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Dietary Tryptophan Supplements Attenuate Amphetamine Self-Administration in the Rat

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SMITH, F. L., D. S. L. YU, D. G. SMITH, A. P. LECCESE AND W. H. LYNESS. *Dietary tryptophan supplements attenuate amphetamine self-administration in the rat.* PHARMACOL BIOCHEM BEHAV 25(4) 849–855, 1986.— Previously, it had been shown that lesions of cerebral 5-hydroxytryptamine (5-HT)-containing neurons and injections of drugs affecting 5-HT synthesis or receptor mediated function would alter amphetamine self-administration in the rat. The present study sought to ascertain whether diets enriched in L-tryptophan (L-TRY), the amino acid precursor to 5-HT, would: (1) elevate cerebral 5-HT concentrations and (2) affect amphetamine self-administration behavior. Diets containing 2.0 and 4.0% L-TRY increased cerebral 5-HT concentrations above those of rats on normal rat chow (0.26% L-TRY). The 4.0% diet elevated brain 5-HT to the same degree in rats exposed to the diet for 1, 2 or 3 days. When normal diets were restored, brain 5-HT concentrations rapidly returned to normal. Animals trained to self-administer d-amphetamine, when given access to the L-TRY enriched diets, significantly reduced their daily amphetamine self-injection during exposure periods. When normal rat chow was restored a delay in recovery to pre-diet amphetamine self-administration was observed: 1 day with the 2.0% L-TRY diet and 2 days with the 4.0% L-TRY diet. The 4.0% L-TRY diet failed to alter saline-frustration responding indicating the diet did not produce decrements in motor performance. When animals were placed on the 4.0% L-TRY diet and allowed access to amphetamine for 1 day then exposed to saline, a profound decrease in saline-frustration responding was observed. These data suggest that the combination of elevated cerebral 5-HT and amphetamine may produce or unmask some aversive qualities of the stimulant which reduce further drug abuse in the rat. The data is discussed in terms of a suggested modification of the present dopamine-reward hypothesis.

Amphetamine self-administration L-Tryptophan 5-Hydroxytryptamine Diet Negative reinforcement

THE abuse of psychomotor stimulants (cocaine, amphetamine, methamphetamine) is not only a growing international concern but difficult to treat medically. Encouraging reports of success in treating cocaine and amphetamine addicts with desipramine have been reported [4,23], but few medical texts even suggest treatment strategies for stimulant abuse. The reasons are that, for the most part, the neuronal substrates involved in drug seeking behavior, positive reinforcement and withdrawal are not well understood.

It is known, however, that cerebral dopamine (DA)-containing neurons are of major import in not only psychomotor stimulant abuse but perhaps even other agents of addiction [27]. It has been shown that the rat will self-administer stimulant type drugs, maintain stable rates of response and plasma levels of these drugs [27, 31–34]. Injection of DA receptor antagonists (e.g., haloperidol) lead to increased lever pressing behavior [3,32] similar to that observed when saline is substituted for the stimulant (frustration-extinction [33]). These findings have led to the DA-reward hypothesis, i.e., stimulation of DA receptors is necessary for the positive reinforcing effects of the psychomotor stimulants [27]. This hypothesis was further corroborated by the finding that: (1) non-contingent injection of DA receptor agonists reduce self-administration for periods consistent with their duration of action [34], (2) lesions of DA-containing neurons within the nucleus accumbens septi abolish the acquisition of cocaine and amphetamine self-administration behavior [14,20] and (3) human studies in which the subjective ratings of amphetamine-induced euphoria were significantly reduced in individuals who had received α-methyltyrosine, a drug which inhibits DA synthesis [8,9].

