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LETTERS TO THE EDITOR

Flow decrease through rat hind limb vasculature by (±)-carnitine, (±)-acetylcarnitine and (±)-chloroacetylcarnitine chlorides

The occurrence of carnitine and various acyl carnitine derivatives in mammalian tissues is well documented (Pearson & Tubbs, 1964); however, the pharmacological effects of these biosubstrates have not yet been clearly elucidated. (±)-Acetylcarnitine (Dallemagne, Philippot & others, 1955; Fritz, 1963) and carnitine (Charlier, 1954; Yoshimi, Takaori & Shimamoto, 1965) produce cholinergic effects. We synthesized (±)- acetylcarnitine chloride (II) and (±)-chloroacetylcarnitine chloride (III) [$Me_3N^+{\cdot}CH_2{\cdot}CH(CH_2{\cdot}COOH)O\text{-}XCl^-$: I, X-H; II, X = COMe; III, X = $COCH_2Cl$] for comparison of the effect of these derivatives with (±)-carnitine chloride (I) on rat hind limb vasculature preparations *in situ*. Experiments now reported suggest that (±)-carnitine, (±)-acetylcarnitine and (±)-chloroacetylcarnitine possess potent vasoconstrictive properties.

Female albino Sprague Dawley rats, 250–300 g, were used for *in situ* hind limb vasculature preparations. (±)-Carnitine, (±)-acetylcarnitine and (±)-chloroacetylcarnitine chlorides significantly reduced flow rate through hind limb vasculature (Table 1). Reductions in flow rates were related to amounts of test compounds infused. At concentrations producing no discernible effects, test compounds potentiated the inhibitory effect of adrenaline on the isolated duodenum of the rabbit. To see if these compounds could potentiate the effect of noradrenaline on arterial smooth musculature, we examined the effect of (±)-acetylcarnitine on perfusate flow through rat caudal artery preparations (Kosegarten, De Feo & De Fanti, 1969, 1970). The flow rate response to noradrenaline was not altered by (±)-acetylcarnitine (5×10^{-8} g/ml). (±)-Carnitine alone elicited no demonstrable effect on arterial smooth musculature preparations at 1×10^{-8} and 5×10^{-9} g/ml.

Our evidence constrasts with published reports (Dallemagne & others, 1955; Fritz, 1963; Charlier, 1954; Yoshimi & others, 1965) of *in vivo* and *in vitro* acetylcholine-

Table 1. *Inhibition of flow through rat hind limb vasculature by carnitine and carnitine derivatives.* Each point represents the mean of at least two determinations. Animals were anaesthetized with sodium pentobarbitone (40 mg/kg, i.p.). Perfusate, collected from a polyethylene (PE 90) cannula in the inferior vena cava, was recorded using an automatic drop counter and E & M Physiograph. Test compounds were added directly to the perfusion fluid following control flow rate determination (29·3 ± 2·5, mean drops ± s.e.). Responses of all preparations were standardized with methacholine, acetylcholine and adrenaline.

Amount infused (mg)	Flow decrease (%) (±)-Carnitine	(±)-Acetylcarnitine	(±)-Chloroacetyl-carnitine
2·0	78	50	76
4·0	63	48	—
6·0	—	—	86
8·0	63	88	—
10·0	—	—	—
12·0	—	100	—
20·0	—	—	100

like activities of carnitine and acyl carnitine derivatives. Since these compounds have been administered to man (Gravina & Gravina-Sanvitale, 1969) further experiments are being made on the physiological significance of these findings.

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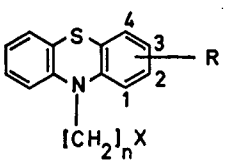
On the local anaesthetic action of chlorpromazine and some non-tranquillizing analogues

Chlorpromazine has been found in several tests to be a more potent local anaesthetic than procaine (Courvoisier, Fournel & others, 1953; Kopera & Armitage, 1954; Rosenberg & Ehrenpreis, 1961). In man, chlorpromazine has been successfully used to produce long-lasting local anaesthesia for the relief of post-surgical pain (Terrier, 1953), its subsequent abandonment for this purpose being possibly due to side-effects such as orthostatic hypotension. Other phenothiazines also cause local anaesthesia. In man promethazine is slightly less active than procaine, but it has been recommended for use in patients hypersensitive to local anaesthetics of the procaine type (Kalz & Fekete, 1960; Meltzer, 1960). The tranquillizer prochlorperazine has been reported to be ten times as potent as xylocaine in blocking conduction along single myelinated nerve fibres from the frog (Hille, 1966). It is not known whether the central depressant and local anaesthetic properties of these drugs have a common underlying mechanism.

The structural requirements for potent tranquillizing activity in the aminoalkylphenothiazine series (formula below) are well defined (Gordon, 1967). The ring



	R	n	X
I (chlorpromazine)	2-Cl	3	NMe_2
II (prochlorperazine)	2-Cl	3	N NMe
III	4-Cl	3	NMe_2
IV	2-Cl	4	NMe_2