Pergamon

Pharmacology Biochemistry and Behavior, Vol. 51, Nos. 2/3, pp. 473–475, 1995
Copyright © 1995 Elsevier Science Ltd
Printed in the USA. All rights reserved
0091-3057/95 $9.50 + .00

0091-3057(95)00013-5

A Behavioral Comparison of Nexus, Cathinone, BDB, and MDA

M. E. BRONSON,[1] W. JIANG, J. DeRUITER AND C. R. CLARK

Department of Pharmacal Sciences, School of Pharmacy, Auburn University, Auburn University, AL 36849-5503

Received 31 October 1994

BRONSON, M. E., W. JIANG, J. DeRUITER AND C. R. CLARK. *A behavioral comparison of Nexus, cathinone, BDB, and MDA*. PHARMACOL BIOCHEM BEHAV 51(2/3) 473–475, 1995.—The effects of 4-bromo-2,5-dimethoxyphenethylamine (Nexus), 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyphenyl-2-butanamine (BDB), and cathinone were studied in the newly hatched chicken and compared to the effects of *d*-amphetamine and three hallucinogens in the same species. Cathinone, a psychomotor stimulant in man (6), produced effects that were qualitatively similar to effects seen after administration of *d*-amphetamine (i.e., distress vocalization, wing extension, inability to stand, and loss of righting reflex). BDB, a compound with unknown activity in man, and two known hallucinogens, Nexus (5) and MDA (1), produced effects in the chicken that are common to both stimulants and hallucinogens in this species. For example, both MDA and BDB produced abnormal body posture that was identical to that reported after administration of hallucinogens such as lysergic acid diethylamide (LSD) and harmine (11). Nexus, on the other hand, produced rigid penguin-like posture, an effect seen in the chicken after administration of another hallucinogen, mescaline (12). BDB also produced bursting forward movements, an effect commonly observed after LSD and harmine. Our findings suggest that the young chicken can be used as an alternative, nonmammalian, model for predicting classification of new compounds.

Designer drugs Amphetamine derivatives Nexus BDB Cathinone

THE YOUNG chicken provides an interesting model for studying drug effects because of the wide array of behaviors elicited by various drugs. For example, behavioral depressants such as chlorpromazine produce a synchronous EEG, sedation, decreased motor activity, and reduced reactivity to external stimuli in the chicken (11), and these effects are similar to those seen in mammals (2,7). Hallucinogenic compounds such as LSD and harmine produce EEG arousal in both the chicken (11) and human (4), and behavioral effects in the chicken include distress vocalization, wing extension, tremor, hyperpnia, abnormal posture, and compulsive locomotion with head outstretched and near the floor (11). Mescaline produces similar effects, but whereas the postural effects of LSD and harmine include sitting on the shanks with the tail in the air and the head touching the floor, mescaline has been reported to produce an upright, rigid, penguin-like posture (12). Administration of a psychomotor stimulant drug such as amphetamine results in a low-voltage, fast-pattern EEG and motor excitement in both the chicken (11) and the human (10). In the chicken, behavioral effects of psychomotor stimulants are manifested as continuous vocalization (up to 250 chirps/minute), wing extension, and tremor at low doses of *d*-amphetamine, and inability to stand, loss of righting reflex, and convulsant-like kicking occurring at higher doses (3,11). Recovery from the debilitating effects of amphetamine also produces an interesting and unique phenomenon of increased aggression against other chicks [(11) and unpublished observations], and amphetamine has also been linked to aggression in a number of other species, including humans [see (8) for a review].

The purpose of the current study was to examine the effects of three primary amine drugs of abuse including cathinone, a psychomotor stimulant, and two known hallucinogens, MDA and Nexus, in the newly hatched chicken, and to compare the effects of these compounds to those of other psychomotor stimulants and hallucinogens in this species. BDB, another primary amine with unknown activity in mammals, was also examined.

[1] To whom requests for reprints should be addressed.