Another monoamine of importance in stimulant abuse, and apparently independent of cerebral DA and the DA-reward hypothesis, is 5-HT. Lesions of cerebral 5-HT-containing neurons with the neurotoxin 5,7-dihydroxy-

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TABLE 1

EFFECT OF DIETARY TRYPTOPHAN SUPPLEMENTS ON BRAIN 5-HT AND 5-HIAA

	Time (hr)			
	Monoamine/Metabolite (ng/g)			
	0900		1300	
Diet	5-HT	5-HIAA	5-HT	5-HIAA
Control	243.4 ± 12.9 (7)	397.7 ± 17.4	153.2 ± 6.8 (10)	350.6 ± 14.4
2.0% TRY	355.8 ± 17.2* (6)	474.4 ± 21.3	181.7 ± 14.3 (6)	344.7 ± 23.3
4.0% TRY	476.1 ± 37.5* (6)	516.7 ± 34.1*	256.8 ± 6.7* (6)	404.3 ± 11.6*

Amphetamine naive animals were placed in individual cages and allowed access to diets containing 0.26% L-tryptophan (control) or supplemented tryptophan diets with either 2.0 or 4.0% of the amino acid from 1700 hr the preceding day until 0900 hr the next day. At this time groups of animals were sacrificed at 0900 or 1300 hr and the dietary influence on the indoleamine and its metabolite ascertained in whole brain using methods already described. Values represent the mean ± 1 S.E. Numbers in parentheses indicate the number of animals in each group. Asterisks indicate statistically significant differences from the appropriate control group and time period ($p<0.05$, Students t-test).

tryptamine increase amphetamine self-injection by nearly 2-fold [10,15]. Injections of L-tryptophan (L-TRY), which elevate brain 5-HT [30], decrease intravenous amphetamine self-administration [10,12] as do IP injections of the 5-HT reuptake blocker fluoxetine and the indoleamine receptor agonist quipazine [10]. Lesions of 5-HT neurons have been shown to abolish the attenuation of drug self-administration induced by fluoxetine and L-TRY suggesting the actions of these agents are mediated by 5-HT neurons [10].

The present study was designed to determine whether a diet enriched with L-TRY would produce an attenuation of amphetamine self-administration, as IP injections of the amino acid are known to do, and to determine whether tolerance developed to the dietary influence on behavior. While the latter goal was not achieved, L-TRY enriched diets markedly affected amphetamine self-administration. Further experiments, in fact, suggest a possible mechanism of L-TRY action in stimulant abuse.

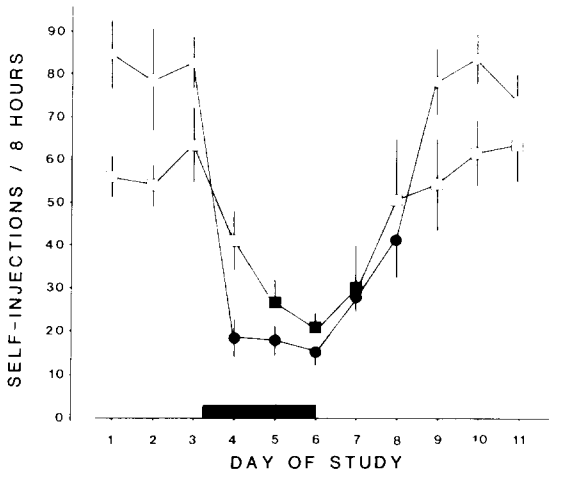

FIG. 1. Two different groups of animals are shown with the number of amphetamine self-injections 3 days prior to diet changes. Dark bar at the bottom of the graph indicates the diet substitution [2.0% L-TRY diet (□) and 4.0% L-TRY diet (○)]. Values shown are the mean±S.E. of 6–8 animals. Darkened symbols indicate statistically significant differences from the control diet period (ANOVA).

METHOD

Male Sprague-Dawley rats (King Animal Labs, Oregon, WI; 250–300 g) were used throughout these studies. Upon receipt, animals were allowed access to food (Purina Rat Chow 5001) and water ad lib.

Animals which were to be used in self-administration studies were anesthetized with pentobarbital (50 mg/kg) and halothane (as necessary) and implanted with a chronic silastic jugular cannula exiting subcutaneously as has been already described [12, 14, 25]. Rats were housed in individual cages and allowed a 7 day post-surgical recovery period before access to the self-administration apparatus.

