(TEA) (BDH), tetramethylammonium bromide (TMA) (BDH), and tetra *n*-butylammonium iodide (TBA) (BDH). Contractions of the chick biventer cervicis muscle were recorded *in vitro* using an isometric transducer. Indirect stimulation of the muscle was employed using a twice maximal stimulus (usually 50–100 μs pulses of 2.5–5.0 volts, for further details see Elliott (1977). TMA closely resembled suxamethonium in producing a contracture which varied in amplitude with the dose employed, low concentrations of TMA ($3.9–7.8 \times 10^{-5}$ M) produced a small facilitation of transmission (up to 20%), larger doses ($> 1.6 \times 10^{-4}$ M) produced neuromuscular block. The contractures produced by TMA were abolished by $3.5–5.3 \times 10^{-4}$ M METHO, TMA nevertheless still produced neuromuscular block. TEA ($0.2–7.6 \times 10^{-3}$ M) produced no contracture but facilitated transmission in a dose responsive manner, there was no neuromuscular block in the dose range tested. In the presence of low concentrations of METHO ($0.35–1.8 \times 10^{-4}$ M) TEA produced marked contractures, with higher concentrations ($3.5–5.3 \times 10^{-4}$ M) of METHO the contractures were abolished and TEA ($0.6–3.8 \times 10^{-3}$ M) now produced neuromuscular blockade.

TBA ($5.4 \times 10^{-5}–1.7 \times 10^{-3}$ M) produced neither contracture nor facilitation of transmission. Concentrations above 1.1×10^{-4} M produced a dose responsive block of transmission. In the presence of low concentrations of METHO (8.8×10^{-5} M) TBA in concentrations above 8.7×10^{-4} M now produced contractures.

It is concluded that in the presence of suitable doses of METHO all the quaternary drugs tested can produce contracture and neuromuscular block. This may suggest that although these drugs may differ in their effects on transmission at the avian neuromuscular junction their basic modes of action are the same. It is possible that some of the effects observed with METHO may be accounted for if the drug exerts an hyperpolarizing action on multiply innervated fibres and on presynaptic nerve endings.

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Evidence for the presence of histamine H_1-receptors in guinea-pig brain

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Histamine is present in appreciable amounts in mammalian brain and is stored in both neuronal and non-neuronal compartments, suggesting that it may have multiple roles in brain function. The field of histaminergic mechanisms in brain has been reviewed by Schwartz (1977). Both histamine H_1- and H_2-receptor types have been reported to be involved in histamine function, but in most studies the evidence for H_1-receptors is based on the use of H_1-antagonists at concentrations at which non-specific effects may occur (Schwartz, 1977). To establish whether H_1-receptors are indeed present in guinea-pig brain we have examined the binding of [^{3}H]-mepyramine, which we have recently demonstrated to be a selective ligand for histamine H_1-receptors in homogenates of smooth muscle from guinea-pig intestine (Hill, Young & Marrian, 1977). The results of this study, which we present here, show that there is appreciable binding of [^{3}H]-mepyramine to homogenates of guinea-pig brain, the properties of which are consistent with the presence of histamine H_1-receptors.

Guinea-pig whole brain was homogenized in 5 volumes of 50 mM Na-K phosphate buffer, pH 7.5, treated with a polytron blender at setting 5 for 15 s and centrifuged at 6,000 *g* for 20 minutes. The pellet was resuspended, centrifuged at 8,700 *g* for 1 min in a Beckman microfuge and the resulting pellet suspended in the same buffer. Binding assays were carried out in 50 mM Na-K phosphate buffer, pH 7.5, using a microcentrifugation assay, essentially as described previously (Hill, Young & Marrian, 1977).

The binding of [^{3}H]-mepyramine sensitive to promethazine (2×10^{-6} M), a histamine H_1-selective antagonist, was saturable with an affinity constant near 10^9 M^{-1}, similar to that observed in intestine (Hill, Young & Marrian, 1977) and in the range of values reported from measurements on the antagonism of the contractile response of intestinal smooth muscle to histamine. (+)-Chlorpheniramine was approximately 100-fold more potent than the (−)-isomer in inhibiting the binding of 10^{-9} M [^{3}H]-mepyramine, consistent with the potency ratio of 100 reported for the antagonism of the contractile response of aortic strips to histamine (O'Neill & Patil, 1975). The binding affinities of promethazine, 7×10^8 M^{-1}, and (+)-chlorpheniramine, 8×10^8

M^{-1}, obtained from the curves of the inhibition of [^{3}H]-mepyramine binding, were in good accord with values reported from organ bath studies.

The total number of H_1-receptors varied somewhat from preparation to preparation, the mean value being 124 pmol/g protein. This value is of the same order as that, 169 pmol/g protein, found in homogenates prepared in a similar way from the longitudinal muscle of guinea-pig intestine, although in that tissue, where measurements have been made over a longer period of time, it has become apparent that the number of H_1-receptors can vary widely (range 94–312 pmol/g protein).

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Comparison of the actions of central and peripheral administration of clonidine and BS 100-141 in the rabbit

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Clonidine is a potent antihypertensive drug that lowers blood pressure and heart rate, mainly by an action on central alpha adrenoceptors. However, rapid reversal of the hypotension on withdrawal and the central nervous side effect of sedation limit its usefulness. BS 100-141 (N-amidino-2-(2,6-dichlorophenyl)-acetamide hydrochloride) also appears to lower blood pressure by central mechanisms (Scholtysik, Lauener, Eichenberger, Bürki, Salzmann, Müller, Schweinitzer & Waite, 1975). We have compared the effects of these two drugs after central and peripheral injection.

Male New Zealand white rabbits (2.5–4 kg) had mean arterial pressure (MAP) recorded directly from the ear artery. Intravenous (i.v.) and intracerebroventricular (i.c.v.) injections were given to conscious animals and intracisternal (i.c.) injections after pentobarbitone anaesthesia.

Clonidine (3–100 μg/kg) and BS 100-141 (30–1000 μg/kg) i.v. had a biphasic effect on MAP, first causing a rise then a longer-lasting fall, together with bradycardia. The rise in MAP lasted 1 min after clonidine (30 μg/kg) and 90 min after BS 100-141 (300 μg/kg). These doses caused a similar hypotensive effect, although it was longer after BS 100-141 than clonidine (4 and 1.5 h respectively).

Clonidine (3 μg/kg) given i.c.v. caused a fall in MAP (14 ± 2 mm Hg) by 5 min which lasted for 90 minutes. There was a delay in the fall in MAP after i.c.v. BS 100-141 (12 μg/kg). MAP was not significantly reduced until 60 min (8 ± 3 mm Hg) and remained so at 6.5 hours. Heart rate did not significantly alter on either drug.

Clonidine (3 μg/kg i.c.) had a hypotensive effect (18 ± 5 mm Hg) apparent by 2 min and lasting for 60 minutes. Heart rate was reduced for 90 min only. The fall in MAP (10 ± 4 mm Hg) after BS 100-141 (12 μg/kg i.c.) occurred within 10 min and lasted for 150 minutes. Heart rate was significantly lowered at 90, 150 and 180 minutes ($P < 0.05$).

BS 100-141 has a similar profile of action to clonidine, however, it is less potent, having about one-tenth the potency after i.v. administration and about one-quarter the potency after central administration. The slow onset and longer duration of action of BS 100-141 after i.v. and i.c.v. administration may be due to delay in reaching its site of action in the central nervous system or a result of the prolonged hypertensive effect. The longer duration of action of BS 100-141 may be clinically relevant and permit oral administration to man as a single daily dose.

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