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Received January 4, 1956. P.S.E.B.M., 1956, v91.

Action of Diethylpropanediol and Diethylbutanediol on Isolated Sciatic Nerve and Ileum.* (22213)

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2,2-diethyl 1,3-propanediol (DEP) is a central nervous system depressant remarkable for its effectiveness in protecting animals against the convulsant action of pentylenetetrazol (Metrazol). Pharmacologically, it has been characterized as an interneuronal depressant with action throughout the neuraxis but with maximal effect in the brain stem (2,3,4). 2,2-diethyl 1,4-butanediol (DEB) which differs from DEP by but one methylene group is a convulsant remarkably similar to metrazol in action(5). It too has its principal action on interneurones throughout the central nervous system with a maximal effectiveness in the brain stem. DEP protects animals from the convulsant action of DEB. The available evidence indicates that this is a non-specific example of pharmacological antagonism since other depressants and stimulants act similarly in combination with the drugs in question.

It seemed of some interest to make a quantitative comparison of the effect of these two compounds on isolated axones and synapses.

Methods. Strength-duration curves were determined for desheathed rat sciatic nerve which was maintained in Tyrode's solution at 36-37°C in a nerve chamber. The nerve was allowed to equilibrate until the curve was reproducible. Increasing concentrations of drug in Tyrode's solution were added and the strength-duration curve was determined at 15 minute intervals until concentrations causing unequivocal depression of the nerve had been added. The nerve was then washed in drug-free Tyrode's solution until a normal level of excitability had been reached. In some experiments the excitability of the nerve was enhanced by calcium ion depletion by using a calcium-free Tyrode's solution and varying concentrations of sodium citrate as suggested by Brink *et al.*(6). As a simple method of evaluating ganglionic transmission, the contraction of the isolated rabbit ileum was used following the method of Feldberg(7). To study simple neuronal pathways in the central nervous system, the segmental reflex was studied in cats in which the spinal cord had been divided at the second cervical vertebra or at both the second cervical and last thor-

* Material in this paper appeared in thesis by Saul Adams in partial fulfillment for the degree of Master of Science at the University of Rochester.

This paper is based on work performed under contract with the U. S. Atomic Energy Commission at The University of Rochester Atomic Energy Project.

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TABLE I. Comparison of Rheobase of Isolated Rat Sciatic Nerve after Soaking in Drug.

Pre-drug, mM	DEB, 100%	DEP, 100%
4	117 ± 1	120 ± 4
8	122 ± 5	124 ± 4
16	135 ± 3	140 ± 2
32	180 ± 6	182 ± 6

Mean of 8 nerves ± S.E. of mean.

acic vertebra. The last lumbar or first sacral dorsal root was divided and placed on bipolar platinum electrodes. Stimuli of 0.05-0.2 msec. duration and less than 5 volt amplitude were delivered at 10 second intervals. The response was recorded from the corresponding ventral root from platinum electrodes by a RC coupled amplifier. Each drug was tested in 6 cats, 3 with high and 3 with both high and low spinal transection. DEB was given in 1 mg/kg doses repeated at 3-5 minute intervals and effects were usually seen when about 5 mg/kg had been given. DEP was given in a dose of 100 mg/kg; occasionally a second dose of 50 mg/kg was administered.

Results. In experiments on isolated desheathed rat sciatic nerve both DEP and DEB caused a reversible increase in rheobase with little change in chronaxie. The data presented in Table I show that both drugs were effective in causing an elevation in rheobase at 4 mM. Over a wide range, 0.001 mM-2.6 mM, no concentration of either drug was found which caused an increase in excitability.

Table II summarizes the experiments in which the excitability of the nerve was enhanced by depletion of calcium ion. At doses as low as 1 mM which caused no appreciable change in the threshold of normal nerve both the anticonvulsant and the convulsant drug caused a decrease in the hyperexcitable state.

TABLE II. Comparison of Percentage Increase in Rheobase on Calcium Deficient Isolated Peripheral Nerve.

