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Tyrosine Influence on Amphetamine Self-Administration and Brain Catecholamines in the Rat

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GEIS, L. S., D. G. SMITH, F. L. SMITH, D. S. L. YU AND W. H. LYNESS. *Tyrosine influence on amphetamine self-administration and brain catecholamines in the rat.* PHARMACOL BIOCHEM BEHAV **25**(5) 1027–1033, 1986.—Earlier work had shown that L-tyrosine administration, precursor to both dopamine (DA) and norepinephrine (NE), could increase brain DA metabolite concentrations after amphetamine treatment and restore amphetamine-induced decreases in whole brain NE. Both monoamines have been suggested to participate in some aspects of continued drug abuse. Rats trained to self-administer IV d-amphetamine were treated with IP tyrosine during test sessions to examine the behavioral and neurochemical response. In animals with less than 35 days of amphetamine exposure, L-tyrosine treatments did not alter amphetamine self-administration. Experiments using a computer-controlled injection apparatus which administered IV amphetamine to naive rats in patterns mimicking those of self-administration animals indicated tyrosine could antagonize amphetamine-induced NE depletions. The increases in DA metabolite dihydroxyphenylacetic acid (DOPAC) were found limited to the striatum, an area not involved in the positive reinforcing effects of amphetamine. Concentrations of DOPAC in nucleus accumbens septi were unchanged by the amphetamine or the amphetamine-tyrosine regimen. In rats with 4–6 months of chronic amphetamine exposure, however, L-tyrosine administration significantly reduced daily drug self-injection. While neurochemical responses to tyrosine could not be performed, it is speculated that chronic long-term amphetamine abuse might alter the tyrosine-induced changes in DA and/or NE synthesis and release compared to that in the acute or short-term amphetamine abuse animals. These data suggest that the success or failure of an experimental pharmacologic treatment strategy in psychomotor stimulant abusers might be dependent on the subjects history of drug abuse.

L-Tyrosine Short-term amphetamine abuse Long-term amphetamine abuse Norepinephrine Dopamine

RATS can be trained to self-administer intravenous d-amphetamine and other psychomotor stimulants (cocaine, methamphetamine). These animals maintain relatively constant plasma levels of drug despite experimental manipulation of the dose per injection or fixed ratio schedule of injections (cf. review, [35]). This paradigm has thus become an experimental model of drug abuse. Its importance can only be underscored by the fact that pharmacologic treatment strategies for human psychomotor stimulant abusers are, for the most part, absent from the literature or textbooks.

The animal model of stimulant abuse has shown that cerebral dopamine (DA)-containing neurons are of major importance in the positive-reinforcing components of the psychomotor stimulants (cf. review, [35]). These data have been corroborated by human studies which have shown that interference with DA synthesis and release markedly attenuates the subjective rating of amphetamine-induced euphoria [5,8]. The role of another brain catecholamine, norepinephrine (NE), in the animal model of stimulant abuse is not clearly defined (cf. review, [35]). However, brain NE concentrations in animals are decreased by both acute and chronic amphetamine injections [21,25]. Studies in humans have demonstrated significant decreases in NE metabolites in those addicted to psychomotor stimulants, suggestive of decreased brain NE concentrations [32]. It has been suggested that these decreased NE levels are, in part, responsible for withdrawal depression and/or withdrawal cravings [31]. This hypothesis led to clinical use of desmethylimipramine, the NE reuptake inhibitor, in human psychomotor stimulant addicts. These studies have suggested significant benefit from this therapy [2,31].

Both NE and DA rely on the precursor amino acid tyrosine for their synthesis. Manipulation of precursor availability by tyrosine enriched diets or by systemic injection have been shown to have profound effects on the neurochemistry of these monoamines and associated behaviors in

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both animals and humans. Tyrosine administration, under normal conditions, has been shown to have little effect on the synthesis of either DA or NE. However, when the frequency of neuronal firing is enhanced or when tyrosine hydroxylase is activated, tyrosine administration can increase the synthesis of both catecholamines. For example, after γ-butyrolactone injection (an agent which decreases the activity of DA-containing neurons but increases DA synthesis), IP tyrosine injection increases DA synthesis further [30]. Partial lesions of the nigro-striatal tract with 6-hydroxydopamine, which leads to increased neuronal activity in the remaining intact DA neurons, also allows tyrosine injections to further increase DA synthesis [20]. In humans afflicted with Parkinson's disease, a condition characterized by damage to DA containing neurons, oral tyrosine administration significantly increased lumbar spinal fluid concentrations of DA metabolite homovanillic acid [4]. Similar reports of tyrosine-induced activation of DA synthesis have been demonstrated after haloperidol administration [27].

