These preliminary experiments show an uptake and binding of calcium by the motor endplate region of the muscle in the presence of carbachol and ACh. During normal motor nerve activity, it is unlikely that calcium accumulates in the quantities which have been demonstrated here, but it does seem possible that some calcium may be bound at the motor endplate during the transmission of each impulse.

This work was partly supported by a grant from the National Fund for Research into Crippling Diseases.

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Pharmacological interaction of lorazepam with thiopentone sodium and skeletal neuromuscular blocking drugs

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Lorazepam (Wy 4036; 7-chloro-5-(*O*-chlorophenyl)-3-hydroxy-1,3-dihydro-2*H*-1,4-benzodiazepin-2-one) is a highly active tranquillizing drug (Haider, 1971; Turner & Harry, 1971) which also has an application in preanaesthetic medication (Norris, 1971). In view of the recent reports by Feldman & Crawley (1970a, b) of a hazardous anaesthetic interaction of diazepam, experiments have been performed to investigate the pharmacological interactions of lorazepam with thiopentone and skeletal neuromuscular blocking drugs.

In mice infused intravenously with thiopentone sodium, oral doses of lorazepam (0·1–10 mg/kg) reduced the time to induction of hypnosis and arrest of respiration. Furthermore, the duration of the loss of righting reflex after a single intravenous injection of thiopentone (50 mg/kg) was increased by lorazepam in doses of 1·25–6·25 mg/kg. Comparative tests with diazepam, meprobamate and glutethimide showed a similar enhancement of the effects of thiopentone. To investigate whether these effects represented a potentiating or an additive action of lorazepam with thiopentone, the effect of various dose combinations of the drugs on loss of righting reflex in mice was examined. The results indicated that lorazepam and thiopentone interacted to produce an effect greater than that expected from simple addition.

Experiments in decerebrate cats in which contractions of the gastrocnemius muscles elicited by stimulation of the sciatic nerves were measured, showed that intravenous injection of lorazepam (0·5 and 2 mg/kg) or diazepam (0·5 and 2 mg/kg) failed to alter significantly the responses either to intravenous suxamethonium (10–50 μg/kg) or to intravenous gallamine (100–500 μg/kg).

These animal experiments have shown no untoward pharmacological interactions when lorazepam or diazepam are combined with thiopentone or skeletal neuromuscular blocking drugs.

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Action of edrophonium on acetylcholinesterase at the mammalian neuromuscular junction

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A new method has been developed for estimating the degree of inhibition of the physiologically important acetylcholinesterase at the neuromuscular junction (Ferry & Marshall, 1971). This method is based on the prolongation of the extracellularly recorded endplate potential of a curarized rat diaphragm after treatment with anticholinesterase drugs.

In this work, endplate potentials were recorded extracellularly from the fully curarized rat phrenic nerve-diaphragm preparation with an insulated wire electrode located at the endplate region. The preparation was immersed in a saline medium (Liley, 1956) at 36°C. The effect of edrophonium in concentrations ranging from $0{\cdot}5 \times 10^{-6}$ M to 10^{-4} M was investigated; the duration of the endplate potential at half amplitude was measured. After the lowest concentration of edrophonium the duration was $1{\cdot}13 \pm 0{\cdot}025$ ($n=7$), and after the highest concentration, $3{\cdot}71 \pm 0{\cdot}27$ ($n=11$) relative to the individual controls.

In curarized preparations, the mean quantal content of the endplate potential of each of a number of cells was calculated from the variance of the amplitude of a series of intracellularly recorded endplate potentials elicited at 1 Hz. Under control conditions the overall mean quantal content was 178 (thirty-one cells) and after edrophonium 5×10^{-5} M it was 167 (twenty-three cells). There is no significant difference between these values ($P=0{\cdot}05$).

The effect of edrophonium on the contraction of the partially curarized diaphragm after indirect stimulation was investigated. With edrophonium ($0{\cdot}5 \times 10^{-6}$M) some reversal of the block was evident. From the electrophysiological work it was estimated that this concentration of edrophonium produced about 15% inhibition of the physiologically important acetylcholinesterase.

It is concluded that edrophonium inhibits the physiologically important acetylcholinesterase at the neuromuscular junction and that even a small degree of inhibition of the enzyme will facilitate transmission in the curarized phrenic nerve-diaphragm preparation.

This work was supported by the Muscular Dystrophy Group of Great Britain.

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