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Clobenzorex: Evidence for Amphetamine-Like Behavioral Actions

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YOUNG, R; N. A. DARMANI; E. L. ELDER; D. DUMAS AND R. A. GLENNON. *Clobenzorex: Evidence for amphetamine-like behavioral actions.* PHARMACOL BIOCHEM BEHAV **56**(2) 311–316, 1997.—Clobenzorex, an optically active *N*-substituted derivative of (+)amphetamine, has been identified on the illicit market. Because so little is known regarding the pharmacology or abuse potential of this agent, it was examined in tests of stimulus generalization in rats trained to discriminate 1 mg/kg of (+)amphetamine from vehicle to determine if it would produce amphetamine-appropriate responding. Clobenzorex (ED_{50} = 6.6 mg/kg) substituted for (+)amphetamine (ED_{50} = 0.3 mg/kg) but was approximately twenty times less potent than the training drug. Clobenzorex was also compared with (+)amphetamine and cocaine for its ability to induce locomotor stimulation and rearing frequency in mice. Clobenzorex was active in both assays but was less potent than either (+)amphetamine or cocaine. It is concluded that, although weaker than (+)amphetamine, clobenzorex constitutes an agent with amphetamine-like central stimulant behavioral properties. **Copyright © 1997 Elsevier Science Inc.**

(+)Amphetamine Clobenzorex Cocaine Drug discrimination Locomotor activity Rearing behavior Central stimulants Anorectics

CLOBENZOREX or S(+)1-phenyl-2-[(2-chorobenzyl)amino]propane (see Fig. 1 for structure), is an amine-substituted derivative of S(+)amphetamine available in Mexico, Spain, Argentina, and France as an anorectic agent (17). Amphetamine is a prototypical phenylalkylamine stimulant, and optimal stimulant potency is associated with a primary amine, or a secondary amine where the amine substituent is a methyl group (12). Amphetamine derivatives with amine substituents larger than a methyl group typically display reduced central stimulant properties (12,25). Indeed, it has been suggested that clobenzorex differs from amphetamine as an anorectic in that it doesn't produce central excitation or insomnia at therapeutic doses (19). The anorectic potency and toxicity (LD_{50} = 103 mg/kg; mouse) of clobenzorex is also less than that of (+)amphetamine (1). Although there have been reports describing the spectroscopic and structural character of clobenzorex (e.g., (2,3,10,18) extraordinarily little has been published on its pharmacology since it was first reported by Boissier et al in 1966 (1).

Clobenzorex recently came to our attention when it was identified as an adulterant or contaminant of some Chinese herbal medicines by the National Laboratory of Foods and Drugs in Taiwan (Dr. Y. Sheu, personal communication). There is almost no literature on clobenzorex as a potential drug of abuse. For example, clobenzorex appears to have been responsible for producing an acute psychosis, including visual and auditory hallucinations, in one individual, but this response may have resulted from a drug interaction (16). There is also a report of abuse by another individual who was reportedly addicted to clobenzorex (5). With little compelling evidence supporting the possibility that clobenzorex may be an amphetamine-like agent, even though clobenzorex has been encountered recently in forensic samples (18), we thought that further evaluation of this agent was in order.

Being a derivative of the central stimulant amphetamine, clobenzorex (if indeed a central stimulant) may behave in a manner similar to that of amphetamine. Amphetamine and amphetamine-like agents produce significant stimulant effects

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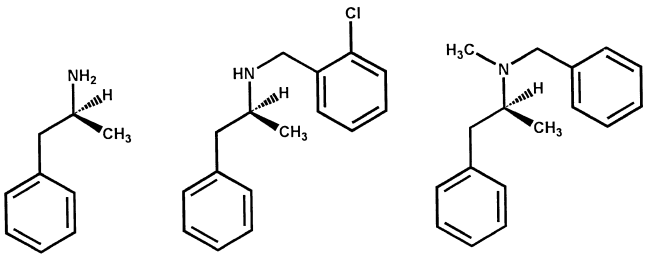

FIG. 1. Structures of S(+)amphetamine (left), clobenzorex (center), and S(+)*N*-benzphetamine (right).

