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.

Department of Pharmacology & Toxicology and
Department of Pharmaceutical Chemistry,
University of Rhode Island.
Kingston, Rhode Island 02881, *U.S.A.*

May 1, 1970

R. T. LOUIS-FERDINAND
K. R. CUTRONEO
D. C. KOSEGARTEN
R. C. VASAVADA
J. G. TURCOTTE
D. R. DEFANTI

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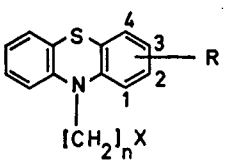
On the local anaesthetic action of chlorpromazine and some non-tranquillizing analogues

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

substituent (R) must be in the 2-position, and the tertiary amino-group (X) must be separated from the ring nitrogen by a trimethylene chain (n = 3). To test whether the local anaesthetic and tranquillizing properties in this series are related, the local anaesthetic activities of two tranquillizers, chlorpromazine (I) and prochlorperazine (II), have been compared in mice, using the tail clip method of Bianchi (1956), with those of two closely-related chlorpromazine analogues (III and IV), whose structures do not conform to the above requirements for tranquillizing activity and which cause only slight central depression in animals (Green, 1967).

The drugs, together with adrenaline tartrate (15 μg/ml), were dissolved in 0·9% NaCl. Four groups of ten adult mice were used for each compound, and the potency was assessed from the approximate concentration (EC50) required to cause a loss of withdrawal reflex to an artery clip on the tail in 50% of the mice 15 min after subcutaneous injection of 0·1 ml of the drug solution near the root of the tail. All four phenothiazines, irrespective of whether or not they were tranquillizers, had about the same EC50 (0·03 to 0·05%). All were more active than procaine (EC50, 0·1%) and all had a more prolonged action than procaine.

Higher concentrations (0·1 and 0·2%, total dose 3–6 mg/kg) of chlorpromazine and prochlorperazine ultimately caused marked sedation. However, whereas this sedation took 2–4 h to reach its maximum extent, the local anaesthesia had declined by this time (EC50 about 0·1%), hence the failure of the mice to respond to the artery clip on the tail after treatment with these drugs is unlikely to be attributable solely to a depressant action of central origin. The phenothiazines (III) and (IV) caused no sedation at these concentrations.

These results suggest that aminoalkylphenothiazines which do not have the requisite structural features to be potent tranquillizers may be a fruitful source of new long-lasting local anaesthetics. They also indicate that the action of chlorpromazine-like compounds on nerve cell membranes, which results in a depression of nerve conduction, is not the primary mechanism behind their tranquillizing effect.

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Department of Biochemistry,
University of Strathclyde,
*Glasgow, C.*1., *U.K.*

A. L. GREEN

May 4, 1970

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