Rats were placed in the self-administration apparatus from 0900–1700 hr each day with access to water but not food. The apparatus consisted of cages (18×20×26 cm; width, height and length, respectively) equipped with an operant lever which, when activated, initiated the intravenous injection of 0.125 mg/kg d-amphetamine (Sigma Chemical Co., St. Louis, MO). The volume per injection was 200 μl/kg. Details of the cages, pneumatic syringe device and recording techniques have already been described [13, 14, 26]. Within 5–10 days most rats achieved stable rates of amphetamine self-administration. At least 5 days before recording any self-administration data, the animals' diet was changed from Purina Rat Chow 5001 to an AIN-76 diet (Bio-Serv, Inc., Frenchtown, NJ), hereafter referred to as the control diet. While the two diets are comparable in content of the nutritional elements, the AIN-76 diet was certified as to content by the manufacturer and considered more appropriate for these studies. The AIN-76 diet consists of 18% protein (0.26% L-TRY), 5% fat, 72% carbohydrate and the remaining percentages accounted for by fiber, ash and moisture.

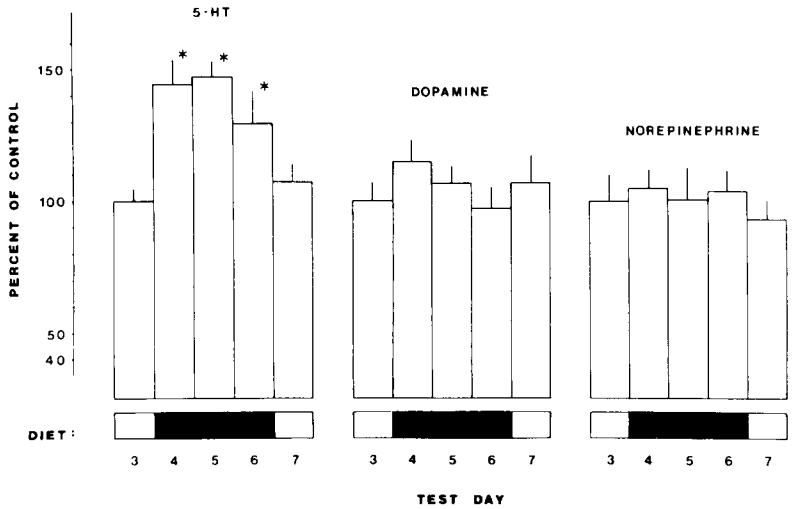

FIG. 2. Five separate groups of drug naive rats were fed as follows: (1) only control rat chow, (2) 1 day of 4.0% L-TRY diet, (3) 2 days of the 4.0% L-TRY diet, (4) 3 days of the 4.0% L-TRY diet or (5) 3 days of the 4.0% L-TRY diet and 1 day of control rat chow. Access to food was from 1700 to 0900 hr each day. Animals were sacrificed at 1300 hr on the next day. Analyses of whole brain 5-HT, DA and NE were performed. Values shown are the mean±S.E. determined from 6 animals per group. Statistical comparisons were made against the pre-diet change values (test day 3; corresponding to test day legend of Fig. 1). Dark bar at the bottom of the graph indicates the exposure to the 4.0% L-TRY diet.

A specially prepared AIN-76 diet containing 5.0% L-TRY was prepared by Bio-Serv, Inc. and served as a stock diet consisting of 22% protein, 5% fat and 66% carbohydrate. This stock diet was mixed with the appropriate volumes of control AIN-76 chow to yield diets containing 2.0 and 4.0% L-TRY. All animals, both amphetamine naive and self-administration animals were allowed access to food only during a 16 hr period (1700–0900 hr). Food consumption and body weight were recorded daily (0900 hr).

Neurochemical analyses of brain 5-HT, 5-HIAA, DA and NE were performed using whole brain (cerebellum and lower brain stem removed after sacrifice). The brain was weighed, homogenized with a Brinkman Polytron® and centrifuged at 10,000 × g. Aliquots of the supernatant were injected onto a BioAnalytical Systems (West Lafayette, IN) high pressure liquid chromatograph with an amperometric detector. The mobile phase consisted of 10% methanol and 40 mg/l sodium octyl sulfate in a 0.1 M citrate-phosphate buffer. A 5 μ C_{18} μBondapak chromatographic column was used. Electrode potential was +0.72 V vs. Ag/AgCl reference electrode and flow rate was 1.0 ml/min at ambient temperature. Further details are described elsewhere [11].

Statistical analyses were performed using analysis of variance with Duncan's Multiple Range Test (α level 0.05) or the Student's t-test (values where $p<0.05$ were considered statistically significant).

