amplitude of the indirectly or directly evoked maximal twitches of the tibialis anterior muscle. The maximal effect (> 100% increase in twitch tension in 8 cats) was produced by doses of 2 or 3 mg/kg i.v. The effect of a small dose (0.5 mg/kg) was slow to develop, taking from 14 to 23 min from injection to the peak of the effect. Once developed, however, the effect persisted for at least 2 h. The effect on the twitch tension of the tibialis anterior muscle was unaccompanied by any change in the amplitude of the gross muscle action potential; nor was there any evidence of repetitive firing. In some experiments, a prolongation of the second wave of the biphasic action potential was detectable. This effect probably reflected prolongation of the individual muscle fibre action potentials arising from the known effect of 4-aminopyridine to block potassium channels in excitable membranes, including those of muscle fibres (Gillespie & Hutter, 1975). 4-Aminopyridine was without effect on the tension of maximal twitches of the soleus muscle. It did not increase the tension of maximal tetani of either muscle. When maximal twitches of the tibialis anterior muscle were depressed by 70–90% by dantrolene sodium (4 mg/kg), 4-aminopyridine (0.5–2 mg/kg) slowly restored the twitches to, or to slightly above, the control amplitude. It is concluded that 4-aminopyridine can enhance the contractility of cat skeletal muscles, and it is suggested that the effect is evident only when activation of the contractile mechanism is submaximal.

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Tachyphylaxis after repeated dosage of decamethonium in anaesthetized man

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In a previous study we used the tetanic and single twitch responses of the adductor pollicis muscle to demonstrate tachyphylaxis with suxamethonium in anaesthetized man (Sugai, Hughes & Payne, 1975). We have now applied this technique to assess the neuromuscular effects of repeated dosage of decamethonium.

Studies were undertaken in a total of 8 anaesthetized patients who had given their informed consent and were about to undergo urological surgery. The methods used have already been described (Hughes, Ingram & Payne, 1976).

Decamethonium was administered in divided doses to 5 anaesthetized patients and the total dose was repeated after full recovery from neuromuscular blockade. Tachyphylaxis developed after the second or third series of injections; the tetanic response was affected more than single twitch and its pattern was more consistent. In 2 of these patients when the same total dose of decamethonium was administered on 3 occasions, blockade of the tetanic response was diminished after the third treatment (Table 1). In the other 3 patients tachyphylaxis was evident after the second series of injections when the total dose administered was at least twice that given in the first treatment (Table 1). In 4 of these 5 patients who were given neostigmine (2.5 mg i.v.), blockade of the tetanic response was antagonised. Furthermore, in 4 patients who received 2% halothane during recovery from decamethonium, the neuromuscular block was potentiated—an effect we had observed previously with competitive neuromuscular blocking agents (Hughes & Payne, 1977).

In contrast, in a group of 3 patients who were given only one series of injections of decamethonium, ie. before tachyphylaxis had developed, blockade of the tetanic response was potentiated by neostigmine and was not affected by 2% halothane.

Table 1

Patient	1st Treatment Total Dose (mg/kg i.v.)	1st Treatment % Block (Tetanus)	2nd Treatment Total Dose (mg/kg i.v.)	2nd Treatment % Block (Tetanus)	3rd Treatment Total Dose (mg/kg i.v.)	3rd Treatment % Block (Tetanus)
1	0.03	90	0.03	93	0.03	58
2	0.02	68	0.02	75	0.02	24
3	0.03	99	0.06	87		
4	0.02	95	0.05	88		
5	0.02	93	0.05	76		

Thus, the neuromuscular blocking action of decamethonium, like that of suxamethonium, changes after repeated dosage when its properties resemble more those of the competitive neuromuscular blocking agents.

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Analysis of dopamine interactions with [^{3}H]-spiperone binding sites on rat corpus striatum membranes

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Initial studies using [^{3}H]-neuroleptics revealed the existence of binding sites in brain tissue which showed properties characteristic of an association with dopamine (DA) receptors (Burt, Creese & Snyder, 1976; Howlett & Nahorski, 1978; Titeler, Weinreich, Sinclair & Seeman, 1978). More recent reports however, have focussed attention on the complexity of DA agonist-antagonist interactions at these sites (Titeler *et al.*, 1978; Howlett, Morris & Nahorski, 1979). We have previously shown that while the DA antagonist [^{3}H]-spiperone appears, from saturation analyses, to bind to a single population of high affinity sites on rat corpus striatum membranes (Howlett & Nahorski, 1978), DA agonists interact with the [^{3}H]-spiperone for more than one site (Howlett *et al.*, 1979). In this present communication, we have further examined these interactions by studying the dopamine/[^{3}H]-spiperone competition at various degrees of occupancy of the antagonist binding sites.

The methods used were as previously described (Howlett & Nahorski, 1978), except that the corpus striatum membrane preparation examined was an homogenate in Tris/HCl (50 mM, pH 7.8), with no washing or purification. The binding studied was that displaced by (+)-butaclamol (10^{-6} M), and constituted 80–90% of the total binding.

Five concentrations of [^{3}H]-spiperone, ranging from 90 pM to 2.2 nM, were incubated with increasing amounts of DA (10 nM–100 μM). In the absence of any competing DA, 90 pM [^{3}H]-spiperone occupied approximately 40% of the maximum (+)-butaclamol displaceable binding sites. This occupancy increased to 50% at 230 pM and was virtually 100% at 1.5 nM [^{3}H]-spiperone.

At all five [^{3}H]-spiperone concentrations studied, DA produced displacement curves of a 'flattened' nature which Scatchard analyses resolved into two components. The affinities of dopamine for these two sites (0.3 and 40 μM) were comparable with our previous findings (Howlett *et al.*, 1979). The relative amounts of the two sites however, were proportional to the [^{3}H]-spiperone concentration. Even at the lowest concentration of ligand (90 pM), the occupancy of the high affinity site was maximal and comprised 85% of the total specific binding. Increasing the [^{3}H]-spiperone concentrations further occupied only those sites that had a low affinity for DA, such that at 2.2 nM [^{3}H]-spiperone, when both sites were fully occupied, the high affinity site comprised only 30% of the total. Thus, [^{3}H]-spiperone appears to bind to two sites on rat corpus striatum membranes with similar affinities, while DA displaces [^{3}H]-spiperone