Tyrosine pretreatment has also been demonstrated to influence NE concentrations under certain non-drug conditions. Rats in chronic stress paradigms have reduced brain NE concentrations and are hypoactive in regard to locomotor activity in a novel environment. Restoration of both NE concentrations and locomotor behavior were observed after exposure to a tyrosine-enriched diet [12]. Similarly, when rats are administered IV d-amphetamine in patterns resembling those in self-administration studies, a 27% decrease in brain NE was observed. Tyrosine administration to these animals not only restored brain NE to control levels but led to 35% increases in whole brain dihydroxyphenylacetic acid (DOPAC), suggesting increased DA synthesis and/or release [29].

Given that tyrosine injection produced neurochemical changes in catecholamine neurons in animals under the influence of amphetamine, and that both neurotransmitters appear to be or have been speculated to participate in continued drug abuse, the present study sought to establish whether tyrosine administration, in animals trained to self-administer amphetamine, would alter subsequent drug abuse. If so, it might provide an alternative to desipramine use in those addicted to psychomotor stimulants.

METHOD

Animals

Male Sprague-Dawley rats (250–300 g; King Animal Labs, Oregon, WI) were anesthetized with pentobarbital (50 mg/kg), halothane supplements as necessary, and implanted with chronic silastic jugular catheters exiting subcutaneously as previously described [33]. Animals were allowed 7 days post-operative recovery before self-administration studies began.

Self-Administration Apparatus

The self-administration apparatus consisted of cages (18×20×26 cm, width, height and length, respectively) equipped with an operant lever which, when activated, delivered 0.125 mg/kg IV d-amphetamine in sterile saline (200 μl/kg volume). The pneumatic and electronic components of the apparatus are described in detail elsewhere [10, 17, 34]. Daily training sessions consisted of 8 hr (0900–1700 hr) seven days per week. Most animals achieve stable daily drug intake in 5–10 days. Hourly rates of drug injection were determined using event recorders (Cole-Parmer, Chicago, IL). All rats used in the initial studies had at least 21 but not more than 35 days of drug self-injection experience before testing. The 3 long-term self-administration animals had histories of drug exposure as follows: Rat 1, 147 days total with 4 "days off" during testing; Rat 5, 152 days of testing with 4 "days off"; and Rat 6, 181 days with 7 "days off" during testing. The term "days off" refers to non-consecutive days when the animal could not be tested due to cannula repair or repair work done on components of the test apparatus.

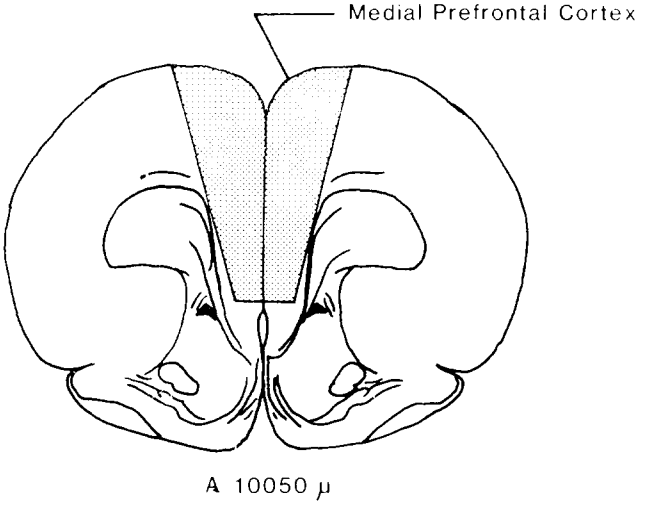

FIG. 1. Area designated as medial prefrontal cortex. The shaded area represents the section of cortical tissue subject to chromatographic analysis of DA and DOPAC in the neurochemical studies and referred to as medial prefrontal cortex. The tissue section extended from A 10050 μ to A 9650 μ [9].