RESULTS

Diets enriched in L-TRY induce increases in cerebral 5-HT and 5-HIAA in part, because the competition for neutral amino acid uptake by the brain is shifted in favor of L-TRY and the rate limiting enzyme in 5-HT synthesis, tryptophan hydroxylase, is normally unsaturated [30]. The data illustrated in Table 1 shows that the diets utilized in this study do indeed increase brain 5-HT. Two time points were examined: 0900 and 1300 hr. The first point, 0900 hr, corresponds with the beginning of a self-administration test session, immediately after the diets are removed from the rats' cages. The second time point, 1300 hr, corresponds with the 4 hr midpoint of a self-administration test session.

The 2.0% L-TRY diet increased brain 5-HT at 0900 hr but not at 1300 hr. Concentrations of 5-HIAA were high at 0900 but not statistically different from animals on the control rat chow. The concentrations of both 5-HT and 5-HIAA were comparable to control diet values at 1300 hr. Thus, the 2.0% diet alters cerebral indoleamine concentrations only transiently. The 4.0% L-TRY diet nearly doubled brain 5-HT and significantly increased 5-HIAA at the first time point (0900 hr). While the values are still significantly increased 4 hr later (1300 hr), the trend is clear that these values are decreasing and approaching normal, control indoleamine concentrations.

Figure 1 shows the effects of the 2.0 and 4.0% L-TRY diets on the behavior of animals trained to self-administer d-amphetamine. The range of experience in these rats (both groups) was from 27–42 consecutive days of amphetamine exposure (8 hr test sessions). The 4.0% L-TRY diet produced a dramatic decrease in the number of amphetamine self-injections after the first night and the two subsequent days on the diet. After the normal rat chow (AIN-76) was restored the number of amphetamine self-injections was still significantly reduced for an additional 2 days.

Rats in the 2.0% L-TRY diet study were also affected. After the first night on the diet, the number of self-injections was reduced on the first day but not significantly. The second and third nights on the diet did produce a significant attenuation of drug intake. Again, some delay in the resumption of normal self-injection behavior occurred since, after restoration of a normal diet, the number of amphetamine

TABLE 2

EFFECTS OF A TRYPTOPHAN SUPPLEMENTED DIET ON FOOD INTAKE IN NAIVE AND CHRONIC AMPHETAMINE SELF-ADMINISTRATION ANIMALS

Pretreatment	Diet	Body Wt (g)	Food intake (g) Day 1	Day 2	Day 3
Naive	Control (6)	367.2 ± 28.1	34.0 ± 1.7	27.1 ± 2.6	28.4 ± 2.2
	4.0% TRY (6)	395.0 ± 16.0	33.9 ± 2.8	30.7 ± 4.5	29.3 ± 2.9
Chronic	Control (5)	350.0 ± 22.5	26.0 ± 3.2	28.6 ± 2.9	28.6 ± 3.6
Amphetamine	4.0% TRY (6)	361.2 ± 22.8	24.4 ± 2.4	30.4 ± 3.3	26.1 ± 5.7

Body weights of drug naive and chronic amphetamine self-administration rats (Range 27–42 consecutive days) were measured before dietary changes. Daily food intake was monitored (access to food 1700–0900 hr) using a 0.26% L-TRY diet (control) and the 4.0% L-TRY supplemented diet. Statistical comparisons of daily food intake indicated that neither the supplemented L-TRY diet nor an animal's past drug history altered total food intake ($p<0.05$).

