Short communications

Some characteristics of the adrenergic neurone blocking action of dehydroemetine

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The uptake of dehydroemetine by adrenergic neurones was studied indirectly by testing the ability of various procedures to prevent or reverse adrenergic neurone blockade in the periarterially stimulated rabbit isolated ileum. Adrenergic neurone blockade was prevented but not reversed by equilibration with dehydroemetine at low temperature (0° C), in the absence of sodium or in the presence of tetrodotoxin. Noradrenaline, cocaine, potassium deprivation and potassium excess did not modify the adrenergic neurone blocking action of dehydroemetine.

Dehydroemetine exerts an adrenergic neurone blocking action on the Finkleman (1930) preparation of the rabbit ileum (Ng & Ng, 1970; Salako, 1970) and on adrenergic nerves supplying the cat nictitating membrane (Salako, 1970). Recently Salako (1972) reported the pharmacodynamic effects of dehydroemetine, and concluded that dehydroemetine exerts a non-specific effect on sympathetic nerves. However, the negative chronotropic and inotropic effects of dehydroemetine are reported to be due to increased efflux of potassium (Durotoye & Salako, 1972). Using indirect procedures, Gulati & Jaykar (1971) suggested that the uptake of guanethidine by the adrenergic neurone was similar to the uptake of noradrenaline. Based on the same rationale, an attempt is made in the present study to determine whether the neurone blocking effect of dehydroemetine and, therefore, its uptake by the neurone resembles that of guanethidine.

Methods.—Segments of terminal ileum (2–3 cm long) from adult rabbits of either sex weighing 1·5–2 kg, were prepared with their sympathetic nerves intact by the method of Finkleman (1930), and set up in a 33 ml organ bath containing McEwen's solution at $35{\cdot}5 \pm 1°$ C. The details of the stimulation parameters and the method of recording were the same as those described by Gulati & Jaykar (1971). Two preparations from the same animal were set up at the same time. After control responses to different frequencies had been recorded, one preparation (test) was subjected for a specified period of time to any one of the procedures described below. This was followed by the administration to both preparations of dehydroemetine which was allowed to act for 30 minutes. The preparations were then washed 6–8 times and responses of both the preparations to different frequencies were obtained once more. The various procedures employed were: (i) addition to the bath of noradrenaline (6×10^{-4}M) immediately before dehydroemetine (4 experiments); (ii) exposure of the preparations for 30 min to McEwen's solution at 0° C (4 experiments); (iii) exposure of the preparations for 30 min to sodium-free McEwen's solution, the osmotic pressure and pH of which were maintained with sucrose and $KHCO_3$ respectively (4 experiments); (iv) exposure of the preparations for 20 min to tetrodotoxin ($1{\cdot}4 \times 10^{-6}$M) (5 experiments); (v) exposure of the preparations for 5 min to cocaine ($5{\cdot}8 \times 10^{-5}$M) (4 experiments); (vi) exposure of the preparations for 30 min to potassium-free McEwen's solution (3 experiments); (vii) exposure of the preparations for 20 min to McEwen's solution containing excess of potassium (8·4 mM) (3 experiments).

After the blocking effect of dehydroemetine had been studied in control preparations they were subjected to any one of the procedures described above, the object being to determine the ability of these procedures to reverse the neurone blocking action of the drug.

Dehydroemetine was used in a concentration of ($1{\cdot}8 \times 10^{-5}$M) throughout, except in experiments with excess of potassium where a concentration of ($1{\cdot}8 \times 10^{-7}$M) was employed.

Drugs: Cocaine hydrochloride (May & Baker); dehydroemetine dihydrochloride (Roche); (−)-noradrenaline (Rhone-Poulenc); tetrodotoxin (Calbiochem).