L-Tyrosine hydrochloride (Sigma Chemical Co.) was dissolved in water prior to IP injection. The dose per injection in the neurochemical analyses and in self-administration studies was 100 mg/kg. Two doses were given: at the start of the test session and 4 hr into the 8 hr test session.

Computer-Controlled Drug Injection

Animals chosen for the computer-controlled injections of amphetamine (neurochemical analyses) were surgically implanted with chronic jugular catheters and allowed a recovery period identical to those in the self-administration testing. Cages in the computer-controlled apparatus are identical to those in the self-injection apparatus except that the operant lever is absent. A microcomputer controlled the schedule of IV injections. The schedule and patterns of injection were taken from those of former self-administration animals and described and illustrated elsewhere [11].

The device was controlled by a Timex Sinclair 1000 ZX-81® microcomputer and a Byte-Back® control module linked to pneumatic syringes (identical to the self-injection apparatus) via a 44 pin edge connector. Activation of the syringes was controlled by the programmed closing of a relay in the Byte-Back® module enabling the closing of a 24 V relay. This results in the simultaneous IV injection of 12 animals (6 amphetamine, 0.125 mg/kg/injection) and 6 saline in individual cages.

Briefly, the patterns of computer-controlled injection are as follows: during the first 30 min, 15 injections are delivered

at 2 min intervals, thereafter injections are programmed at 8 or 10 min intervals. Animals were sacrificed immediately after the last injection and neurochemical analyses performed as described below.

Neurochemical Analysis

Rats were sacrificed by decapitation, the brain removed, frozen and sectioned on a freezing microtome. Tissue punches of striatum and nucleus accumbens were made using 1.5 and 1.0 i.d. stainless steel tubing, respectively, from a frontal section with a rostral cut at ca. A 9650 μ and ending at A 8650 μ [9]. The tissue area designated as medial prefrontal cortex is best described in Fig. 1. The tissue section extended from A 10050 to A 9650 μ [9] and was removed by knife cuts.

Tissues were homogenized in 0.02 M citrate-phosphate buffer containing 0.02% sodium octyl sulfate, and 10% (v/v) methanol (pH 2.8). Samples were centrifuged at 10,000 × g and the concentrations of brain monoamines and metabolites determined using a BioAnalytical Systems (West Lafayette, IN) liquid chromatograph with an amperometric detection system as described earlier [14]. Protein content of the tissue samples was determined using the method of Lowry *et al.* [13]. Values are expressed as ng/monoamine or metabolite per mg protein.

Statistical Analysis

Statistical comparisons were made using analysis of variance (ANOVA) and Duncan's Multiple Range or Scheffe's tests where indicated. Values where $p<0.05$ were considered statistically significant.

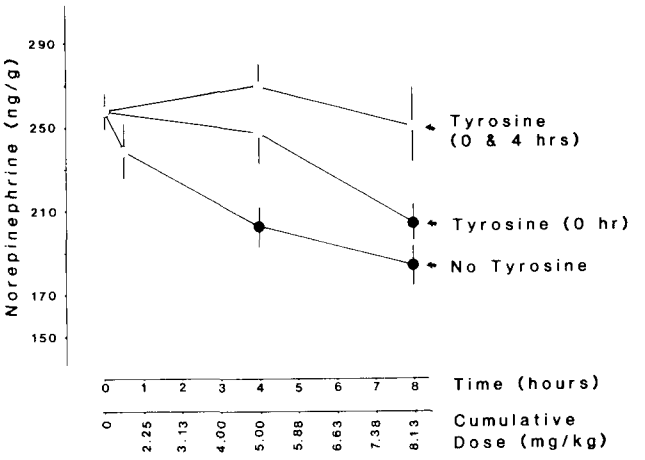

FIG. 2. The effects of IV amphetamine alone and in combination with IP tyrosine injections on brain norepinephrine concentrations. Animals implanted with chronic IV cannulae were placed in the computer-controlled apparatus described and administered amphetamine in patterns mimicking those of self-administration animals. The time in the apparatus, as well as the cumulative dose of d-amphetamine are shown. One group of animals received only amphetamine, a second, IV amphetamine with 1 IP tyrosine injection (100 mg/kg) at the start of the amphetamine regimen (0 hr) and a third group received IV amphetamine injections and 2 doses of tyrosine (100 mg/kg/injection; 0 and 4 hr into the test session. Values shown represent the mean ±1 S.E. of 5–6 animals for each data point. Darkened symbols represent values statistically significant from animals which did not receive amphetamine or tyrosine (0 hr; ANOVA).