in mice (e.g., (12,22); this can be observed by measuring such behaviors as locomotor stimulation and rearing. This is one of the oldest and most widely used methods for assessing the stimulant activity of drugs. Another standard technique for detecting amphetamine-like activity is to examine agents in tests of stimulus generalization in animals (e.g., rats, pigeons) trained to discriminate (+)amphetamine from vehicle (reviewed: 14,26). However, it has been demonstrated that the stimulus properties of amphetamine are not necessarily related to its stimulant actions; that is, the locomotor effects of stimulants may involve dopaminergic pathways in the striatum whereas the stimulus effects of amphetamine seem to be mediated by mesolimbic dopaminergic systems [see Goudie (14) for discussion]. Thus, use of two different types of measures, central stimulation in mice and stimulus generalization in rats trained to discriminate (+)amphetamine, not only offers two independent means of assessing the activity of clobenzorex, but also provides us with data in two species of animals. Furthermore, although many amphetamine-related anorectic agents (e.g., phenmetrazine, phendimetrazine, diethylpropion), as well as some non-amphetaminergic anorectics (mazindol), are capable of producing amphetamine-like stimulus effects, not all (e.g., fenfluramine, benzphetamine) anorectics reliably produce this effect (e.g., (8,26). Certain amphetamine-related anorectics (e.g., phenmetrazine, diethylpropion, phenteramine), as well as mazindol and amphetamine itself, also substitute for cocaine when cocaine is used as training drug, whereas others (e.g., fenfluramine) do not (24). Consequently, we examined doses of clobenzorex in tests of stimulus generalization in rats trained to discriminate 1 mg/kg of (+)amphetamine from vehicle, and for its ability to produce locomotor stimulation and rearing in mice relative to (+)amphetamine and cocaine. Significant effects in all assays would suggest that clobenzorex possesses central stimulant properties.

METHODS

Drug Discrimination Studies

Five naive male Sprague–Dawley rats (ca. 250–300 g), housed individually, were reduced in body weight to approximately 80% of their free-feeding weight. During the entire course of the study, the animals' body weights were maintained at this level by partial food deprivation; in their home cages, the animals were allowed drinking water ad lib. The animals were trained (15-min training session) to discriminate intraperitoneal injections (15-min presession injection interval) of 1.0 mg/kg of (+)amphetamine sulfate from vehicle (sterile 0.9% saline) under a variable interval 15-sec schedule of reinforcement for appetitive (sweetened powdered milk) reward. Standard two-lever operant chambers (Coulbourn Instruments model E10-10) were used. In general, daily training sessions were conducted with (+)amphetamine or 1.0 ml/kg of saline; on every fifth day, learning was assessed during an initial 2.5-min non-reinforced (extinction) session followed by a 12.5-min training session. For approximately half the animals, the left lever was designated the drug-appropriate lever whereas the situation was reversed for the remaining animals. Data collected during the extinction session included responses per minute (i.e., response rate) and number of responses on the drug-appropriate lever (expressed as a percent of total responses). Animals were not used in stimulus generalization studies until they made $> 80\%$ of their responses on the drug-appropriate lever after administration of training drug, and $< 20\%$ of their responses on the same drug-appropriate lever after administration of saline, for three consecutive weeks. The animals were placed in the operant chambers no more than once per day and were in their home cages except during training and extinction sessions.

Tests of stimulus generalization were conducted in order to determine if clobenzorex would substitute for the (+)amphetamine stimulus. During this phase of the study, maintenance of the training drug discrimination was insured by continuation of the training sessions on a daily basis (except on a generalization test day; see below). On one of the two days before a generalization test, approximately half of the animals would receive training drug and half would receive saline; after a 2.5-min extinction session, training was continued for 12.5 min. Animals not meeting the original criteria (i.e., $>$ 80% of total responses on the drug-appropriate lever after administration of training drug and $< 20\%$ of total responses on the same lever after administration of saline) during the extinction session were excluded from the immediately subsequent generalization test session. During the investigations of stimulus generalization, test sessions were interposed among the training sessions. The animals were allowed 2.5 min to respond under non-reinforcement conditions; the animals were then removed from the operant chambers and returned to their home cages. An odd number of training sessions (five) separated any two generalization test sessions. Doses of the challenge drugs were administered in a random order, using a 15-min presession injection interval. Stimulus generalization was said to have occurred when the animals, after a given dose of challenge drug, made r 80% of their responses on the drug-appropriate lever. Animals making fewer than 5 total responses during the 2.5-min extinction session were considered as being disrupted. ED_{50} values (i.e., doses where the animals would be expected to make 50% of their responses on the drug ~appropriate lever) were calculated by the method of Finney (9). Solutions of all drugs were prepared fresh daily using 0.9% sterile saline. All drugs were administered via intraperitoneal injection 15 min prior testing. A total of four doses of (+)amphetamine (0.1, 0.25, 0.5, and 1.0 mg/kg) and six doses of clobenzorex (1.5, 3.0, 7.5, 9.0, 12.0 and 14.0 mg/kg) were examined.

