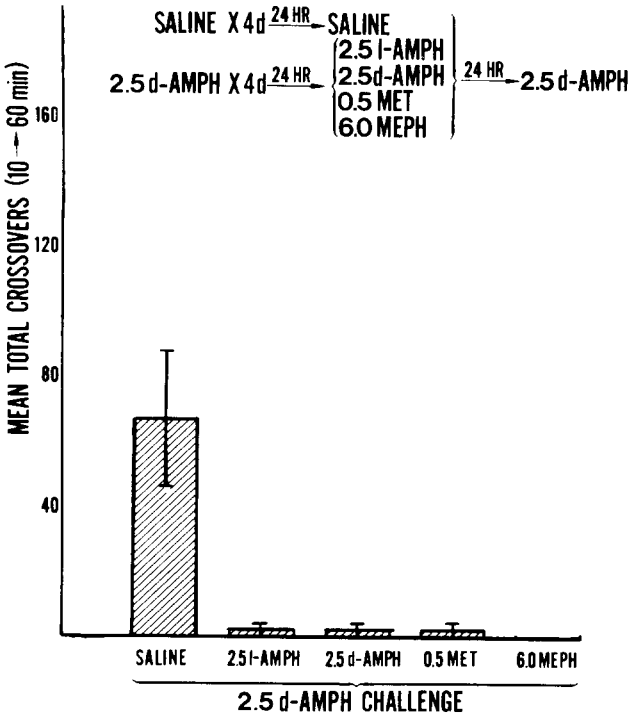

FIG. 3. The effect of an intervening injection of various sympathomimetics on the behavioral augmentation associated with repeated administration of AMPH. Mean crossovers during the 10–60 min interval following a test injection of d-AMPH (2.5 mg/kg). The intervening injection of sympathomimetics did not alter the behavioral augmentation which is evidenced by decreased crossovers compared to saline pretreated controls. N=9 for each group.

hanced locomotion followed by a continuous stereotypy phase during which forward locomotion was absent. A prolonged period of locomotion emerged after the stereotypy (Fig. 1a). The pattern of rearing behavior paralleled forward locomotion. Animals receiving saline exhibited a brief period of post-injection activity which persisted for approximately 10 min.

The typical pattern of behavioral augmentation following repeated AMPH administration included a more rapid onset of stereotypy reflected by fewer crossovers during the first hr (Fig. 1b). Observation of the animals confirmed a more rapid onset and enhanced intensity of repetitive movements with a corresponding decrease in locomotion. In this and all subsequent experiments, statistical evaluation of observational data revealed no qualitative differences in the stereotypy responses between repeated AMPH groups, and confirmed the inverse relationship between the level of locomotor activity and the onset of focused stereotypy. The level of locomotor activity as reflected in number of crossovers during the first hr after AMPH administration was inversely related to the degree of focused stereotyed behavior, and the decrease in crossovers during this period following repeated AMPH pretreatment provides an accurate and reliable index of the more rapid onset of stereotypy, characteristic of the behavioral augmentation (Fig. 2).

Animals pretreated with AMPH for four days and then subjected to foot-shock 24 hr prior to the challenge injection of AMPH exhibited a behavioral response pattern (Fig. 1b), including a marked decline in latency to onset of stereotypy and corresponding decline in locomotor activity (Fig. 2) which was virtually identical to the non-shocked chronic AMPH pretreated control animals (Figs. 1a, 2).