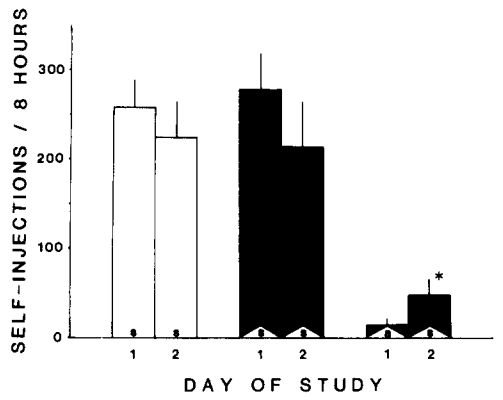

FIG. 3. Animals trained to self-administer d-amphetamine for at least 20 days were placed in cages which delivered intravenous saline. Open bars (far left) indicate the number of lever presses during 2 consecutive 8 hr test sessions in rats on a normal diet (0.26% L-TRY, N=12). Animals on a 4.0% L-TRY enriched diet, commencing 1 day prior to the saline-frustration testing are shown in the middle (dark bars, N=10). The third group (far right) was allowed access to the 4.0% L-TRY diet and 1 test session with intravenous d-amphetamine with each lever press. The following day saline was received with each lever press (N=9). Values represent the mean±S.E. of the total number of lever presses recorded with each session. The letters in each bar represent the substance self-injected (s: saline, a: amphetamine). Asterisk indicates a statistically significant difference from test day 2 values in both normal rat chow and 4.0% L-TRY diet groups ($p<0.05$).

self-injections was still significantly reduced. On subsequent days the daily drug intake was comparable to pre-diet periods. Preliminary experiments using a 1.0% L-TRY enriched diet have failed to induce statistically significant changes in d-amphetamine self-administration.

Of some concern are the pre-diet differences in the number of daily amphetamine self-injections between the 2.0 and 4.0% L-TRY diet groups (Fig. 1). The 2.0% L-TRY group consistently self-injected less amphetamine during the control diet period. The reasons for this are uncertain. This group was initiated approximately 2 months after the 4.0% L-TRY diet studies were concluded. However, the rats were allowed comparable drug exposure and self-administered amphetamine in consistent patterns. Whether the difference in control diet self-administration reflects a seasonal variation in some unknown parameters is uncertain. While the differences in control amphetamine self-administration could alter the possible comparative magnitude of the L-TRY-induced responses, it is clear that both the 2.0 and 4.0% L-TRY diets did attenuate amphetamine abuse in rats.

Table 1 had shown that, at least acutely, one night of an L-TRY enriched diet could elevate cerebral 5-HT concentrations. It was important to ascertain whether successive exposures to the diet produced consistent changes in 5-HT concentrations, and whether other monoamines, i.e., DA and norepinephrine (NE) were altered in some manner. Figure 2 shows that the diet, on 3 consecutive nights of exposure, increased 5-HT each day to roughly the same extent. When the normal rat chow (AIN-76) was reinstated, after 3 days of the 4.0% L-TRY diet, brain 5-HT concentrations returned to normal. Thus, the diet-induced changes in 5-HT were transient. Whole brain concentrations of DA and NE were unaffected by the diet.

Logistically, it would be difficult to use animals trained to self-administer d-amphetamine for the neurochemical analyses and the effects of diet on cerebral monoamines. Amphetamine naive rats were used for these purposes. However, a concern which had to be addressed was whether chronic amphetamine exposure altered food intake and more seriously, whether the consumption of the L-TRY enriched diet in combination with amphetamine was reduced. If this were so, i.e., less food was consumed, the neurochemical changes in 5-HT concentrations would undoubtedly be reduced.

Although amphetamine is a well known anorexigenic agent, the chronic self-administration animals did not eat less food than weight matched drug naive animals (Table 2). Tolerance to amphetamine-induced anorexia is documented to be very rapid. Our animals may have been tolerant to this effect by the time of our observations. It can also be seen (Table 2) that the 4.0% L-TRY enriched diet was also consumed to the same extent as control rat chow in both the drug naive and chronic amphetamine self-administration animals.

The final series of experiments was designed to determine whether L-TRY enriched diets produced decrements in motor performance capable of reducing lever pressing behavior to the extent observed in Fig. 1. Animals trained to self-administer d-amphetamine with a normal rat chow were

given access to the self-injection apparatus for 2 days in which the amphetamine solution had been replaced with saline. These animals lever press quite frequently, a phenomenon observed by others [31–33] and termed saline frustration. This behavior did not show signs of extinction during the two test days (Fig. 3). A second group of animals was given a 4.0% L-TRY enriched diet the night before access to the saline substitution test (1700–0900): a protocol identical to that used in Fig. 1. The number of lever presses recorded during the 2 days of saline-substitution were comparable to those animals consuming the control diet (Fig. 3). This would strongly indicate that the high L-TRY diet did not reduce motor performance.

