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Structure–Activity Relationships of BDB and Its Monomethyl and Dimethyl Derivatives

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BRONSON, M. E., W. JIANG, J. DeRUITER AND C. R. CLARK. *Structure-activity relationships of BDB and its monomethyl and dimethyl derivatives.* PHARMACOL BIOCHEM BEHAV **51**(2/3) 477–479, 1995.—The purpose of the present study was to evaluate the behavioral effects of 3,4-methylenedioxyphenyl-2-butanamine (BDB), *N*-methyl BDB (MBDB), and *N,N*-dimethyl BDB (MMBDB) in the newly hatched chicken. The primary amine, BDB, produced effects that are commonly seen in the chicken after administration of both hallucinogens and psychomotor stimulants (i.e., distress vocalization, tremor, and wing extension). It also produced abnormal body posture and bursting forward locomotion, effects elicited only by hallucinogens. Loss of righting reflex also occurred at the highest (16 mg/kg) dose of BDB, and this effect is typical of *d*-amphetamine but has not been reported for hallucinogens. The monomethylated derivative of BDB, MBDB, was less potent than BDB, and the *N,N*-dimethyl analogue of BDB, MMBDB, had no effect on behavior at the doses tested.

Designer drugs 3,4-Methylenedioxyphenyl-2-butanamine BDB Chickens

BDB IS A 3,4-methylenedioxymethamphetamine (MDMA or "ecstasy") designer analogue, and although BDB is relatively unknown in the clandestine drug world, its monomethylated derivative, MBDB, shares discriminative stimulus properties with MDMA (3). The parent compound, BDB, has also been shown to produce potent behavioral effects in the newly hatched chicken (2), and these effects are similar to those produced by both hallucinogenic compounds and psychomotor stimulants in the same species (6). In 1978, Shulgin (5) found that when hallucinogenic phenethylamine derivatives were *N*-methylated, the result was a decrease in hallucinogenic activity. Although it is not known whether BDB is hallucinogenic in man, the current study was designed to investigate the behavioral properties of BDB and its *N*-methyl derivatives in the newly hatched chicken and to compare them to those of known hallucinogens in the same model.

METHOD

Behavioral Analysis

Five minutes prior to injection of drug or vehicle, 1-day-old chickens were observed by two investigators for the presence of signs such as distress vocalization, head shaking, wing extension, tremor, abnormal body posture, loss of righting reflex, bursting forward locomotion, rigidity, or convulsant-like kicking movements. They were then administered cumulative doses of each drug (4, 8, 16, and sometimes 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. Ten to 12 chickens were used for each drug or water treatment, and chickens were used only once. After determination of the dose-effect curves for the various drugs, chickens were euthanized with CO_2.

Drugs

The 1-(3,4-methylenedioxyphenyl)-2-butanamines BDB, MBDB, and MMBDB were 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 (4). 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 con-

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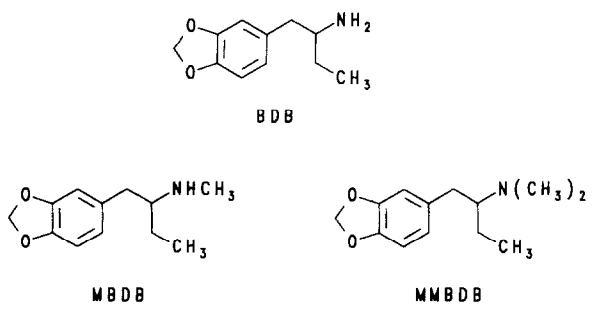

FIG. 1. Structures of 3,4-methylenedioxyphenyl-2-butanamine (BDB), *N*-methyl-BDB (MBDB), and *N*,*N*-dimethyl-BDB (MMBDB).

firmed by chromatographic methods and elemental analysis (Atlantic Microlabs, Atlanta, GA).

Data Analysis

Data were analyzed by chi-square analysis.