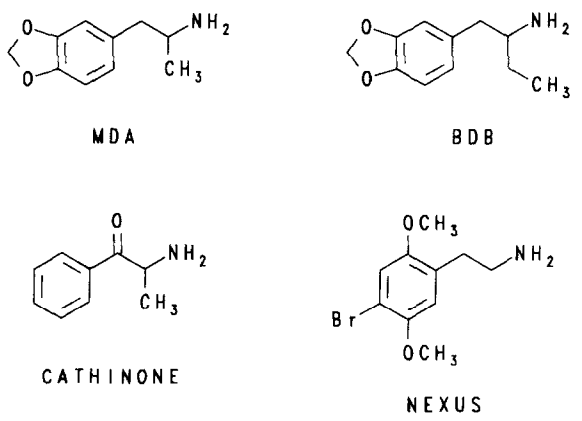

FIG. 1. Structures of 3,4-methylenedioxyamphetamine (MDA), 3,4-methylenedioxyphenyl-2-butanamine (BDB), 1-phenyl-2-aminopropan-1-one (cathinone), and 4-bromo-2,5-dimethoxyphenethylamine (Nexus).

METHOD

Behavioral Analysis

Five minutes prior to injection of drug or vehicle, 1-day-old chickens were observed by two investigators for presence or absence of overt signs such as distress vocalization, head shaking, wing extension, tremor, inability to stand, abnormal body posture, loss of righting reflex, or bursting forward movements. They were then administered cumulative doses of each drug (4, 8, 16, and in the case of cathinone, 24 mg/kg), or serial injections of water in a volume of 0.04 ml/kg. One investigator gave the injections, whereas the two observers were blind to treatment. Data for each drug were compared to water injections and were analyzed by chi-square analysis, with p set at < 0.05.

Drugs

BDB was prepared by reductive amination of 1-(3,4-methylenedioxyphenyl)-2-butanone. The butanone was synthesized by reductive hydrolysis of the corresponding methylenedioxynitrostyrene. The nitrostyrene was prepared by reaction of piperonal and nitropropane as reported previously (9). Cathinone was prepared by dichromate oxidation of norephedrine. Nexus was synthesized from 2,5-dimethoxybenzaldehyde in a multistep sequence. Thus, treatment of the aldehyde with nitromethane yielded the nitroalkene intermediate. Reduction of the nitroalkene with lithium aluminum hydride afforded the phenalkylamine, which was brominated with Br_2 to yield Nexus. All of the amine products were converted to the corresponding hydrochloride salts by treatment with ethereal HCl. Prior to behavioral and pharmacological testing, the structures of all products were established by standard spectroscopic techniques (IR, NMR, and MS) and purity was confirmed by chromatographic methods and elemental analysis (Atlantic Microlabs, Atlanta, GA).

RESULTS

Figure 1 shows the structure of the various compounds, and Table 1 shows the effects of the last water injection compared to the highest dose of each compound. All of the compounds tested in the current study produced some stimulant-like effects such as wing extension and loss of righting reflex. With the exception of Nexus, all of the compounds produced distress vocalization, and all of the drugs but cathinone also produced tremor, another typical stimulant effect. Cathinone was similar to *d*-amphetamine in that it produced flat body posture, manifest as the chicken lying prone. Nexus, BDB, and MDA all produced abnormal body posture, but there were qualitative differences. Nexus, for example, produced a very rigid posture that has been referred to as penguin-like posture (12), whereas with BDB and MDA, the chickens sat on their shanks with their tails in the air and their beaks touching the floor. From this position, chickens that had received BDB would suddenly start running foreward with their tails in the air and their heads close to the ground (bursting forward locomotion).

DISCUSSION

In the current study, the known psychomotor stimulant, cathinone, produced effects that were very similar to the effects of *d*-amphetamine in this species (3,11). These included distress vocalization, wing extension, inability to stand and loss of righting reflex. Although Nexus, BDB, and MDA also produced some effects that were similar to *d*-amphetamine, they also produced effects that were qualitatively different. For example, both BDB and MDA produced abnormal posturing that is very typical of two hallucinogens, LSD and harmine (i.e., sitting on the shanks with the tail in the air and the beak on the ground) (11). Nexus, on the other hand, produced an effect typical of another hallucinogen, mescaline (i.e., penguin-like posture) (12). Although the effects of BDB are not known in man, both MDA and Nexus have been reported to be hallucinogens (1,5); therefore, because of the similarities of these compounds in the chicken, it is possible that BDB would also be hallucinogenic in man. Furthermore, when the EEG