Sympathomimetics. An alternative method of mobilizing a potential pool of accumulated AMPH in peripheral sympathetically innervated systems involves the use of other sympathomimetic agents which possess relatively lower central to peripheral potency ratios compared to d-AMPH. For these studies groups of animals were pretreated with d-AMPH (2.5 mg/kg daily for four days) or saline, and 24 hr after the last pretreatment injection, received saline or the sympathomimetic l-AMPH (2.5 mg/kg), mephentermine (6.0 mg/kg, IP), or metaraminol (0.5 mg/kg, IP). These doses of the sympathomimetics were chosen to mimic the peripheral sympathetic activation achieved with 2.5 mg/kg d-AMPH. Thus, metaraminol has been shown to be 5–20 times more potent than d-AMPH in releasing norepineprhine (NE) from sympathetic nerves [24], in depleting heart NE [26], or in increasing arterial blood pressure [17], while possessing virtual no central activity [27]. Mephentermine is slightly less potent or equipotent to d-AMPH in its sympathomimetic effects [1, 6, 28] and l- and d-AMPH are approximately equipotent in cardiovascular effects [9], in affecting the efflux of NE from periperal NE nerves [16] and in depleting heart NE [4]. Twenty-four hr later, all animals were challenged with 2.5 mg/kg d-AMPH.

The results are presented in Fig. 3; at the doses tested, both l-AMPH and mephentermine induced pronounced locomotor stimulation, whereas metaraminol did not induce a motor activation. Irrespective of the apparent central potency of these sympathomimetics, however, their adminis-