Locomotor Activity and Rearing

Albino ICR mice (male and female) weighing 25–30 g were used throughout the study. Male and female mice were housed separately in groups of five on a 12-h L: 12-h D cycle at a room temperature of 21 $\pm$ 1°C with free access to food and water. All experiments were performed between 0800 and 1700 h. On the test day, animals were acclimated in black plastic dummy observation cages ($28 \times 28 \times 28$ cm) for 30 min prior to drug administration. The animals were then injected

intraperitoneally with either vehicle (water, n = 6–7) or varying doses of either amphetamine (0.1, 0.5, 1.0, 2.0 mg/kg, n = 6–7/group), cocaine (5.0, 10.0, 20.0 mg/kg, n = 6–7/group) or clobenzorex (5.0, 10.0, 20.0 mg/kg, n = 6–7/group). Following these injections, the animals were returned to the dummy observation cages. Ten minutes later, the mice were transferred and placed individually in four black experimental observation cages of similar dimension. Both locomotor activity and rearing frequency were recorded simultaneously for the next 40 min by a computerized video tracking, motion analysis, and behavior recognition system [Ethovision (version 1.7), Noldus Information Technology, Costerweg, Netherlands]. In order to see whether clobenzorex might have a long duration of action, the morning-treated animals were again observed, for 40 min as described above, 3 h after the initial injection. The data were analyzed either for the total 40-min session or at 10-min intervals for the 40-min observation period. Different versions of this system have been previously used for determination of locomotor activity (i.e., distance traversed) in different animal species (20,23). Version 1.7 of this system also automatically detects rearing frequency. Rearing behavior in rats has been validated (Ethovision manual, version 1.7). The detection of rearing is based on the change in the surface area of the animal as seen by overhead video camera when the animal stands on its hind legs. Our preliminary experiments indicated that a 5% change in surface area for mice is equivalent to 90% to 110% of manual recording of rearing frequency. Thus, a 5% setting in surface area change was used throughout the experiments.

Drugs

(+)Amphetamine sulfate and cocaine hydrochloride were purchased from Sigma Chemical Company. Clobenzorex was synthesized in our laboratory from (+)amphetamine and isolated as its hydrochloride salt. A mixture of equimolar (13.4 mmol) amounts of (+)amphetamine (free base), 2-chlorobenzyl chloride, and potassium carbonate in xylene was heated under reflux for 3 h; water was added and the mixture was extracted with xylene (3 × 10 ml). The organic portion was washed successively with water (2 × 10 ml) and brine (10 ml), dried ($MgSO_4$), and evaporated to dryness. The crude product was purified by column chromatography (silica gel, EtOAc/petroleum ether 2:8) to give the free base of clobenzorex as a pale yellow oil which was homogeneous by thin layer chromatography. An ethereal solution of the free base was treated with HCl gas at 0°C to obtain the salt as white crystals. Infrared (film, free base) and proton magnetic resonance (GE Q-300; HCl salt in deuterated water) spectra were consistent with the assigned structure. The melting point (176–178°C) and optical rotation ($[\alpha]_D^{20}$ = +25.5 ± 1.0; 1%, H_20) of the salt were consistent with what has been previously published in the literature (mp = 182–183°C; $[\alpha]_D^{20}$ = +26.3 ± 1.0) (1); (mp = 174–176°C) (18).

Statistics

Data were analyzed by one way analysis of variance (ANOVA), and post hoc analysis was performed by Dunnetts t-test or Fishers PLSD test. For comparison of morning versus afternoon data (locomotor and rearing experiments), a 2-factor repeated measure of ANOVA was used. A p value of < 0.05 was necessary to achieve statistical significance.