	DEB, 1 mM (%)	DEP, 1 mM (%)
Pre-calcium	100	100
Post-calcium	37 ± 12	36 ± 10
Post-drug	88 ± 9	77 ± 10

Mean of 8 nerves ± S.E. of mean.

Spontaneous firing when present stopped after drug treatment when either compound was used in a concentration of 1 mM. The more dilute solutions of DEB or DEP were without effect.

In the experiments on rabbit intestine designed to test the action of the drugs on parasympathetic ganglia, both DEP and DEB had the same depressant action. Both compounds caused a decrease in the spontaneous motility of intestinal strips. As shown in Table III these effects were comparable at

TABLE III. Decrease in Spontaneous Contraction of Rabbit Intestine.

Dose, mM	% reduction DEP	DEB
1	22 ± 1	18 ± 2
2	30 ± 2	22 ± 3
4	33 ± 2	26 ± 1
6	40 ± 1	40 ± 2

Mean of 6 strips ± S.E. of mean.

various dose levels.

When 2 mM of DEB or DEP was added to the bath, 0.01 mM of nicotine or 0.4 mM/l of barium chloride failed to cause the usual increase in motility and tone. On the other hand, 0.025 mM of acetylcholine, 0.002 mM of pilocarpine or 0.005 mM of histamine still had significant stimulant effects. These findings are consistent with the view that the depression noted with DEP and DEB was indeed related to a ganglionic action.

In contrast to these results on isolated portions of the peripheral nervous system, the studies on the spinal cord confirmed the fact that DEP is a central nervous system depressant and DEB is a central nervous system stimulant. In 3 cats in which the spinal cord was divided at the level of the second cervical vertebra, DEP caused a depression of multisynaptic activity and some increase in the height of the monosynaptic spike. When the spinal cord was divided at the level of the last thoracic vertebra, DEP in each of the three cats caused a decrease in the height of both monosynaptic and polysynaptic response. Similar findings have been reported for mephenesin(8) and have been interpreted as evidence of a depression of interneural activity. The increase in the monosynaptic

spike in the high spinal animals probably represents a release from inhibition.

DEB, 5 mg/kg, had an action which resembled that of strychnine(9). The decrease in monosynaptic response in the high spinal preparation associated with an increase in multisynaptic action suggests an increase in multisynaptic inhibitory action. In the three animals with the cord divided at a low level, the stimulant action is clearly demonstrated. Thus in a preparation which represents a sample of a segment of the central nervous system little influenced by diverse inhibitory and facilitory impulses, the stimulant action of DEB and the depressant action of DEP is clearly demonstrated.

Discussion. In the experiments on isolated axones and synapses taken from the peripheral nervous system, the action of DEP and DEB was depressant. The compounds appeared to be similar qualitatively and quantitatively. It is conceivable that different tests of axonal or synaptic functions might have demonstrated some difference but we do not feel that this possibility is very great. Studies of refractory period, accommodation, period of latent addition and so on did not seem to represent a profitable line of endeavor. In support of this point of view, it can be pointed out that cocaine which is a central nervous system stimulant has been shown to have the actions on peripheral structures that are associated with the "stabilizing" group of central nervous system depressants(1). At this point it seems reasonable to suggest that for study the cellular phenomena associated with the action of drugs on the brain and spinal cord methods utilizing the central nervous system should be sought.

Summary. 1. The action of 2,2-diethyl 1, 3-propanediol (DEP), a central nervous system depressant with anticonvulsant activity and 2,2-diethyl 1,4-butanediol (DEB), a central nervous system stimulant with convulsant action have been compared on isolated synapses and axons. 2. Both compounds caused an elevation of rheobase of desheathed rat sciatic nerve at a concentration of 4 mM/l and no concentration tested caused an increase in excitability. Similarly, the treatment with each of these drugs of nerves rendered hyperexcitable with calcium ion deprivation showed only a depressant action 3. Experiments on isolated rabbit intestine showed that both compounds acted only as depressants. At 1 mM/l there was a depression of ganglionic transmission. 4. When the compounds were tested on simple reflex arcs in low spinal cats, DEP was depressant and DEB stimulatory.

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Received November 15, 1954. P.S.E.B.M., 1956, v91.