A third and separate group of animals was allowed access to only the 4.0% L-TRY enriched diet for 2 days. After the first night the animals were allowed access to the self-administration apparatus. This time d-amphetamine was delivered IV to the rats with each lever press. This led to a significant attenuation of amphetamine self-injection (16.2±4.9 injections over an 8 hr test session; Fig. 3). After removal from the test cages, animals were exposed, again, to the high L-TRY diet (1700–0900 hr) and the amphetamine reservoir replaced with one containing normal saline. These animals, when allowed to press a lever the next day in which they received IV saline, accumulated a mere 47.1±19.3 self-injections. These results were significantly different from the 233.1±43.1 and 212.6±50 injections accumulated by the 2 day exposure to saline in control and high L-TRY diet groups, respectively. This observation may, in fact, give a clue as to the mechanism of L-TRY action in the attenuation of amphetamine self-administration.

DISCUSSION

The actions of 5-HT in psychomotor stimulant abuse could not be explained in the confines of the DA-reward hypothesis. Lesions, both general whole brain 5,7-DHT-induced or discrete nuclear neurotoxin injections, fail to alter either DA synthesis or turnover [13, 16, 19]. This does remain controversial, however, since some authors have observed increased DA turnover [4] or decreased turnover [22] after similar lesions. Injections of L-TRY (100 mg/kg), a dose which produced a marked attenuation of amphetamine self-administration, fail to alter DA turnover in either whole brain or nucleus accumbens [12], a brain region of import in the DA-reward hypothesis. It would appear then that the mechanisms of 5-HT action are independent of a direct action upon DA-containing nerve terminals.

The attenuation of amphetamine self-administration by L-TRY could, however, have several explanations. First, L-TRY and other drugs which enhance the indoleamine receptor interaction could be euphorigenic, i.e., positive reinforcers by themselves. This does not appear to be the case. Clinical literature would certainly indicate if this were so. Furthermore, IP L-TRY fails to affect a place preference in rats given a range of doses 25–100 mg/kg (Yu, Smith, Smith, Geis and Lyness, in preparation). The data presented in Fig. 1 and 2 also suggest L-TRY is not a positive reinforcing compound. Rats given the 4.0% L-TRY diet require 2 days after normal diets are restored before a resumption of pre-diet amphetamine intake is observed. The neurochemical analyses (Fig. 2) show the dietary changes in cerebral 5-HT concentrations are transient and rapidly return to normal, as one might expect from other studies which have examined the effects of this amino acid on brain chemistry [24].

A second possibility is that diets high in L-TRY produce decrements in motor performance rendering the animal incapable of lever pressing at pre-diet levels. L-TRY has after all been used as a sedative in man [2]. This hypothesis is as equally a poor explanation of our findings. The amino acid is only efficacious when administered at the normal onset of sleep in humans [2]. In the rat, doses of 100 mg/kg IP fail to alter shuttle escape behavior [1]. Similarly 120 mg/kg IP L-TRY did not alter EEG or EMG recordings in rats [29], failed to alter lever pressing response in an FR-40 food reinforced paradigm [12] and only began to affect the locomotor activity in mice at doses in excess of 700 mg/kg [17]: doses likely to also affect the synthesis and release of other important monoamines, e.g., DA and NE [30]. Finally, the data presented in Fig. 3 show that the 4.0% L-TRY diet failed to alter saline-frustration responding. The diet only reduces lever pressing for IV amphetamine.

There is a third hypothesis. It relies on somewhat circumstantial evidence but is a hypothesis our data may support and, in actuality, supports some of the inexplicable findings associated with the DA-reward hypothesis. The third hypothesis is that procedures which enhance the synaptic availability of 5-HT, in the presence of amphetamine, may induce or exaggerate an aversive or negative reinforcing property of the stimulant.

The evidence for this hypothesis stems from several findings. Under certain test conditions, amphetamine can be used as an aversive stimulus even though it is most known for its positive reinforcing component [28]. The use of acute IP doses of L-TRY appeared to attenuate amphetamine self-administration for periods consistent with the elevations in the cerebral indoleamine and its metabolite [12]. The chronic 4.0% L-TRY diet attenuated drug self-injection for 2 days following the restoration of a normal diet. This occurred despite normal 5-HT concentrations the day after the normal diet was reinstated. The neurochemical changes and behavior are divergent at this point. While speculative, if enhancement of 5-HT function (mediated by L-TRY) exaggerated an aversive component of amphetamine, rats might be expected to reduce or even abolish lever pressing for drug self-injection. If during the 3 days on the high L-TRY diet the animals learned that such behavior led to unpleasant sensations, one might expect a delay in the re-learning of previously positive-reinforced behaviors. Hence the delay in recovery to pre-diet drug intake.