Results.—Dehydroemetine ($1{\cdot}8 \times 10^{-5}$M) abolished the pendular movements within 5–10 min of its addition to the bath. The

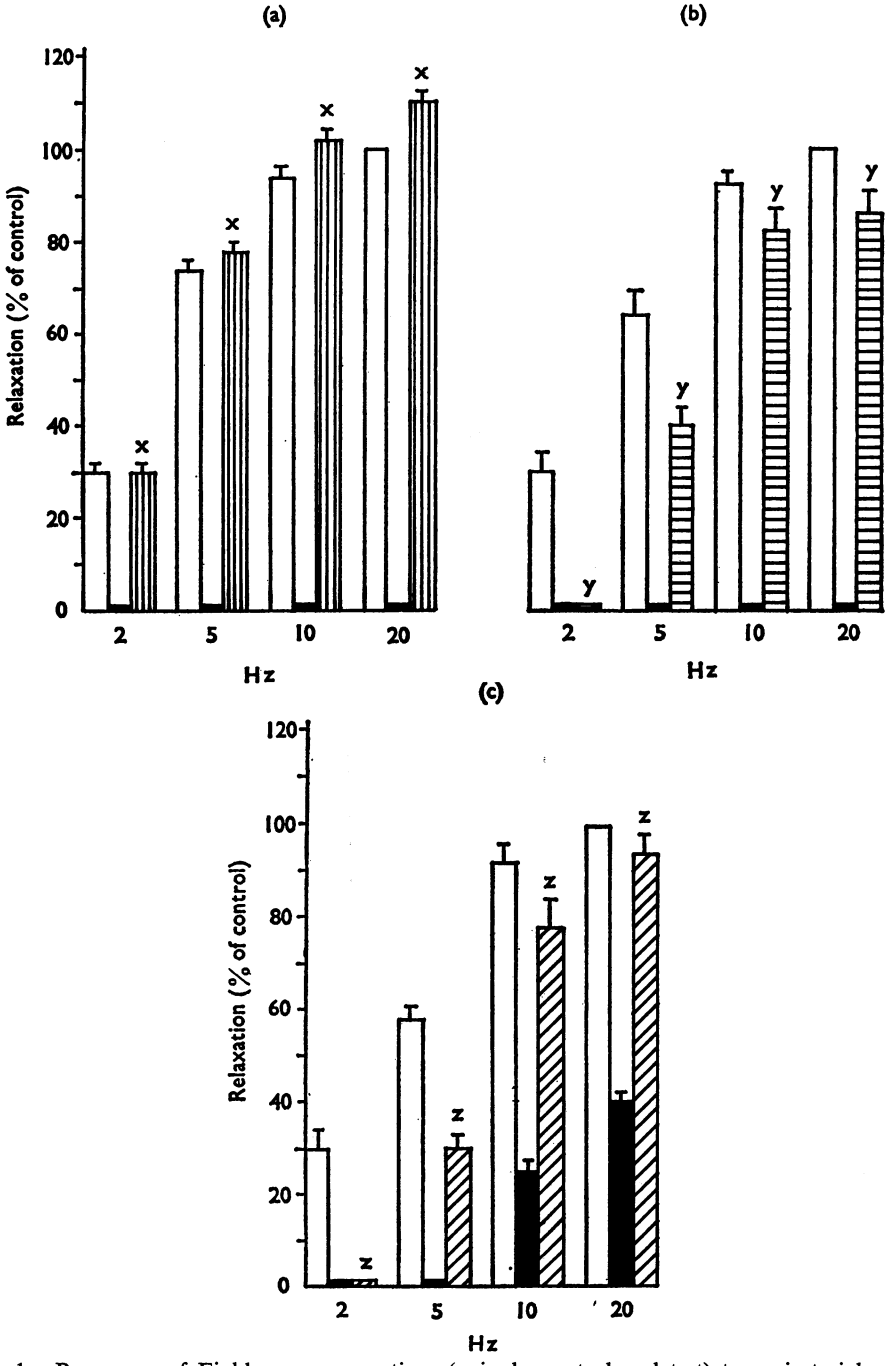

FIG. 1. Responses of Finkleman preparations (paired ; control and test) to periarterial nerve stimulation (5 ms for 45 s, every 4 min) at various frequencies which are indicated below each panel in Hz. The responses are expressed as a percentage of the maximum inhibition achieved in the first control frequency-response curve. Control responses—open columns ; control preparations after exposure to dehydroemetine ($1{\cdot}8\times10^{-5}$M) for 30 min—closed columns; test preparations exposed to McEwen's solution at 0° C for 30 min in (a)—columns labelled x; test preparations exposed to tetrodotoxin ($1{\cdot}4\times10^{-6}$M) for 20 min in (b)—columns labelled y and test preparations exposed to sodium-free McEwen's solution for 30 min in (c)—columns labelled z. The procedures in a, b, and c were followed by further exposure to dehydroemetine ($1{\cdot}8\times10^{-5}$M). Vertical lines indicate S.E.M.

pendular movements were completely restored after 6–8 washes. In many experiments, this concentration of dehydroemetine completely blocked responses to nerve stimulation at all frequencies (Fig. 1a and b). In some experiments the block at higher frequencies was partial (Fig. 1c). In spite of repeated washes the block was irreversible over the entire experimental period (4–6 hours). During this time the preparation was as responsive to noradrenaline ($5{\cdot}9\times10^{-6}$M) as it was before exposure to dehydroemetine.

Following exposure to noradrenaline or low temperature or potassium-free McEwen's solution or cocaine, the preparations were relaxed and the pendular movements were abolished. Complete restoration occurred after 6–8 washes. Tetrodotoxin ($1{\cdot}4\times10^{-6}$M) or excess of potassium or sodium deprivation had no effect on the preparations.

Prior exposure of the preparations to low temperature completely prevented the neurone blocking action of dehydroemetine (Fig. 1a) while exposure to tetrodotoxin or sodium-free McEwen's solution partially prevented the blocking action (Fig. 1b and c). On the other hand, noradrenaline, cocaine and potassium-free McEwen's solution did not prevent the neurone block and none of the procedures reversed it.