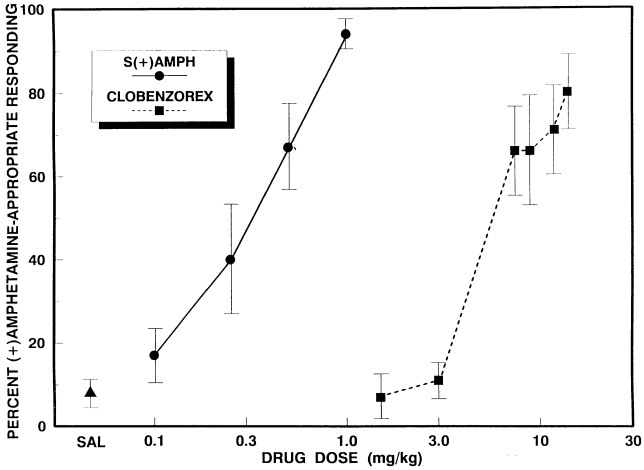

FIG. 2. Percent (mean ± SEM.) amphetamine-appropriate responding occasioned by 1 ml/kg of saline (SAL), and doses of (+)amphetamine (circles) and clobenzorex (squares) 15 min following administration to rats (n = 5) trained to discriminate 1 mg/kg of (+)amphetamine from saline vehicle.

RESULTS AND DISCUSSION

Drug Discrimination Studies

The results of the drug discrimination studies demonstrate that clobenzorex is capable of producing amphetamine-like effects; Figure 2 shows that the (+)amphetamine stimulus (ED_{50} = 0.3 mg/kg; 95%CL = 0.1–0.6 mg/kg) generalizes to clobenzorex (ED_{50} =6.6 mg/kg; 95%CL = 4.0–10.8 mg/kg). The animals' response rates following the administration of doses of clobenzorex (10.6–15.3 responses/min) were similar to those following administration of doses of (+)amphetamine (11.9–14.7 responses/min) or saline (14.5 responses/min). All five animals responded under all conditions except that one animal was disrupted following administration of 14 mg/kg of clobenzorex. In the drug discrimination assay then, clobenzorex (ED_{50} = 25.3 μmoles/kg) is about twenty times less potent than (+)amphetamine (ED_{50} = 1.2 μmoles/kg).

Central Stimulation in the Mouse

Administration of low to moderate doses of clobenzorex (i.e., 5 and 10 mg/kg) to groups of 6-7 mice showed no significant increase in locomotor activity over water control. At a dose of 20 mg/kg, locomotor stimulation was significantly greater than that for control [$F(4, 29)$ = 41.4, $p < 0.0001$] (Fig. 3), and was approximately half that obtained with 2 mg/kg of (+)amphetamine or 20 mg/kg of cocaine. The 20 mg/kg clobenzorex-treated animals were also examined three h post injection (data not shown); at this time, locomotor activity was not significantly different from those animals that had been treated three h earlier with water. The effect of clobenzorex on rearing frequency (Fig. 4) essentially paralleled the effect on locomotor activity. That is, 5 and 10 mg/kg of clobenzorex produced no significant increase in rearing frequency; 20 mg/kg of clobenzorex increased rearing frequency by about 40% over control. At 2 mg/kg of (+)amphetamine and 20 mg/kg of cocaine, rearing frequency increased by about 60% and 70%, respectively, over water control. At 20 mg/kg, clobenzorex produced about 75% of the increase in rearing frequency obtained with 20 mg/kg of cocaine.

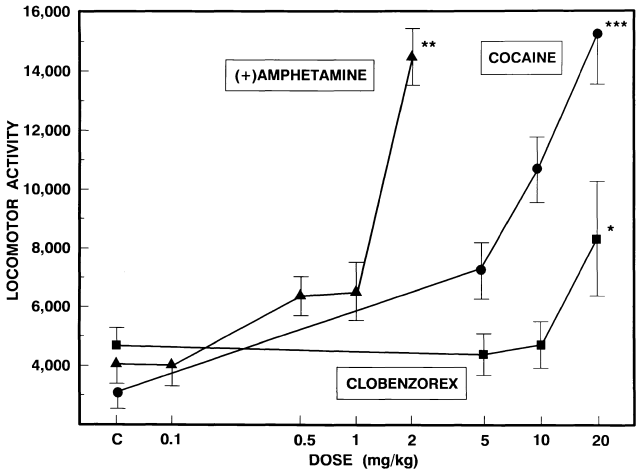

FIG. 3. Effect (mean ± SEM.) of (+)amphetamine, cocaine, and clobenzorex doses on the locomotor activity of mice (n = 6–7 animals/dose). Locomotor activity is expressed as the distance traversed (in cm) per 40 min; C = the effect of water administration. * = Significantly different from control by Dunnett t-test [$F(7, 46) = 4.1$, $p < 0.001$]. ** = Significantly different from control by Dunnett t-test [$F(4, 29) = 41.4$, $p < 0.0001$]. *** Significantly different from control by Dunnett t-test [$F(3, 23) = 27.7$ $p < 0.0001$].

