LETTERS TO THE EDITOR

[Brief letters to the Editor that make specific scientific reference to papers published previously in THE JOURNAL OF GENERAL PHYSIOLOGY are invited. Receipt of such letters will be acknowledged, and those containing pertinent scientific comments and scientific criticisms will be published.]

Calcium, Magnesium, and Local Anesthesia

Dear Sir:

In support of a new hypothesis on the mechanism of action of local anesthetics (L.A.) Feinstein (1) described experiments in which L.A. are shown to inhibit phospholipid-facilitated Ca^{++} transport into chloroform from a methanol:water phase. A reinvestigation of this action of L.A. in our laboratory by the use of essentially the same experimental techniques, provided additional information of possible interest to the readers of this *Journal*.

TABLE I

INHIBITION OF CEPHALIN-FACILITATED Ca^{++} TRANSPORT, BY INCREASING CONCENTRATIONS OF Mg^{++}

	Total Mg^{++}	Mg^{++}	Total Ca^{++}	Ca^{++}
	mmole	%	*mmole*	%
Cephalin	0	—	0.2	6.6
No cephalin (control)	0	—	3.0	100
Cephalin	0.6	42	0.4	13
No cephalin (control)	1.4	100	3.0	100
Cephalin	1.2	41	0.8	26
No cephalin (control)	2.9	100	3.0	100
Cephalin	4.6	54	1.2	40
No cephalin (control)	8.4	100	3.0	100
Cephalin	10.4	60	1.6	53
No cephalin (control)	17.2	100	3.0	100
Cephalin	23.8	62	2.0	66
No cephalin (control)	32.0	100	3.0	100

5 ml aliquots of chloroform: methanol (2:1) containing 5 mg of cephalin (animal)/ml were agitated for 10 min with 2.0 ml aqueous solution containing NaCl 116 mM, KCl 2.5 mM, $CaCl_2$ 1.5 mM, and $MgCl_2$ in concentrations ranging from 0.7 up to 16 mM at pH 6.0. After centrifugation and separation of the two phases Ca^{++} and Mg^{++} concentrations were determined in the upper (water + methanol) layer.

Experiments in which cephalin was substituted by extracted lipids (uterus, brain) and $MgCl_2$ substituted by $MgSO_4$ have given similar results.

It was found that:

(*a*) L.A. (procaine HCl 4.4 mM or tetracaine HCl 2.2 mM) not only inhibits the phospholipid-facilitated Ca^{++} transport into chloroform but also induces the return

to the aqueous phase of Ca^{++} previously transported. The release of Ca^{++} from the chloroform phase is accomplished by adding the L.A. to the methanol:water phase and agitating for another 10 min.

(*b*) Mg^{++} inhibits the phospholipid-facilitated Ca^{++} transport into the chloroform. Inhibition increases with increased [Mg^{++}] as shown in Table I.

(*c*) Mg^{++} also has the ability to displace Ca^{++} previously transported into chloroform by phospholipid. The amount of Ca^{++} released from the chloroform into the aqueous phase is proportional to the amount of Mg^{++} transported into the chloroform phase.

(*d*) The inhibition exerted by a given concentration of L.A. on phospholipid-facilitated Ca^{++} transport is greater when Mg^{++} is present. The inhibitory effects of L.A. and Mg^{++} are additive. This was observed by comparing the effect of L.A. on the inhibition of Ca^{++} transport in the absence and in the presence of physiological concentrations of Mg^{++} (1.0 to 1.5 mM).

These observations not only provide a possible explanation for Mg^{++} anesthesia (2) itself (substitution of Ca^{++} by Mg^{++} at the cell membrane phospholipid) but also indicate the possibility that Mg^{++} is involved in the action of local anesthetics.

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