In chronic toxicity studies metiamide has been shown at high doses to produce kidney damage and agranulocytosis in some dogs (Brimblecombe, Duncan & Walker, 1973). In tests so far carried out cimetidine at equivalent doses has not shown similar toxicity.

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Observations on the effect of dibenzoxazepine (CR) and N-nonoyl-vanillylamide (VAN) on sensory nerves

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VAN and CR cause a burning pain when applied to the human skin (Ballantyne, Beswick & Price-Thomas, 1973). This action has been investigated in cats by the application to a burn blister and to intact skin on the hindleg. Recordings were made from the sensory nerves innervating these areas.

Cats were anaesthetized with α-chloralose 70-90 mg/kg, and the blood pressure was monitored. The saphenous nerve was exposed in the thigh. The nerve was immersed in liquid paraffin and prepared for multifibre and single unit recording (Iggo, 1960). Nerve activity was recorded by bipolar silver electrodes, displayed on an oscilloscope for photography and stored on magnetic tape for further analysis using a small computer. Sensory units were identified by their response to mechanical stimulation of the skin, and by the conduction velocity and/or duration of the action potential in the related nerve fibres. Burn blisters were prepared by placing a metal disc (2 cm) at 100°C on the skin for 10 seconds. Close-i.a. injection of drugs employed the saphenous artery.

Only in four out of ten experiments where a blister had been prepared were the nerves innervating the blister identified. Isotonic KCl was applied in all four experiments to the blister base and found to cause activity in the isolated nerve fibres. Onset of action varied between 5 s and 1 min 45 seconds. On application of CR or VAN 10^{-4} M in saline no effects attributed to the drugs were observed. To test whether the preparations had been desensitized isotonic KCl was added again and was found to be effective in all cases.

Application of CR 10^{-4} M to intact skin. In six out of twenty-one preparations C-fibre units were isolated. These fine strands of nerves also contained in most cases alpha mechanoreceptors which were of low threshold and failed to respond. Five of these C-fibre units responded to CR and comprised 2 moderate threshold mechnoreceptors, 1 high threshold mechanoreceptor, 1 thermoreceptor and 1 unidentified receptor unit. Onset of activity in these units ranged between 5-8 min except for high threshold unit where the skin area was broken and activity occurred in 5 seconds. All these units showed immediate tachyphylaxis but still responded to physical stimulation. In some of these units, especially the thermoreceptor, saline was applied to the skin 45 min after CR response had subsided. Activity occurred within 5 min 5 seconds. This could be related to a similar phenomenon observed on human skin (Ballantyne, Beswick & Price-Thomas, 1973). All fibres affected by CR responded to 30 μg 5-HT and to 30 μg bradykinin injected close-i.a. Both compounds showed tachyphylaxis, but 5-HT more readily. Only some α fibres were affected by these compounds, probably the slowly adapting units (Fjallbrant & Iggo, 1961; Beck & Handwerker, 1974).

The observations suggest that CR acts on specific sensory units related to unmyelinated fibres. Research is continuing to clarify if the effect is indirect or direct and rigidly classify the fibre units which these compounds excite.

We wish to thank Professor A. Iggo for very helpful discussions and for demonstrating the technique.

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Actions of glutamate and kainic acid on the lobster muscle fibre and the frog spinal cord

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As kainic acid (Kai) is a potent glutamate agonist in the mammalian central nervous system (Shinozaki & Konishi, 1970; Johnston, Curtis, Davies & McCulloch, 1974), we have investigated the effect of Kai on two non-mammalian preparations where glutamate is a putative excitatory transmitter (Johnson, 1972). (1) Intracellular recordings were made from single muscle fibres in the lobster walking leg and the effects of Kai and of glutamate were measured as membrane depolarizations. (2) The frog isolated spinal cord preparation was studied according to the method of Mitchell & Phillis (1962) and the spinal acetylcholine (ACh) output was bioassayed every 10 minutes.

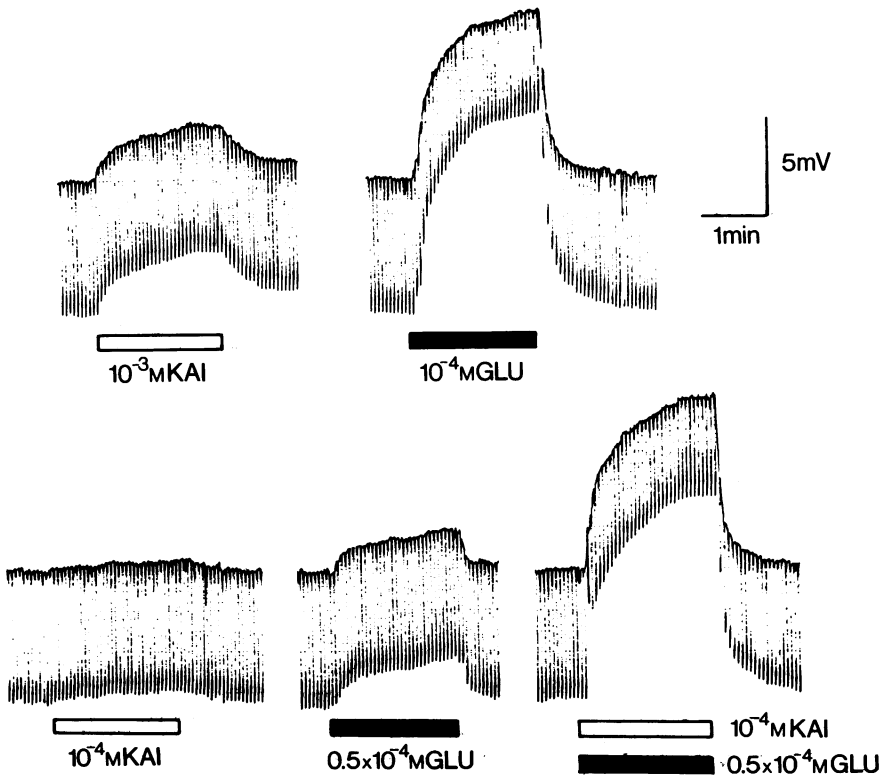

Figure 1 Depolarizations (upward deflections) induced by L-glutamate (GLU: solid bars) and kainic acid (KAI: open bars) in a single lobster muscle fibre. One voltage recording and one current (1.3×10^{-7} A) passing microelectrode were inserted into the middle of the fibre; the resultant electronic potentials were recorded as downward deflections. Concentrations of GLU higher than 1.5×10^{-4} M often caused muscle contraction with microelectrode displacement.