Drug and Alcohol Dependence, 17 (1986) 143—150
Elsevier Scientific Publishers Ireland Ltd.

A REVIEW OF THE EFFECTS OF REPEATED ADMINISTRATION OF SELECTED PHENYLETHYLAMINES

WILLIAM L. WOOLVERTON

University of Chicago, Department of Pharmacological and Physiological Sciences, The Drug Abuse Research Center, Pritzker School of Medicine, Chicago, IL 60637 (U.S.A.)

SUMMARY

Several phenylethylamines are under consideration for international control. The effects of repeated administration of these compounds, including tolerance, physical dependence and central nervous system (CNS) toxicity, are reviewed here. The compounds can be divided into two major chemical groups: those with substituents on the ethylamine portion of the molecule and those with substituents on the phenyl ring. Although the effects of repeated administration have not been directly determined for most of the compounds, certain representative compounds of each chemical group have been examined in some detail. Prominent among the effects of repeated administration are CNS toxicity and tolerance development. Physical dependence has not been reported for any of these compounds. Future research with these compounds should emphasize the investigation of the CNS toxicity and the functional consequences of such effects for the organism.

Key words: Phenylethylamines — Repeated administration — Neurotoxicity — Tolerance — Physical dependence

INTRODUCTION

The purpose of this paper is to review the information that is available concerning the effects of repeated administration of several phenylethylamines that are under consideration for international control (Table I). The effects of principal concern herein are the development of tolerance and/or physical dependence and as well as the development of long-lasting toxic

Address reprint requests to Dr. Woolverton at University of Chicago, Department of Pharmacological and Physiological Sciences, 947 E. 58th Street, Chicago, IL 60637, U.S.A.

0376-8716/86/$03.50

TABLE I

PHENYLETHYLAMINES UNDER CONSIDERATION FOR INTERNATIONAL CONTROL

Compounds with ethylamine substituents	Compounds with phenyl ring substituents
Cathine	Dimethoxybromoamphetamine
Cathinone	Methoxyamphetamine
Clobenzorex	Methoxymethylenedioxyamphetamine
Ethylamphetamine	Methylenedioxyamphetamine
Fenbutrazate	*Para*-oxyamphetamine
Fencamfamine	Trimethoxyamphetamine
Fenetylline	4-Bromo-2,5-dimethoxyphenethylamine
Fenproporex	*N*-Ethyl-3,4-methylenedioxyamphetamine
Levamfetamine	3,4-Methylenedioxymethamphetamine
Levomethamphetamine	
Mefenorex	
Morazone	
Pemoline	
Propylhexedrine	
Pyrovalerone	
N,N-Dimethylamphetamine	

effects, especially in the CNS. These effects are important for two major reasons. Many of these compounds are used clinically as anorectics putting the patient population using these drugs at risk of experiencing effects of repeated administration other than appetite suppression. In addition, many of the compounds have effects, including CNS stimulation and hallucinations, that may encourage their repeated self-administration for non-medical reasons. In this context, the effects of repeated administration of this class of compounds becomes a significant public health problem.

The general approach to reviewing these compounds has been to group them according to chemical structure. They can somewhat arbitrarily, but conveniently, be divided into those compounds with substituents on the ethylamine portion of the molecule and those with substituents on the phenyl ring. In general, although there is some important overlap, and some exceptions, compounds in the former group act as CNS stimulants and are often used as anorectics while compounds in the latter group are largely hallucinogens. In addition, the two groups are generally believed to have different mechanisms of action, the stimulants/anorectics exerting their effects via catecholamines and the hallucinogens via serotonin. Since information is scarce for most of these compounds, the effects of a prototype drug for which the most information is available is described in some detail with the implication that there is better-than-chance probability of finding these effects in other members of the group. Animal data and, where possible, human data are presented. It is clear, however, that much research is needed before the effects of most of these compounds are known with certainty.

COMPOUNDS WITH ETHYLAMINE SUBSTITUENTS

This group includes the phenylethylamines that have one or more amphetamine-like behavioral effects which may include anorexia, psychomotor stimulation and generation of stereotyped behavior. Biochemically these compounds have indirect catecholaminergic effects that are generally thought to be involved in these behavioral effects.