Locomotor activity following administration of 20 mg/kg of clobenzorex was monitored for 40 min in 10-min intervals. Actual distance traversed (in cm) for each of the 10-min periods (following the initial 10-min delay) is as follows: 0-10 min (2745 ± 507), 10-20 (1980 ± 545), 20–30 min (1795 ± 526), and 30-40 min (1760 ± 298). That is, there was no progressive increase in activity per successive 10-min period ($p > 0.05$).

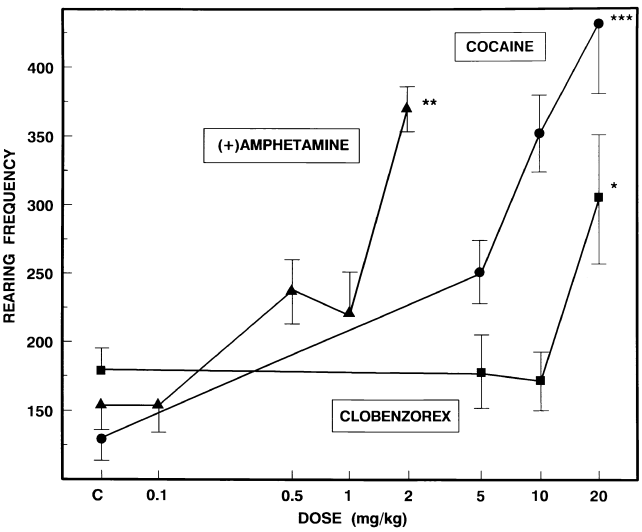

FIG. 4. Effect (mean ± SEM.) of (+)amphetamine, cocaine, and clobenzorex doses on the frequency of rearing using mice (n = 6–7 animals/dose) as subjects. Rearing frequency is expressed as the number of rearings occurring in a 40-min period; C = the effect of water administration. * = Significantly different from control [$F(7, 46) = 2.89$, $p < 0.01$]. ** = Significantly different from control [$F(4, 29) = 17.1$, $p < 0.0001$]. *** = Significantly different from control [$F(3, 23) = 19$, $p < 0.001$].

Similar results were obtained with rearing frequency for the corresponding four time periods (i.e., 85 ± 12, 66 ± 15, 62 ± 15, and 69 ± 10 rearings).

Clobenzorex as an Amphetaminergic Agent

(+)Amphetamine is a central stimulant that serves as a discriminative stimulus in animals (26). *N*-Monomethylation of amphetamine results in enhancement of potency both in studies of locomotor stimulation (22) and in tests of stimulus generalization (26). Substitution on the terminal amine of amphetamine with progressively larger alkyl groups results in a progressive reduction in potency (12,13,22,25). For example, *N*-benzylamphetamine is only 8% as potent as amphetamine as a central stimulant in mice (22); benzphetamine (Fig. 1), the *N*-benzyl analog of methamphetamine, is also a weaker central stimulant than amphetamine (6). In tests of stimulus generalization using pigeons, monkeys, or humans trained to discriminate amphetamine from vehicle (or placebo), results are mixed. In pigeons, stimulus generalization failed to occur up to doses of 100 mg/kg (8). Although benzphetamine substituted for (+)amphetamine in three of four monkeys (7), a majority of human subjects failed to recognize doses of up to 50 mg of benzphetamine as being like amphetamine (4).