RESULTS

Tyrosine: Influence on Brain Norepinephrine

When tyrosine was administered to animals receiving IV amphetamine in patterns mimicking those of self-administration rats, two neurochemical findings were in evidence: (1) amphetamine-induced decreases in NE were restored to normal (saline) control values and (2) increases in whole brain DOPAC occurred [29]. If cerebral NE were involved in drug cravings, as has been suggested by human studies [31,32], one might expect a decrease in drug self-injection as NE concentrations were restored. Similarly, activation of DA containing neurons, if increased DOPAC can be taken as evidence of increased DA release, might be predicted to decrease amphetamine self-injection in a manner like that which occurs after the injection of DA agonists to amphetamine self-administration rats [36].

If the effects of tyrosine on drug abuse behavior were to be examined, it was necessary to determine the duration of action of the tyrosine influence on brain chemistry. The previous neurochemical study administered tyrosine 1 hr prior to sacrifice [29]. Figure 2 illustrates the effects of d-amphetamine, administered in patterns resembling drug abuse, on whole brain NE. Norepinephrine decreased over the course of the 8 hr injection regimen, being statistically significant at 4 and 8 hr of drug exposure. One injection of tyrosine (100 mg/kg) at the start of the amphetamine injection regimen restored cerebral NE concentrations at 4 hr but did not after the decreased NE concentrations after 8 hr of amphetamine exposure. Two injections of tyrosine (100 mg/kg), at the start and 4 hr into the amphetamine regimen, completely antagonized the amphetamine-induced brain NE depletions. The tyrosine injection schedule of two injections, at the start and 4 hr into the test session were therefore utilized to study the behavioral effects of the amino acid on amphetamine self-administration behavior.

Tyrosine: Influence on Amphetamine Self-Administration

From the neurochemical data obtained in the amphetamine-tyrosine studies one might predict a decreased responding for IV amphetamine after tyrosine as was stated above. This did not occur. Animals trained to self-administer d-amphetamine (21–35 days experience) were given 2 IP injections of tyrosine (100 mg/kg), at the start and 4 hr into the test session, self-injected the stimulant in patterns identical to those of the day before when IP saline injections were administered (ANOVA). While cerebral NE has never been shown to participate in stimulant self-injection, the role of DA neurons in this paradigm is clearly established and well corroborated. For this reason the increases in DOPAC observed earlier with the amphetamine-tyrosine regimen were studied in detail using a regional brain analysis.

Amphetamine-Tyrosine Regimen: Its Effects on Regional DA Metabolites

Three DA-rich brain regions were examined in detail. Nucleus accumbens septi was chosen since DA neurons at this loci appear to be of import in the positive reinforcing properties of the psychomotor stimulants (cf. review, [35]). The striatum was chosen since it has been shown that am-

TABLE 1

EFFECT OF TYROSINE INJECTIONS IN RATS TREATED WITH IV AMPHETAMINE: REGIONAL CHANGES IN BRAIN DA AND DOPAC CONCENTRATIONS

Area	Drugs		Monoamine metabolite (ng/mg Protein)	
	Amphetamine	Tyrosine	DA	DOPAC
N. Accumbens	0*	0†	62.4 ± 5.3	5.9 ± 0.7
	+	0	69.6 ± 7.2	7.0 ± 1.1
	+	100 mg/kg	64.4 ± 5.9	6.5 ± 0.7
Striatum	0	0	129.6 ± 8.4	17.7 ± 1.0
	+	0	109.2 ± 11.3	16.4 ± 2.3
	+	100 mg/kg	122.2 ± 12.7	26.3 ± 1.4‡
Med. Prefrontal Cortex	0	0	1.21 ± 0.26	0.46 ± 0.10
	+	0	0.96 ± 0.17	0.24 ± 0.06‡
	+	100 mg/kg	1.06 ± 0.12	0.59 ± 0.11

Animals were implanted with IV cannulae as described and placed in the computer-controlled apparatus which delivered either saline or d-amphetamine using an injection pattern resembling that of self-administration rats. The test session lasted 8 hrs. Injections (IP) of either saline or tyrosine (100 mg/kg/injection) were given at the start of the IV injections and 4 hr into the test sessions. Animals were sacrificed after an additional 4 hr, the brains removed and sectioned. Analyses of DA and DOPAC were made as described in the Method section. Values shown represent the mean ± 1 S.E. of 6 animals per group.