TABLE 1

EFFECTS OF WATER OR CUMULATIVE DOSES OF CATHINONE, MDA, NEXUS OR BDB ON 1 DAY OLD CHICKENS

	NO. CHICKENS SHOWING SIGN/TOTAL NUMBER OF CHICKENS							
Posthatch Treatment	DV	WE	T	PP	LP	MP	B	LRR
Water	1/10	0/10	0/10	0/10	0/10	0/10	0/10	0/10
Cathinone (24 mg/kg)	0/10*	10/10*	0/10	10/10*	0/10	0/10	0/10	6/10*
MDA (16 mg/kg)	8/10*	10/10*	5/10*	0/10	10/10*	0/10	2/10	9/10*
Nexus (16 mg/kg)	2/10	10/10*	8/10*	0/10	0/10	8/10*	0/10	7/10*
BDB (16 mg/kg)	12/12*	12/12*	6/12*	0/12*	12/12*	0/12	12/12*	0/12

*Significantly different from posthatch water injection, $p < .05$.

effects of drugs of abuse are compared in the chicken and in man, the effects are remarkably similar (2,4,7,10,11). The current findings and those of other laboratories suggest that the young chicken may be a useful alternative model for predicting classification of novel compounds.

ACKNOWLEDGEMENTS

We would like to thank Auburn University Pharmacy students Jerry Smith, Marcia Mandoki, Wai Yung Chan, Jeff Blackburn, Linda Clune, and Tiffany Foster for their excellent help in the laboratory. This research was supported in part by NIDA grant DA 06637.

REFERENCES

1. Anthony, J. C.; Trinkoff, A. M. Epidemiologic issues pertinent to international regulation of 28 stimulant-hallucinogen drugs. Drug Alcohol Depend. 17:193–211; 1986.
2. Brodie, B. B.; Sulser, F.; Costa, E. Theories on mechanism of action of psychotherapeutic drugs. In: Brodeleau, J., ed. Extrapyramidal system and neuroleptics. Montreal: Editions Psychiatriques; 1961:183–189.
3. Bronson, M. E.; Jiang, W.; Clark, C. R.; DeRuiter, J. Effects of designer drugs on the chicken embryo and 1-day-old chicken. Brain Res. Bull. 34:143–150; 1994.
4. Evarts, E. V. A review of the neurophysiological effects of lysergic acid diethylamide (LSD) and other psychotomimetic agents. Ann. NY Acad. Sci. 66:479–495; 1957.
5. Federal Register 59:671; 1994.
6. Kalix, P. The pharmacology of khat. Gen. Pharmacol. 15:179–187; 1984.
7. Killam, E. K. Drug action on the brain-stem reticular formation. Pharmacol. Rev. 14:175–223; 1962.
8. Miczek, K. A.; Tidey, J. W. Amphetamines: Aggressive and social behavior. In: Asghar, K.; DeSouza, E., eds, Pharmacology and toxicology of amphetamine and related designer drugs. Rockville, MD: U.S. Government Printing Office; 1989:68–100.
9. Noggle, F. T.; Clark, C. R.; DeRuiter, J. Liquid chromatographic and mass spectral analysis of 1-(3,4-methylenedioxyphenyl)-3-butanamines: Homologues of 3,4-methylenedioxyamphetamines. J. Chromatogr. Sci. 27:240–243; 1989.
10. Pfanz, M.; Schrader, A. Experimental study of the influence of central stimulants on the EEG of the human. Klin. Wschr. 37: 483–485; 1959.
11. Spooner, C. E.; Winters, W. D. Neuropharmacological profile of the young chick. Int. J. Neuropharmacol. 5:217–236; 1966.
12. Zaimis, E. Discussion. In: Vane, J. R.; Wolstenholme, G. E. W.; O'Connor, M., eds. Ciba Foundation Symposium on Adrenergic Mechanisms. London: Churchill; 1985:562.