LETTER TO THE EDITOR

NEGATIVE IONOTROPIC EFFECT OF SODIUM VALPROATE ON SOME ISOLATED HEART PREPARATIONS

Sir,

(Received on April 1, 1983)

Sodium Valproate (SV) has a broad spectrum of anticonvulsive activity involving several types of chemically or electrically induced convulsions in a variety of species (1). The drug is stated to lack significant cardiovascular effects (2), but while reinvestigating its effects, we observed a depressant effect on cardiac tissue, in isolated heart muscle preparations, which is described below.

Isolated tissue preparations used included perfused heart of frog (Rana tigrina), rabbit (Langendorff preparations) and rabbit isolated atria (3). The latter were set up in Ringer Lock Solution at 37'C and gased with 5% CO_2 in O_2. Sodium valproate was used as aqueous solution. The doses refer to the salt. SV in the doses studied showed dose dependent inhibitory effect on force of contraction, in frog heart, rabbit heart and rabbit atria (Table I), but did not show any significant effect on heart rate.

Concentrations higher than 4 *mg* of SV completely inhibited the frog heart. SV (0.5 to 4 *mg*) did not modify the responses induced by adrenaline hydrochloride (400 *ng*) and acetylcholine chloride (100 *ng*) on frog heart as well as rabbit heart. Atropine sulphate (1 *mcg*) had no effect on inhibitory responses of SV in any of the three preparations. Histamine (upto 100 *mcg*) showed both positive ionotropic and chronotropic effect on frog as well as rabbit heart, but it showed negative ionotropic effect on frog heart in higher doses (more than 100 *mcg*). Mepyramine maleate (10 *mg*) blocked the negative ionotropic effect of histamine on frog heart, but not of SV. When the same doses of SV were repeatedly administered at five minutes intervals the responses were reproducible and there was no evidence of tachyphylaxis.

Use of high Ca^{++} Ringer (3X0.8 *mmol*) and high Ca^{++} Ringer Lock (3X1.6 *mmol*) produce increase in force and frequency of frog and rabbit heart, respectively, but failed to modify the responses of SV. K^{+}–free Ringer solution also increases force and frequency of frog heart. Frog heart perfused with K^{+}–free Ringer solution responded with a reduced inhibitory responses to SV (100% in case of 0.5, 1 and 2 *mg*; 50 to 75% in case of 3 and 4 *mg*).

SV thus produced dose-related inhibition of force of contraction, without affecting the rate of contraction in three different isolated tissue preparations. The doses studied

TABLE I : Inhibitory effect of sodium valproate on force of contraction of isolated heart preparations.

Preparation	*Dose of sodium valproate*	*Mean height (force) of contraction (mm. ± S.E.)*
Perfused frog heart (n = 8)	Control	17.5 ± 1.25
	0.5 *mg*	12.7 ± 0.7**
	1 *mg*	10.7 ± 0.66 ***
	2 *mg*	8.3 ± 0.61 ****
	4 *mg*	2.8 ± 0.4 ****
Perfused rabbit heart (n = 5)	Control	10.8 ± 1.02
	0.5 *mg*	7.8 ± 0.8
	1 *mg*	6.2 ± 0.67 **
	2 *mg*	4.8 ± 0.5 ***
	4 *mg*	3.6 ± 0.68 ***
Isolated rabbit atria (n = 4)	Control	6.0 ± 0.63
	0.5 *mg/ml*	3.0 ± 0.45*
	1 *mg/ml*	2.2 ± 0.2 **
	2 *mg/ml*	1.1 ± 0.24 ***
	4 *mg/ml*	0.4 ± 0.24 ***

n = number of experiments

Value significantly differs from control (*P<0.05, **P<0.02, *** P<0.01, ****P<0.001; t-test).

were, however, relatively high. Atropine or mepyramine did not alter the inhibitory responses of SV, which rules out the cholinergic or histaminergic mechanisms in this inhibition. Lack of tachyphylaxis in all the three preparations preliminarily may indicate a direct depressant effect rather than one mediated through an inhibitory transmitter release. Use of media containing high Ca^{++} content did not affect the SV responses which shows that an interaction with Ca^{++} permeability is not involved in SV-responses. SV-responses of frog heart were partially reduced in K^+ free medium indicates that the responses may be partly mediated through increased K^+ permeability.

ACKNOWLEDGEMENTS

Authors are greatful to the Directors, for the facilities provided and constant encouragement during studies. We are also thankful to Mr. M. T. Makwana for the technical assistance.

G. F. SHAH, J. D. RAVAL, T. P. GANDHI AND M. R. PATEL

Department of Pharmacology,

R & D. Cadila Laboratories Private Limited,

Ahmedabad - 380 008

REFERENCES

1. Frey, H.H. and W. Loscher Di-n-propylacetic acid - profile of anticonvulsant activity in mice. *Arznemittel-Forschung*, **26** : 299-301, 1976.
2. Shuto, K. and T. Nishigaki. Pharmacological studies on sodium dipropyl-acetate. Anticonvulsant activities and general pharmacologic actions. *Pharmacometrics*, **4** : 937-940, 1970.
3. Sheth, U.K., N.K. Dadkar and U.G. Kamat. Selected topics in Experimental Pharmacology. Ist Edition, Kothari Book Depot., Bombay-12, 100-124, 1972.