*Animals not receiving IV amphetamine received IV saline in an identical injection pattern.

†Animals not receiving IP tyrosine received an equivalent volume of saline.

‡$p<0.05$, Student's t-test.

phetamine injections increase DA synthesis within this structure [16, 18, 22]. Finally, the medial prefrontal cortex was examined since earlier reports have indicated rats will self-administer cocaine into this region, a behavior which appears DA-dependent [3].

The computer controlled injection regimen was utilized in these experiments. Mimicking amphetamine self-injection patterns the effects of IV saline, amphetamine and amphetamine with 2 tyrosine injections (0 and 4 hr, 100 mg/kg IP) on DA and DOPAC concentrations were examined in the 3 brain regions. The results ware shown in Table 1.

The DA and DOPAC concentrations in the nucleus accumbens, a site strongly implicated in psychomotor stimulant abuse, were unaffected by amphetamine-tyrosine regimen. In the striatum, the amphetamine schedule failed to alter DOPAC concentrations when compared to saline-injected controls. The amphetamine-tyrosine regimen, however, induced a 49% increase in DOPAC concentrations. In the medial prefrontal cortex amphetamine injections produced a 48% decrease in regional DOPAC concentrations which was antagonized completely by the 2 tyrosine injections ($p>0.05$ vs. saline controls). Concentrations of DA were unaffected by either amphetamine or the amphetamine tyrosine regimen in all 3 brain areas.

Tyrosine Influence on Chronic Self-Administration Rats

The studies indicating the failure of tyrosine to influence amphetamine self-administration (Fig. 3) were performed using short-term amphetamine exposure animals (21–35 consecutive days). Previously it has been noted that long-term amphetamine exposure alters both behavior and brain chemistry [25]. Several animals were allowed long-term amphetamine exposure for the purpose of conducting behavioral and neurochemical analyses in the future. When tyrosine was administered to these rats, decreases in amphetamine self-administration were noted (Fig. 4).

DISCUSSION

The injection of tyrosine to animals receiving IV amphetamine, in patterns resembling those of animals trained to abuse this substance, indicated that the whole brain NE depletions induced by the stimulant could be antagonized [29]. The present study demonstrated that 2 injections over the course of an 8 hr test session were required to maintain the NE concentrations. The question is whether the restoration of brain NE concentrations is of any benefit in drug abuse. In the short-term self-administration animals, tyrosine did not significantly alter self-injection behavior. In these animals we might conclude that the manipulation of brain NE was of no benefit. However, whole brain NE was measured. It is entirely possible that specific anatomic nuclei in the brain respond neurochemically in a different manner to both amphetamine, tyrosine and/or the combination of drugs. Of the areas studied, the greatest amphetamine-induced depression of NE concentrations occurred in the medial prefrontal cortex with and no decreases occurring in nucleus accumbens. Tyrosine administration restored the depressed cortical NE concentrations (data not shown). These areas were chosen, however, on the basis of their speculated dopaminergic involvement in stimulant abuse and if NE is participatory, it is entirely possible that an area of the brain unresponsive to tyrosine treatment might be unaffected and conceivably, using whole brain studies, go undetected.

While there is some doubt as to a role of NE in the animal model of drug abuse (cf. review, [35]), the participation of DA containing neurons is well established. The increased

