good, because in the mouse vas deferens the ID_{50} values were inversely related to concentration. On the other hand, the values of relative antagonist activities obtained by the two methods showed close correlation.

It would appear that the morphine receptors in the mouse vas deferens and the guinea-pig ileum are similar in principle but exhibit differences in detail.

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Modification of the antinociceptive activity of narcotic agonists and antagonists by intraventricular injection of biogenic amines in mice

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It has been reported that intracerebroventricular (i.c.v.) injections of 5-hydroxytryptamine (5-HT) potentiate, and those of noradrenaline (NA) attenuate, the antinociceptive activity of morphine in rats, although neither amine given alone acutely alters the nociceptive threshold (Sparkes & Spencer, 1969, 1971). Although further studies in mice confirmed these observations (Calcutt & Spencer, 1971), the results of studies with partial agonists were not clear since nalorphine was potentiated by 5-HT whilst pentazocine was not, and the antagonist naloxone abolished the prolongation in reaction time produced by 5-HT.

The present communication represents a further study of the interactions of i.c.v.-injected amines with narcotic agonist and partial agonist/antagonist drugs. Male mice of the ICI albino strain, weighing 18-22 g, were injected subcutaneously with agonist or partial agonist/antagonist agents, and the nociceptive threshold determined repeatedly during the next 3 h, using a tail-immersion technique similar to that described by Ben-Bassat, Peretz & Sulman (1959). In these experiments, mice were held in individual ventilated plastic containers at a room temperature of 21-22° C and nociceptive reaction times determined when the tail was immersed in a water bath maintained at 48° C.

Intraventricular 5-HT (10-100 μg) produced only brief increases in reaction time which were not dose-related. When injected 15 min before the peak effects of morphine (2.5 mg/kg), diacetylmorphine (0.75 mg/kg), pethidine (15 mg/kg) or etorphine (0.5 μg/kg), 5-HT (10 μg/mouse i.c.v.), produced a potentiation and prolongation of antinociceptive effect in each case. Conversely, when NA (10 μg/mouse i.c.v.) was injected 15 min prior to the peak effect of morphine (5 mg/kg), diacetylmorphine (1.5 mg/kg), pethidine (50 mg/kg) or etorphine (2 μg/kg), there was attenuation of the antinociceptive effects in each case.

In this tail immersion test, nalorphine, pentazocine and cyclazocine injected subcutaneously produced a dose-related antinociceptive effect which exhibited a low 'ceiling effect' when compared with predominantly agonist agents.

Concurrent injection of 5-HT (10 μg/mouse i.c.v.) potentiated and prolonged the antinociceptive effects of nalorphine (10 mg/kg), pentazocine (5 mg/kg) or cyclazocine (5 mg/kg), while concurrent injection of NA (10 μg/mouse i.c.v.) attenuated the effects of these agents administered in the same doses. Naloxone (5 mg/kg) was almost inactive in this test and its effects were not potentiated by 5-HT (10 μg/mouse i.c.v.).

It is suggested from these results that the possible dependence of the antinociceptive activity of morphine on the balance between concentrations of 5-HT and NA in the brain may be extended to the effects of other narcotic agonist and partial agonist agents.

The failure of other workers to show the effects of 5-HT and NA on narcotic partial agonists may

be due to the fact that previous testing methods were not sufficiently sensitive to show dose-related antinociceptive effects in these drugs *per se*, nor did they take into account the different durations of action of individual antinociceptive agents.

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The effect of tetraethylammonium (TEA) on the anococcygeus muscle and on its response to motor and to inhibitory nerve stimulation

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Tetraethylammonium (TEA) has several known effects on neurotransmission. At cholinergic junctions it possesses both ganglion blocking and curare-like activity (Acheson & Pereira, 1946; Koketsu, 1958). TEA also increases the liberation of transmitter at both cholinergic and adrenergic junctions probably by prolonging the nerve action potential by abolishing the rise in K^+ permeability which is responsible for delayed rectification (Koketsu, 1958; Tasaki & Hagiwara, 1957; Thoenen, Haefely & Staehelin, 1967). The anococcygeus muscle in the rat possesses both a motor adrenergic innervation and an inhibitory innervation whose transmitter is unknown (Gillespie, 1972). The purpose of this investigation was to determine whether TEA increases the release of transmitter from these inhibitory nerves and so potentiates the response, and to compare this with the effect on the more familiar adrenergic pathway. We also examined the effect of TEA on the action of the agonists noradrenaline (NA) and carbachol as well as the direct effects of the drug on the muscle.

TEA in concentrations from 0.1-20 mM potentiates the motor response to field stimulation. The effect is greatest at low, submaximal stimulation frequencies (2 Hz). The potentiation is unaffected by hexamethonium (10^{-5} M-10^{-4} M), atropine (3×10^{-7} M-3×10^{-6} M) or curare (3×10^{-6} M). Potentiation is not due to an increased effectiveness of NA whose action is little affected by TEA. However, the blocking action of phentolamine on the motor response was reversed by TEA suggesting an increased release of transmitter.

The effect of TEA on the inhibitory response depends on its concentration. Low concentrations from 0.1-1.0 mM potentiate the inhibitory response especially at low frequencies of stimulation; higher concentrations of 5-20 mM progressively depress the response.

The effect of TEA on the response to NA and to carbachol was examined. In concentrations from 0.1-5 mM TEA slightly potentiates the response to NA and more markedly inhibits the response to carbachol. Finally, the direct effect on the smooth muscle was examined. At concentrations below 5 mM TEA has no observable effect. Higher concentrations (5-20 mM) induce rhythmic activity and tone. Part of this effect is abolished by phentolamine suggesting it is mediated by the release of NA; the presence of a residual stimulation suggests an additional direct effect on the smooth muscle.

In summary all concentrations of TEA tested enhance the release of NA from the adrenergic nerves to the anococcygeus and so potentiate the motor response. Low concentrations of TEA similarly potentiate the inhibitory response but high concentrations reduce this inhibition. This reduction in nerve mediated inhibition may be due to an antagonistic motor action on the smooth muscle.

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