Dehydroemetine, ($1{\cdot}8\times10^{-7}$M) had no effect on pendular movements. This concentration of dehydroemetine produced 100% block at 2 Hz, 74% block at 5 Hz, 46% block at 10 Hz, 12% block at 20 Hz and 8% block at 60 Hz. The blocking action of this concentration lasted for 60–90 minutes. In test preparations, following exposure to McEwen's solution containing excess potassium, the block produced by dehydroemetine ($1{\cdot}8\times10^{-7}$M) was not significantly ($P>0{\cdot}1$) different from that in control experiments. Similarly the block once produced (in control preparations) was not influenced by subsequent exposure to solutions containing excess of potassium.

Discussion.—The present study has shown that the adrenergic neurone blocking action of dehydroemetine is temperature-sensitive since prior exposure of the preparations to solutions at 0° C completely prevented the blocking action. This suggests that the uptake of dehydroemetine into the neurone is an energy-dependent active process. The involvement of sodium in the uptake of dehydroemetine is indicated by the results of experiments involving sodium deprivation and tetrodotoxin which blocks the permeability of the neuronal membrane to the sodium ion (Kao, 1966; Cheymol & Bourillet, 1966). Both procedures prevented the neurone blocking action of dehydroemetine. The neurone blocking action of dehydroemetine was not prevented by noradrenaline or cocaine. Salako (1970) also failed to observe any prevention with cocaine. This indicates that the uptake of dehydroemetine into the neuronal membrane occurs through a mechanism distinct from the one which takes up noradrenaline or guanethidine, the latter two drugs sharing a common uptake mechanism (Chang, Costa & Brodie, 1965; Obianwu, Stitzel & Lundborg, 1968; Gulati & Jaykar, 1971). Another difference is that the neurone blockade produced by guanethidine can be reversed by cocaine (Day, 1962) whereas that produced by dehydroemetine cannot.

The neuronal block produced by dehydroemetine was neither augmented by excess of potassium nor prevented by medium lacking in potassium. This indicates that the mechanisms of the inhibitory action of dehydroemetine on the heart (Durotoye & Salako, 1972) and its neuronal blocking action are different.

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