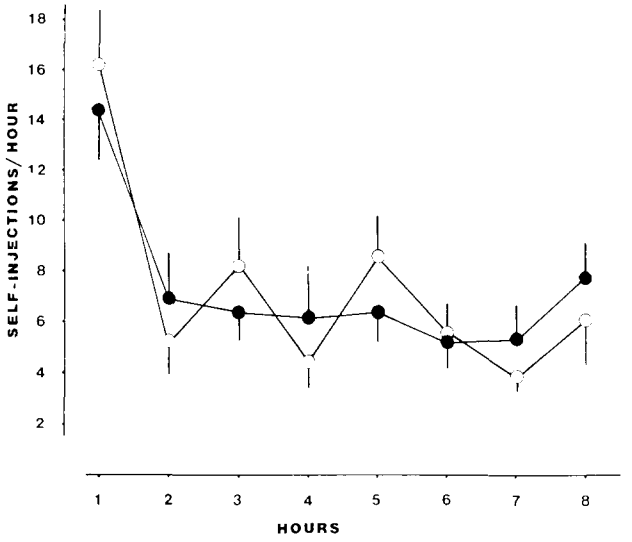

FIG. 3. Failure of L-tyrosine to influence d-amphetamine self-administration. The hourly number of d-amphetamine self-injections (mean ±1 S.E., N=7) from animals with a range of 21–35 days drug experience (short-term abuse animals) is shown for one 8 hr test session (open circles). On the next day the animals received 2 injections of L-tyrosine (100 mg/kg each, at the start and 4 hr into the test session). These points are indicated by the darkened circles. Statistical analysis failed to indicate significant differences between the two groups ($p>0.05$).

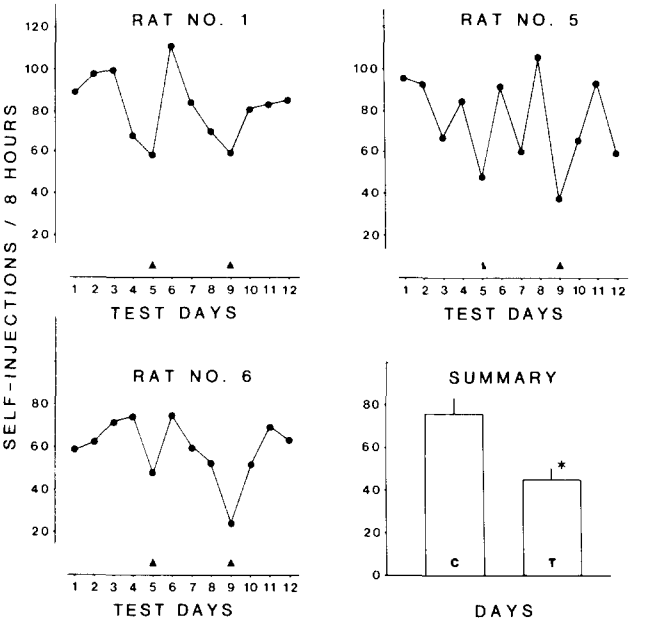

FIG. 4. Influence of L-tyrosine injections on d-amphetamine self-administration in rats with long-term amphetamine exposure. Rats with long term amphetamine exposure were as follows: Rat 1; 147 days, Rat 5; 152 days and Rat 6; 181 days. Days without L-tyrosine treatments are shown as well as days when 2 injections of tyrosine were administered (indicated by dark triangles). Injections (100 mg/kg/injection were given at the start of the test session and 4 hr into the 8 hr test session. The summary section (lower right) compared the mean ±1 S.E. of control days (C; N=30) with the days when tyrosine was administered (T; N=6). Asterisk indicates $p<0.05$ using ANOVA and Scheffe's test.

whole brain DOPAC concentrations observed earlier after the amphetamine-tyrosine combination [29] were examined in detail using regional DA/DOPAC analysis of nucleus accumbens, striatum and medial prefrontal cortex. Concentrations of DA and its metabolite were unaltered by amphetamine or the amphetamine-tyrosine regimen in nucleus accumbens. In the striatum, the amphetamine-tyrosine regimen induced an increase in DOPAC concentrations. In the medial prefrontal cortex DA concentrations were unchanged by either treatment while DOPAC concentrations were decreased by the amphetamine injection schedule and restored by the amphetamine-tyrosine regimen. These findings may in fact explain the failure of tyrosine to influence amphetamine self-administration. Nucleus accumbens DA containing neurons have been suggested to be a central component in the positive reinforcing effects of the psychomotor stimulants. Animals will self-administer amphetamine into this loci [6] and 6-OHDA-induced lesions of the nucleus abolish the acquisition and maintenance of both cocaine and amphetamine self-administration [17,26]. While it is puzzling that amphetamine does not alter DA or DOPAC concentrations in nucleus accumbens, this has been observed earlier. Amphetamine injection failed to alter DA synthesis in nucleus accumbens after a wide range of doses, while DA synthesis is increased in the striatum [16,22]. Although amphetamine alone failed to alter DOPAC concentrations in our study, the combination of amphetamine and tyrosine led to increases in striatal DOPAC levels. Given that a large percentage of whole brain DA is contained within the striatum, the increases in whole brain DOPAC concentrations observed earlier [29] may have been the result of an activation of DA synthesis by amphetamine and the increased precursor availability (tyrosine). Unfortunately, the striatum does not appear to be involved in the positive reinforcing effects of the psychomotor stimulants.