Among these compounds, the most data are available for cathinone, the principal active component of Khat leaves. Biochemically, cathinone enhances the release of dopamine (DA) from rat and rabbit striatal slices [1,2] and releases as well as blocks reuptake of DA in rat synaptosomes [3]. Other research has suggested noradrenergic (NE) [4] and serotonergic (5-HT) [5] effects as well. Behaviorally, cathinone induces stereotyped behavior [6,7], decreases food intake [8,9] and is amphetamine-like in tests of its discriminative stimulus properties [10]. The compound is self-administered intravenously by rhesus monkeys [11] and appears to have reinforcing efficacy equivalent to that of cocaine [12]. On repeated administration, tolerance develops to the effects of cathinone on food intake and animals that are tolerant to cathinone are cross-tolerant to (+)-amphetamine [8,9]. Also, on repeated administration of cathinone there is a selective and long-lasting depletion of DA in various brain regions of rats and evidence that this is due to destruction of DA-containing neurons [3]. Finally, the toxic psychosis often reported to develop in humans upon repeated administration of amphetamine has rarely been reported with cathinone, perhaps because of the use of the oral route of administration by people who chronically chew Khat leaves.

A second compound under consideration is cathine, also an active component of the Khat leaf. The available data suggest that cathine is biochemically and behaviorally cathinone-like but substantially less potent than cathinone. Cathine has been shown to block the uptake of DA into rat striatal slices with roughly 1/8 the potency of cathinone [2]. As with cathinone, cathine induces ipsilateral rotation in rats with unilateral lesions of the nigro-striatal pathway [2], induces stereotyped behavior [7,13] and substitutes for (+)-amphetamine as a discriminative stimulus [14], behavioral effects thought to involve central DA mechanisms. In these preparations cathine was generally found to be 1/4—1/8 as potent as cathinone. On repeated administration, tolerance seems to develop to the reduction in food intake produced by cathine and some cross-tolerance between cathine and cathinone or amphetamine was noted [9]. However, since only body weight data were presented, the evidence is somewhat indirect. No data are available concerning the CNS toxicity of repeated administration of cathine in animals. However, paranoid psychosis has occasionally been reported in humans using high doses of the drug repeatedly [15,16].

Ethylamphetamine, levamfetamine and levomethamphetamine are synthetic amphetamine-like compounds that are under consideration for sched-

uling. Ethylamphetamine is the *N*-ethyl derivative of amphetamine and levamfetamine is the levo isomer of amphetamine. Each compound has indirect agonist effects on catecholamine systems [17—19]. Ethylamphetamine and levamfetamine have been reported to induce amphetamine-like behavioral effects [17,20] and to be self-administered intravenously by rhesus monkeys [20—22]. Levomethamphetamine is the levo isomer of methamphetamine. Little information is available concerning its biochemical effects, although it is clearly sympathomimetic [18]. Regarding CNS effects, the major difference between this compound and (+)-methamphetamine seems to be one of potency, levomethamphetamine being less potent [18]. Like (+)-methamphetamine, levomethamphetamine has been found to be self-administered intravenously by rats [23].

Although it is well-established that repeated administration of the amphetamines results in the development of tolerance to many of their effects without the development of physical dependence [24], direct testing of this possibility with these three stimulants has been limited. Tolerance develops to the behavioral effects of levamfetamine in rats within 6—10 days. However, only partial cross-tolerance, at best, develops between (+)- and (−)-amphetamine, perhaps indicating that different mechanisms are involved in the behavioral disruptions produced by these compounds [25]. In addition, substantial tolerance develops to the behavioral effects of (+)-methamphetamine [26]. There is no evidence for the development of physical dependence upon any of these compounds and data concerning their CNS toxicity upon repeated administration are not, apparently, available. It is, however, well known that repeated administration of the closely related compounds (+)-amphetamine and (+)-methamphetamine results in long-lasting CNS toxicity in animals [26,27] and paranoid psychosis in humans. It might, therefore, be predicted that these compounds would have similar toxicity. It should be noted that not all amphetamine-like compounds have pronounced CNS toxicity. Pemoline, for example, has biochemical and behavioral effects in common with amphetamine [28,29]. However, administration of 30 mg/kg per day pemoline to rats for 10 days did not alter brain levels of catecholamines [30]. Interestingly, pemoline has also been reported not to be self-administered by rhesus monkeys [31,32] and, thus, is not entirely amphetamine-like in its behavioral effects.

Still less information is available concerning the effects of repeated administration of the other compounds with ethylamine substituents. Fenetylline, fenproporex and mefenorex are at least partially metabolized to amphetamine and might be expected to have amphetamine-like effects on repeated administration [33,34]. Fencamfamine has psychomotor stimulant effects in rats but there appear to be biochemical differences between fencamfamine and amphetamine [35]. It is self-administered intravenously by dogs [36] and monkeys [31], has cocaine-like discriminative stimulus properties in rats [51] and would therefore be predicted to have dependence potential. Pyrovalerone releases and blocks the reuptake of NE in vitro [37],

has typical psychomotor stimulant effects in animals [38] and abuse has been reported in humans [40]. Similarly, propylhexedrine, the active ingredient in the Benzedrex inhaler, has abuse potential and its repeated self-administration by humans has been reported to produce psychosis [33].

