EFFECT OF SODIUM DIPROPYLACETATE ON CONFLICT BEHAVIOR IN RATS

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Accepted July 16, 1980

Sodium dipropylacetate (DPA), a branched chain carboxylic acid, was shown to possess anticonvulsant activities both in clinical and experimentally-induced seizures (1, 2). Recently, the effectiveness of DPA in selected neurotic conditions has been evaluated, and this drug was found to be effective for treatment patients with symptoms of obsessive worry and irritable depression (3, 4). Since improvement in certain forms of anxiety was reported, it was of interest to study this drug using laboratory procedures. Conflict behavior as devised by Geller and Seifter (5) appears to be one of the most useful tests to study anti-anxiety drugs. In this test, benzodiazepines, meprobamate and several barbiturates characteristically attenuate suppression produced by punishment, while major tranquilizers and opiates were found to be inactive (6). In the present study, the effect of DPA was compared with that of diazepam and diphenylhydantoin, in a conflict behavior test.

Eight male Wistar rats weighing 350 to 400 g at the start of the experiment were housed in community cages, and the original body weight was reduced to 80% by limited feedings. Cages were located in a room maintained at $24 \pm 2^\circ\text{C}$ with a relative humidity of 55%, and an artificial day-night cycle (12/12 hr) was produced by electric lighting. The rats used in the conflict behavior test had been trained to this technique. The animals had learned to avoid pressing the lever when the light was on in the conditioning chamber (Grason-Stadlers, model 1101), as each lever pressing was rewarded with milk but at the same time given an electric shock to the feet (DC constant current of 0.5–1.2 mA, 0.1 sec of duration). The conflict schedule of 3 min duration was alternated with a variable interval schedule (VI 2) for 12 min. Each component was repeated 3 times. The rats were all 'drug sophisticated', that is, they had been dosed previously with various benzodiazepine derivatives on a weekly bases for several months. Each test session continued for two successive days. On the first day, the animals were treated with the vehicle 20 min before being placed in the chamber, then their behavior and the rate of lever pressing were recorded for 45 min. On the second day, the same procedure was repeated replacing the vehicle by a drug. Test sessions were spaced at least 1 week apart. Student's *t*-test was employed to determine the statistical significance of the data obtained.

The effects of DPA, diazepam and diphenylhydantoin on responses in both the punished and VI 2 components of the multiple schedule are shown in Fig. 1. DPA in doses between 50 and 400 mg/kg p.o. increased the response rate suppressed by punishment, while only

FIG. 1. Effects of dipropylacetate (DPA), diazepam and diphenylhydantoin on responses in both the punished and VI 2 components of the multiple schedule. Each column shows the mean, and the horizontal lines show S.E., n =number of determinations. Statistically different from the corresponding vehicle treated rats; *, $p < 0.02$.

the highest dose of DPA decreased the response rate in VI 2 component. Diazepam in doses of 10 and 20 mg/kg p.o. increased the response rate in the punished component and decreased the response rate in VI 2 component by 18 and 50%, respectively. In contrast with DPA and diazepam, diphenylhydantoin in a dose of 10 mg/kg had no effect on the response rate in either the punished or the VI 2 component.

These findings indicate that DPA has an anticonflict effect, similar to that seen with diazepam. In previously obtained data, the ED₅₀ values of DPA, diazepam and diphenylhydantoin in inhibition of maximal electroshock convulsive test in rats were 345, 12 and 18 mg/kg p.o., respectively (2). Therefore, the doses at which DPA and diazepam showed an anticonflict effect were the same as the doses at which these drugs showed an anticonvulsive effect. Goldberg and Ciofalo (7) demonstrated that diphenylhydantoin in doses of 7.5 and 15 mg/kg i.p. was ineffective on punished response. Concerning the mechanism of action, it was reported that DPA elevated the GABA levels in the cerebral cortex by inhibiting the degradative enzyme for GABA, GABA transaminase (1, 8). Lust et al. (9) showed that the level of cerebellar cyclic GMP was decreased to less than 40% of control values, whereas that of cyclic AMP was unaffected. On the other hand, there have been many reports that diazepam may act on regulatory GABAergic neurons (10-12). Thus, DPA and diazepam

may differ regarding the site of action (13), but they share at least one common effect, namely the change in GABAergic neuronal activity. The direct mechanism by which DPA attenuates the conflict behavior is now being investigated.

Acknowledgements: We are grateful to Prof. S. Ueki and Dr. Y. Kataoka, Pharmaceutical Sciences, Kyushu University, for pertinent suggestions.

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