The medial prefrontal cortex was examined, in large part, due to recent publications suggesting that this area was of import in stimulant abuse and often inadvertently damaged by 6-OHDA lesions of nucleus accumbens. Rats were found to self-administer cocaine into medial prefrontal cortex and not nucleus accumbens [3], seriously challenging the hypothesis that the stimulus for continued drug abuse arises from DA neurons within the nucleus accumbens. A recent report however, has shifted the momentum back to the nucleus accumbens. Lesions of medial prefrontal cortex DA containing neurons failed to alter cocaine self-administration [19]. Similar results have been observed in this laboratory using amphetamine self-administration (Leccese and Lyness, in preparation).

The response of DA neurons within the medial prefrontal cortex to amphetamine is different than that observed with either the nucleus accumbens or striatum. However, while neurochemically interesting, its relevance to amphetamine self-administration behavior is now questioned. Despite the dramatic restoration of amphetamine-induced DOPAC decreases induced by tyrosine, the self-administration behavior of the short-term rats was unaffected by the amino acid.

The behavior of the long term self-administration animals (4–6 months drug access) was quite distinct from that of the short-term exposure group (≤1 month drug exposure). In the long-term exposure group, tyrosine injections significantly

decreased amphetamine self-administration. Unfortunately, neurochemical analyses of the effects of the amphetamine-tyrosine regimen could not be performed with only 3 animals. While the behavioral effects of the amino acid were reproducible we must rely on speculation to assess what, neurochemically, does actually occur.

As alluded to earlier, the role of cerebral NE containing neurons in the animal model of drug abuse has been questioned [35]. One must assume, however, that most of the animal studies, as well as our own, have used animals experienced with drug self-administration for only short periods of time. Indeed, most studies have given few details as to the animals prior drug abuse history. It has been shown that chronic amphetamine administration can decrease brain NE concentrations [15,21] and it has been suggested that psychomotor stimulant induced changes in noradrenergic function might be responsible for the withdrawal depression often observed in humans [31,32]. Whether tyrosine administration could restore lost or altered noradrenergic function in long-term amphetamine animals or whether NE has any function at all in the related problems of drug abuse remains to be determined but, at this point, cannot be ignored.

The effects of acute and chronic amphetamine on DA containing neurons have been extensively studied. Acute, large doses and chronic amphetamine administration have been shown to have deleterious effects on dopaminergic neurons, particularly those of the nigrostriatal tract [21, 23, 24, 28]. Swollen dopaminergic axons have been identified after chronic amphetamine, indicative of neuronal damage; and decreases in DA concentrations have been reported [23]. While the nigrostriatal pathways are most affected there have been suggestions of amphetamine-induced impairment of the function of DA neurons within nucleus accumbens and other brain regions [24]. Furthermore, several studies suggest changes in DA receptor binding in nucleus accumbens and other brain areas after chronic amphetamine [1,7]. Since DA receptor activity is coupled to DA synthesis and release, changes in receptor density or affinity for neurotransmitter could alter neurochemical events associated with amphetamine and/or the amphetamine-tyrosine combination, ultimately leading to changes in behavior. This, provided the brain areas involved with positive reinforcement or drug cravings are, indeed, altered in some manner by chronic long-term amphetamine abuse.

In summary, tyrosine administration to less experienced amphetamine self-administration rats produced neurochemical changes in brain NE and DA containing neurons but failed to alter drug self-injection. In older, long-term amphetamine abuse rats, tyrosine administration decreased drug self-injection. If the animal model of drug abuse is relevant to the human condition, these findings might have clinical ramifications. It might suggest that a patient's history of drug exposure could influence a particular treatment efficacy. The concept of using dietary supplements to affect neurotransmitter synthesis and ultimately behavior could perhaps prove safer than the use of the tricyclic antidepressants. Furthermore the concept of using dietary constituents is not new. Previous work has shown that the administration of the serotonin precursor, L-tryptophan, can produce a dramatic attenuation of amphetamine self-administration [10,15].

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