Clobenzorex, *N*-benzylamphetamine, and benzphetamine all share a common *N*-benzyl substituent; in clobenzorex, the *N*-benzyl group further possesses an ortho chloro substituent. As such, given the established structure-activity relationships described above, it might be expected that because clobenzorex bears a rather large *N*-substituent it would be, at best, a weak amphetamine-like agent. This expectation is supported by the results of the present investigation. In tests of stimulus generalization using amphetamine-trained rats clobenzorex substitutes for (+)amphetamine but is approximately 20-fold less potent than the training drug. Likewise, clobenzorex behaves as a central stimulant in mice as determined by its effects on locomotor activity (Fig. 3) and rearing (Fig. 4). The results of both of the latter assays suggest that clobenzorex possesses amphetamine-like stimulant character. Although it is rather difficult to make quantitative comparisons with these latter data, the results are not inconsistent with the results of the drug discrimination studies which suggest that clobenzorex is approximately twenty time less potent than (+)amphetamine. It is concluded, on the basis of drug discrimination studies using rats trained to discriminate (+)amphetamine from saline vehicle, as well as on tests of locomotor activity and rearing frequency in mice, that clobenzorex possesses amphetamine-like behavioral character, but is less potent than (+)amphetamine itself.

Possible Role of Metabolism

One final question that should be considered is whether clobenzorex is active per se or whether it is first metabolized to an active metabolite. *N*-benzylamphetamine derivatives are known to undergo *N*-debenzylation in rodents and in humans (e.g., see (15), but the *N*-debenzyl derivatives do not appear to be major metabolites (15). Benzphetamine, for example, is metabolized in rodents and humans, to amphetamine and methamphetamine, but these constitute minor metabolites (15). However, the added role that the chloro substituent of clobenzorex might have on debenzylation is unknown. Thus, the possibility exists that clobenzorex might be metabolized to amphetamine. Indeed, a search of the literature reveals that a single investigation of clobenzorex metabolism has been

reported (11). In rats, 24 h after intraperitoneal clobenzorex administration, amphetamine, *para*-hydroxyamphetamine, and *para*-hydroxyamphetamine conjugates account for 5.5%, 3.1% and 12.7%, respectively, of the administered dose; the major urinary metabolite (40%) is clobenzorex glucuronide (11). Amphetamine has also been identified as a metabolite of clobenzorex in one human volunteer (21). Although clobenzorex can be metabolized to amphetamine, and although clobenzorex is rapidly absorbed and reaches a maximal blood level in rodents 5 min post administration (11), the extent to which clobenzorex is metabolized to amphetamine within 15–50 min (i.e., times used in the present investigation) is unknown.

Approximately 20% of a clobenzorex dose can be accounted for (after 24 h) as amphetamine or an amphetamine metabolite (11); if metabolism occurs very quickly, this might account for the potency of clobenzorex being approximately 20% that of (+)amphetamine in the present investigation. This is particularly possible in the locomotor and rearing studies where activity was monitored until 50 min post injection (i.e., for 40 min following a 10-min delay) as opposed to the drug discrimination studies (where the effect of clobenzorex was examined for only 2.5 min, 15 min after drug administration). We explored this possibility by (a) examining the effect of 20 mg/kg of clobenzorex in successive 10-min blocks following administration to mice so as to note any progressive effect, and by (b) measuring locomotor activity three h post injection of 20 mg/kg of clobenzorex. In both the locomotor and rearing assays, the effect of clobenzorex was no greater at 10–20 min, 20–30 min, or 30–40 min than it was at 0–10 min. In the locomotor assay, the effect of 20 mg/kg of clobenzorex 3 h post administration was not statistically different than the effect seen three h following the administration of water. That is, there was no evidence to suggest that clobenzorex is any more effective after 40 min than it is after the first 10 min.

CONCLUSIONS

Clobenzorex was shown to possess amphetamine-like character both in rats and mice. Amphetamine-stimulus generalization occurs to clobenzorex, and clobenzorex is approximately 20 times less potent than (+)amphetamine. In this respect, it behaves like some other amphetamine-based anorectic agents (8). Clobenzorex is also less potent than (+)amphetamine and cocaine in producing locomotor stimulation and rearing in mice. Although there is evidence in the literature that clobenzorex is metabolized to amphetamine in rodents, it is unlikely that this can account for the stimulant properties of clobenzorex unless extensive metabolism occurs within the first 10 min after administration. This is consistent with previous reports on *N*-benzylamphetamine (i.e., deschloro-clobenzorex) which, although known to be metabolized to amphetamine (15), is only 8% as effective as amphetamine as a locomotor stimulant (22). Further work will be necessary to study the rate of metabolism of clobenzorex and the contribution (if any) of its metabolites to its actions.

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