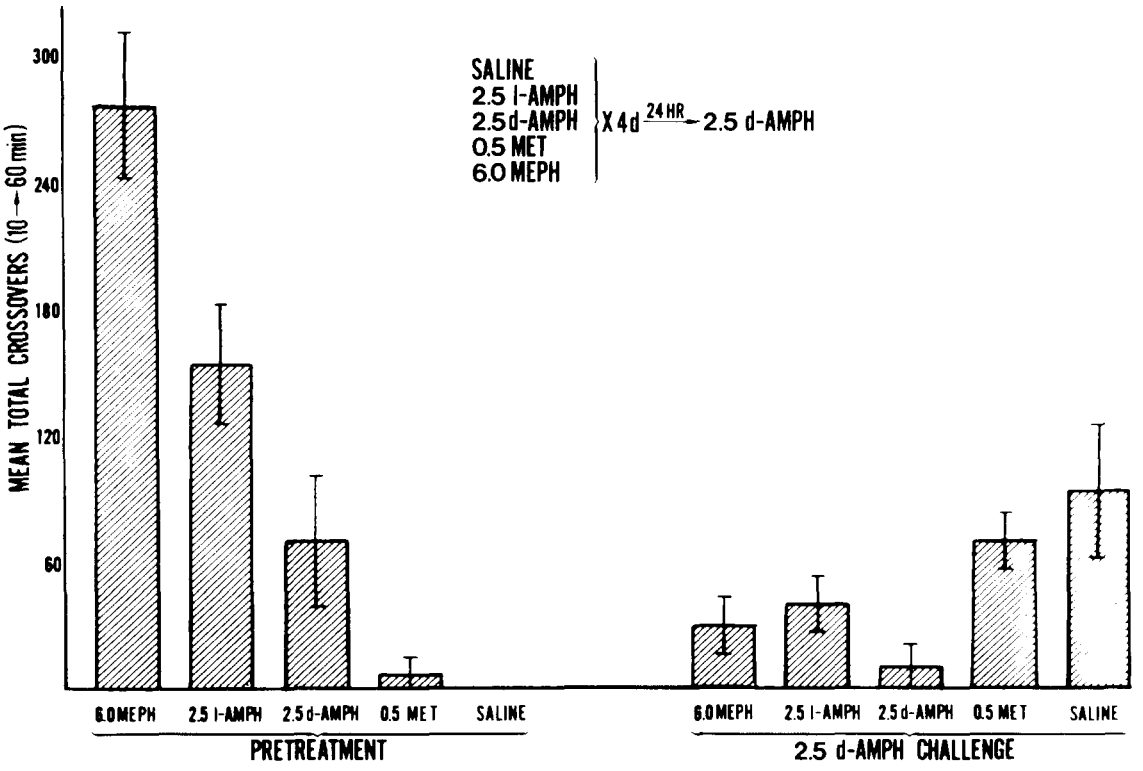

FIG. 4. The effect of repeated sympathetic activation on the response to d-AMPH (2.5 mg/kg). Animals received four daily injections of the indicated doses of sympathomimetics and were tested with d-AMPH 24 hr after the last pretreatment injection. (Left) Mean crossovers (±SEM) during the 10–60 min interval following the first pretreatment injection. (Right) Mean crossovers (±SEM) following the test injection of d-AMPH. Groups of animals pretreated with d-AMPH or mephentermine exhibited on augmented behavioral response as evidenced by a significant decrease in crossovers relative to the saline pretreated group. N=9 in each group.

tration did not alter the more rapid onset of stereotyped induced by repeated AMPH pretreatment (Fig. 3). All groups of AMPH pretreated animals exhibited attenuated locomotor activity and correspondingly more rapid onset and intensity of stereotypy after AMPH challenge as compared to control animals receiving an acute administration of the drug.

Experiment 2: Chronic Sympathetic Activation

To test the possibility that the repeated activation of peripheral sympathetic systems by AMPH may underlie the behavioral augmentation effect, groups of animals were administered saline, d-AMPH (2.5 mg/kg), or the sympathomimetics l-AMPH (2.5 mg/kg), mephentermine (6.0 mg/kg), or metaraminol (0.5 mg/kg) daily for four days. As discussed above, these doses would be expected to mimic, at least partially, the acute peripheral sympathomimetic actions of 2.5 mg/kg d-AMPH. On the fifth day, all animals were challenged with 2.5 mg/kg d-AMPH and locomotor activity and stereotyped behavior were monitored. The acute administration of both l-AMPH and mephentermine at the doses tested produced a substantial stimulation of locomotor activity (Fig. 4) and rearing counts (data not shown) with a duration of approximately 2 hr and 2.5 hr, respectively, and included moderate sniffing behavior comparable to that observed following low (e.g., 0.5–0.75 mg/kg) d-AMPH administration. In contrast, metaraminol failed to produce a locomotor stimulation consistent with its relative inability to cross the blood-brain barrier. Twenty-four hr with 2.5 mg/kg d-AMPH. Animals pretreated with saline exhibited a typical response to acute AMPH challenge, including an initial period of enhanced locomotion, whereas animals pretreated with d-AMPH exhibited a more rapid onset of stereotypy and a corresponding suppression of locomotor activity (Fig. 4). Metaraminol pretreatment did not alter the subsequent response to d-AMPH challenge as compared to saline pretreated animals. However, animals pretreated with l-AMPH or mephentermine exhibited a significant enhancement of stereotyped behavior and a corresponding decrease in locomotor activity intermediate between saline pretreated and d-AMPH pretreated groups.

Experiment 3: Depletion of Peripheral Sympathetic NE by POA and PONE

The administration of moderate to high doses of AMPH produces a dose-related depletion of peripheral stores of NE. This effects appears to be mediated by AMPH-induced release of NE and by displacement of NE by the metabolism of POA and PONE [4,7]. The depletion of NE may lead to an attenuation or elimination of a peripheral effect of the drug which competes with the expression of stereotypy, thus resulting in an apparent behavioral augmentation. Prior depletion of peripheral NE by administration of metabolites of AMPH should therefore eliminate the competing peripheral effect and produce the more rapid onset of stereotypy with

subsequent AMPH challenge. To test this hypothesis, groups of animals were administered a single injection of saline, 2.5mg/kg d-AMPH, or doses of (+)POA or (±)PONE which have been reported to produce a depletion of peripheral NE stores equivalent to or greater than that achieved by 2.5 mg/kg d-AMPH [4]. After 24 hr, animals were challenged with 2.5 mg/kg d-AMPH. The response of AMPH pretreated animals to a subsequent challenge with AMPH included the more rapid onset of stereotypy as evidenced by decreased levels of locomotor activity during the first hr after drug injection (Fig. 5). The finding that PONE (0.05 or 5.0 mg/kg) did not stimulate locomotor activity, is consistent with its apparent limited ability to cross the blood-brain barrier (Fig. 5). Furthermore, PONE pretreatment did not significantly alter the response of these animals to AMPH. Similarly, neither dose of POA alone produced an increase in locomotor activity, or an alteration of the AMPH response (Fig. 4).