The data in Fig. 3 lend further support to this hypothesis. The 4.0% L-TRY diet clearly does not alter the saline-frustration response. These animals were trained to self-administer d-amphetamine, placed on the diet and then allowed access to cages which would only administer saline. If L-TRY induced a euphoria or decrements in motor performance one might expect a decreased responding, even for saline. This did not occur.

When rats are placed on the diet and allowed access to amphetamine a marked decrease in responding occurs. After this time, if rats are allowed access to cages which deliver only saline, one might predict a decreased saline-frustration response if animals had learned the previous day that such behavior produced unpleasant effects. At present, these observations cannot be explained in any manner other than a learned aversion to amphetamine.

The hypothesis that 5-HT mediates an aversive component of amphetamine action might explain some puzzling findings in rats with 6-hydroxydopamine-induced lesions of DA neurons in the nucleus accumens: findings not explicable

by the DA-reward hypothesis. If DA-containing neurons within nucleus accumbens mediate the positive reinforcing effects of the psychomotor stimulants, it is predictable that lesions of these neurons in drug naive animals would produce rats which would not acquire the habit of IV self-administration. Devoid of positive reinforcing properties, the animals would not be motivated to learn the behavior. This, in fact, does occur in animals tested with both cocaine [20] and amphetamine [14]. The difficulty in the DA-reward hypothesis arises with the use of animals trained to self-administer these stimulants then performing 6-OHDA lesions of DA neurons. Removing only the rewarding properties of a drug should produce a saline-frustration type response, i.e., increased lever pressing behavior, if one adheres to the present concepts of the DA-reward hypothesis. Yet this does not occur. Animals trained to self-administer cocaine or amphetamine, when 6-OHDA lesions are performed, do not exhibit saline-frustration behavior. A profound absence of lever pressing was observed by both authors [14,20].

Under normal circumstances, when an animal self-injects a psychomotor stimulant, the positive reinforcing effects, mediated by DA in nucleus accumbens and perhaps the medial prefrontal cortex [7], are the dominant effects instigating further drug abuse behavior. Our studies propose that 5-HT mediates an aversive or negative reinforcing property of amphetamine which is normally masked by the dominance of DA mediated positive reinforcement. If the receptor actions of 5-HT are exaggerated by L-TRY or other serotonergic agents this aversive component may become more dominant and reduce subsequent drug intake. Further, if the euphorigenic component of amphetamine is removed by 6-OHDA-induced lesions, the aversive component is unmasked.

The DA-reward hypothesis is indeed sound but modification of this theory to include 5-HT mediation of an aversive component is conceivable. The concept that 5-HT could mediate aversion to drug intake is not without precedent. Injections of 5-hydroxytryptophan, the immediate precursor to 5-HT, known to elevate cerebral 5-HT concentrations, were able to produce a conditioned taste aversion to ethanol in rats consuming 12% ethanol solutions. The aversion was of such magnitude that a number of the animals died of dehydration since the alcohol solution was their only source of fluids [35]. It is interesting that rats continued to show an avoidance to alcohol for some time after the discontinuation of 5-hydroxytryptophan injections [36]. Fluoxetine, the 5-HT reuptake inhibitor, has also been shown to reduce alcohol consumption in ethanol dependent rats [37]. Zimelidine, another 5-HT reuptake inhibitor, has similar effects in man [18].

The phenomenon of 5-HT receptor active agents modifying drug intake may be applicable over even a wider spectrum of drugs of abuse. Studies with opiate self-administration may yield similar findings. It has been shown that zimelidine decreased oral morphine consumption in dependent rats [21]. Lesions reducing brain 5-HT concentrations have reportedly increased morphine self-administration in non-dependent rats [6].

In summary, the studies reported herein suggest that 5-HT might mediate an aversive component of amphetamine action. If this is so and the animal self-administration model is applicable to human drug abuse, this phenomenon might be clinically exploited. Given the current magnitude of the drug abuse problem the role of 5-HT in addictive states should be examined further.

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