The remaining compounds in this group are clobenzorex, fenbutrazate, furfenorex, morazone and *N,N*-dimethylamphetamine. Clobenzorex, fenbutrazate and furfenorex are used as anorectics. Morazone is used as an analgesic and *N,N*-dimethylamphetamine has CNS stimulant effects. No publications were found concerning the repeated administration of any of these compounds.

COMPOUNDS WITH PHENYL RING SUBSTITUENTS

The other group of compounds under consideration is the ring-substituted phenylethylamines. Most, if not all of these, have hallucinogenic activity; some have a mix of LSD-like and amphetamine-like effects. Their mechanisms of action are believed to be serotonergic, acting either directly on serotonergic receptors or indirectly to release 5-HT.

Only a limited amount of information is available regarding the effects of repeated administration of these compounds. Physical dependence has not been reported. Tolerance to the effects of these compounds has not, apparently, been examined directly, though tolerance to a prototypical member of this group, mescaline, as well as cross-tolerance to other hallucinogenic compounds, have been reported to develop in rats [41] and humans [42]. In addition, dogs tolerant to LSD have been shown to be cross-tolerant to 2,5-dimethoxyamphetamine (DMA) and 2,5-dimethoxy-4-bromoamphetamine (DOB) and partially cross-tolerant to 3,4,5-trimethoxyamphetamine (TMA), 5-methoxy-3,4-methylenedioxyamphetamine (MDMA) and 3,4-methylenedioxyamphetamine (MDA). However, they were not cross-tolerant to para-methoxy-amphetamine (PMA) [43]. Thus, although one would predict the development of tolerance to these compounds upon their repeated administration, cross-tolerance has not been observed among all members of this group.

The CNS toxicity of two of these compounds, MDA [44] and MDMA [45], has been evaluated in rats. With each drug, depletion of 5-HT in various brain regions was observed 2 weeks after a brief (4 day) repeated injection regimen and after a single injection of a higher dose. Uptake studies as well as morphologic evidence suggest that these depletions of 5-HT were due to damage to 5-HT containing neurons. Given the apparent dependence potential of these two compounds [46—49], the generality of these effects should be examined thoroughly in other species. These findings also suggest the possibility that this class of compounds may be generally neurotoxic and so represent a threat to the humans that use them. Currently, this information is not available.

CONCLUSIONS

A search of the literature on these phenylethylamines provided very little information concerning the effects of their repeated administration. However, substantial research has been conducted on a few prototype compounds. Repeated administration of a representative compound of the group with ethylamine substituents, cathinone, results in the development of tolerance, but not physical dependence, and destruction of central DA-containing neurons. Repeated administration of a representative compound of the group with substituents on the phenyl ring, MDA, results in toxicity to central 5-HT-containing neurons and animals that are tolerant to LSD are cross-tolerant to MDA. It might be expected that compounds in each of these general classes with similar behavioral and neurochemical effects would have similar effects when administered repeatedly. However, much research is needed before this can be concluded with confidence.

In establishing priorities for research, several factors should be considered. For example, within each chemical group, compounds that are widely used clinically or have significant potential for abuse should be emphasized over those that have only one or neither of these attributes. Further, in considering what research should be done with such compounds, perhaps the consequences of repeated administration that are of the greatest concern should be examined first. Clearly, this requires some decisions as to the relative importance of the various effects of repeated administration. As stated previously, representative compounds from each group have been found to produce long-lasting depletions of neurotransmitters in the CNS of rats, in some cases after only a single exposure [3,44,45,50]. Although the short-term or long-term functional consequences of these depletions are unclear, this type of toxicity is certainly a major concern for these compounds and should be examined. Tolerance and physical dependence are functional consequences of repeated administration that play a role in escalation of drug dose and maintenance of drug-seeking behavior. In this context, both of these effects are important determinants of CNS toxicity of repeated administration of these compounds. Physical dependence has not, however, been found to develop to prototypical phenylethylamines, making it reasonable to suspect that this is not an important effect of this class of compounds. Moreover, these consequences are generally considered to be reversible and, therefore, may be of less long-range consequence. Therefore, the examination of CNS toxicity and the functional consequences of these effects would appear to be a top priority for these phenylethylamines.

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