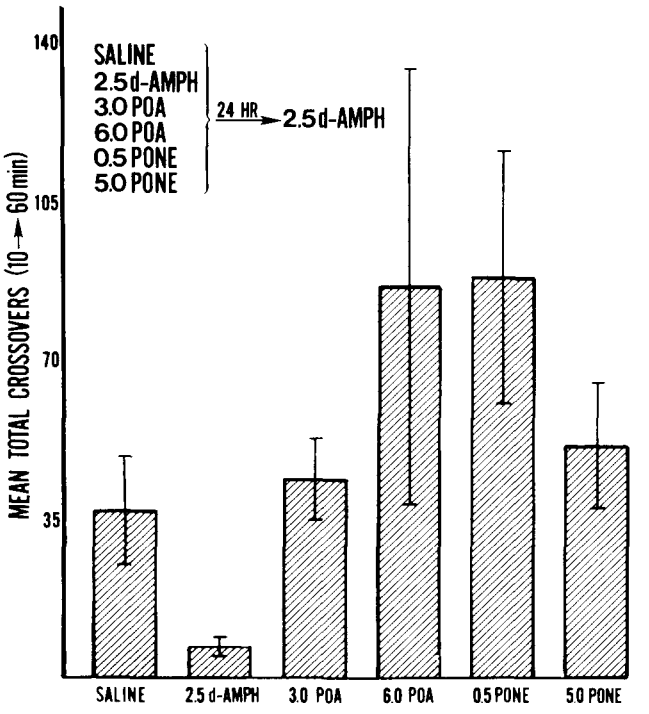

FIG. 5. The effect of a single pretreatment injection of saline, d-AMPH, or the AMPH metabolites POA or PONE on the response to a test injection of 2.5 mg/kg d-AMPH 24 hr later. The augmentation of the behavioral response relative to the saline pretreated group was obtained only in the d-AMPH pretreated group, as evidenced in the significant decrease in mean total crossovers during the 10–60 min post-injection interval. N=8 in each group.

DISCUSSION

The repeated administration of AMPH produces a pattern of behavioral augmentation characterized most prominently by a more rapid onset and increased intensity of focused stereotyped behaviors. A variety of mechanisms may contribute to the development of this altered behavioral response, including drug dispositional factors or the differential tolerance development to potentially competing effects of the drug. The experiments reported above were performed to assess the potential role of these factors in mediating the changes in stereotypy associated with repeated AMPH administration. Our approach was to selectively reduce or mimic the peripheral actions of AMPH through the use of pharmacological and non-pharmacological manipulations which are relatively lacking in AMPH-like central stimulant effects.

To test the possibility that the behavioral augmentation is mediated by accumulation of AMPH in a mobilizable pool, animals were pretreated with AMPH and then subjected to an intervening exposure to foot-shock or administration of a sympathomimetic agent prior to challenge with AMPH. The results (Figs. 2 and 3) indicated that treatments which produce sympathetic activation and thus would be expected to reduce any accumulated pool of AMPH, did not alter the response to subsequent AMPH challenge. Foot-shock parameters were similar to those utilized by Sparber *et al.* [23] to mobilize the pool of AMPH which they found to accumulate in adipose tissue concomitant with repeated AMPH administration. Similarly, pretreatment of animals with doses of sympathomimetics which mimic the peripheral sympathetic activation achieved with 2.5 mg/kg d-AMPH did not alter the behavioral augmentation obtained with subsequent AMPH challenge. Further, if mobilization of a peripheral pool of AMPH mediated the behavioral augmentation, then dosage regimens (2.5 mg/kg daily) which produce the enhanced responsiveness should produce higher brain levels of AMPH. We and others, however, have failed to find changes in regional brain levels of AMPH following its repeated administration at behaviorally relevant doses (Segal and Cho, unpublished; [11]).