RESULTS

Figure 1 shows the structure of the BDB, MBDB, and MMBDB, and Table 1 shows the behavioral effects of these compounds. When compared to water injections, BDB produced significantly more distress vocalization, tremor, wing extension, bursting forward locomotion, abormal body posture, and loss of righting reflex in a dose-dependent manner. Abnormal body posture consisted of the chicken sitting on the shanks with the tail in the air and the beak touching the floor. From this position the chicken would suddenly start to run forward with the head outstretched and close to the ground. When placed on its back to measure loss of righting reflex, the chicken would kick and try to turn over, but was unable to do so at the higher doses of BDB. When compared to BDB, MBDB was significantly less potent in measures of distress vocalization, wing extension, and flat body posture. Also, in contrast to BDB, MBDB did not produce loss of righting reflex, bursting forward locomotion, or tremor. MMBDB had no effect on behavior at the doses tested.

DISCUSSION

The primary amine, BDB, produced effects that are similar to those seen after administration of psychostimulants and hallucinogens in this species (i.e., behavioral excitation as evidenced by distress vocalization, tremor, and wing extension) (2,6). Loss of righting reflex was also observed in all animals at the highest dose of BDB, and this is a common feature of both high-dose *d*-amphetamine (2) and of precipitated opioid withdrawal in the young chicken (1). In addition to stimulant-like effects, BDB also produced abnormal body posture and bursting forward locomotion, which is a typical effect of hallucinogens (6). Thus, although the effects of BDB in man are

TABLE 1

EFFECTS OF WATER OR CUMULATIVE DOSES OF 3,4-METHYLENEDIOXYPHENYL-2-BUTANAMINE (BDB), *N*-METHYL-3,4-METHYLENEDIOXYPHENYL-2-BUTANAMINE (MBDB), OR *N*,*N*-DIMETHYL-3,4-METHYLENEDIOXYPHENYL-2-BUTANAMINE (MMBDB) ON 1-DAY-OLD CHICKENS

	No. Chickens Showing Sign/Total Number of Chickens					
Posthatch Treatment	DV	WE	T	FBP	B	LRR
Water						
Injection 1	0/10	0/10	0/10	0/10	0/10	0/10
Injection 2	0/10	0/10	0/10	0/10	0/10	0/10
Injection 3	1/10	0/10	0/10	0/10	0/10	0/10
BDB						
4 mg/kg	4/12*	5/12*†	0/12	1/12	12/12*†	1/12
8 mg/kg	12/12*†	12/12*†	5/12*†	11/12*†	12/12*†	3/12
16 mg/kg	12/12*	12/12*†	6/12*†	12/12*†	12/12*†	12/12*†
MBDB						
4 mg/kg	4/10*	0/10	0/10	0/10	0/10	0/10
8 mg/kg	4/10*	5/10*‡	0/10	1/10	0/10	0/10
16 mg/kg	6/10*‡	8/10*‡	0/10	1/10	0/10	0/10
24 mg/kg	10/10*‡	9/10*‡	0/10	7/10*‡	1/10	5/10*‡
MMBDB						
4 mg/kg	0/10	0/10	0/10	0/10	0/10	0/10
8 mg/kg	1/10	0/10	0/10	0/10	0/10	0/10
16 mg/kg	1/10	0/10	0/10	0/10	0/10	0/10
24 mg/kg	2/10	0/10	0/10	0/10	0/10	0/10

DV = distress vocalization, WE = wing extension, T = tremor, FBP = flat body posture, B = bursting forward movements from a prior prone position, LRR = loss of righting reflex. Data are presented as number of animals showing an effect/total number of animals.

†BDB different from same dose of MBDB, $p < .05$

‡MBDB different from same dose of MMBDB, $p < .05$

*Different from posthatch water injection, $p < .05$.

unknown, it appears that BDB may be both a stimulant and a hallucinogen.

Successive *N*-methylation of BDB resulted in decreased activity. For example, the monomethyl derivative of BDB, MBDB, did not produce loss of righting reflex, bursting forward movements, or tremor, and it was also less potent than BDB in producing distress vocalization, wing extension, and flat body posture. At the doses tested, the dimethyl derivative of BDB, MMBDB, was behaviorally inactive. These results are in agreement with those of Shulgin (5), who showed that successive *N*-methylation of primary phenethylamines resulted in decreased behavioral effects.

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