The changes in focused stereotyped behaviors following the repeated administration of AMPH may also result from tolerance development to a competing effect of the drug. While it would be difficult to mimic all of the peripheral sympathomimetic effects of AMPH which might differentially, with chronicity, interact with the expression of stereotypy, we sought to obtain converging evidence for the role of such effects of the behavioral augmentation through the use of various sympathomimetic agents with lower central to peripheral potency ratios compared to d-AMPH. The acute administration of 0.5 mg/kg metaraminol failed to elicit a locomotor stimulant effect, consistent with its inability to cross the blood-brain barrier, and the repeated administration of this compound did not alter the stereotypy produced by subsequent AMPH challenge (Fig. 4). In contrast, the acute administration of either 2.5 mg/kg l-AMPH or 6.0 mg/kg mephentermine elicited marked locomotor stimulation, and their repeated administration significantly altered, although to a lesser extent than did pretreatment with d-AMPH, the response to subsequent challenge with d-AMPH. These results indicate that repeated peripheral sympathetic activation cannot account for the behavioral augmentation. Rather, it appears that there is a direct relationship between the degree of augmentation to subsequent challenge with AMPH. Consistent with this apparent relationship is the finding that pretreatment with higher doses of l-AMPH than used in the present studies leads to a behavioral augmentation equivalent to that observed with repeated administration of 2.5 mg/kg d-AMPH [5].

The depletion of NE from sympathetic neurons has been implicated in tolerance development to some of the effects of AMPH, including its anorexia and hypothermia [14]. It is conceivable that a decrease in AMPH, including its anorexia and hypothermia.

The depletion of NE from sympathetic neurons has been implicated in tolerance development to some of the effects of AMPH, including its anorexia and hypothermia [14]. It is conceivable that a decrease in AMPH induces sympathetic activation as a consequence of NE depletion may result in an unmasking of the behavioral response. Brodie *et al.* [4] reported that a depletion of heart NE equivalent to that obtained with 2.5 mg/kg AMPH could be achieved with 3.0 mg/kg POA or 0.5 mg/kg PONE. However, pretreatment of animals with these or higher doses of the AMPH metabolites at doses sufficient to effect a marked depletion of periphera sympathetic NE cannot alone account for the behavioral augmentation. Further, these data support the previous suggestion [5] that the presence of the AMPH metabolites in central NE neurons does not account for the behavioral augmentation since POA administration (Experiment 3) should lead to PONE accumulation in the brain. In addition, behavioral augmentation appears to be a common feature of the repeated administration of CNS stimulant drugs [5] which are not metabolized to POA or PONE.

Finally, we have previously noted [21] that saline injection on the day following long-term AMPH administration produced only predrug levels of activity, suggesting that conditioning to neural stimuli [25] does not underlie the behavioral augmentation. More recent findings further indicate that a conditioned drug response is not implicated [5]. The present results with metaraminol (Fig. 3) extend this interpretation to exclude state dependent conditioning associated with peripheral drug effects. Therefore, under conditions of continuous exposure to the experimental apparatus, conditioning processes do not appear to contribute significantly to the enhanced responsiveness to AMPH following chronic pretreatment with the drug.

We have previously reported [18] that animals pretreated with systemic AMPH for four consecutive days exhibited an enhanced locomotor response to intraventricular infusion of AMPH. The present results complement those findings and suggest that neither the enhanced locomotor or stereotypy response following repeated administration of AMPH is mediated by changes in dispositional or peripheral sympathomimetic effects of AMPH. Rather, these behavioral alterations reflect a change in the responsiveness of brain mechanisms which mediate the behavioral effects of the drug.

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