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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References

BEN-BASSET, J., PERETZ, E. & SULMAN, F.G. (1959). Analgesimetry and ranking of analgesic drugs by the receptacle method. *Arch. Int. Pharmacodyn.*, **122**, 434-447.

CALCUTT, C.R. & SPENCER, P.S.J. (1971). Activities of narcotic and narcotic-antagonist analgesics following the intraventricular injection of various substances. *Br. J. Pharmac.*, **41**, 401P.

SPARKES, C.G. & SPENCER, P.S.J. (1969). Modification of morphine analgesia in the rat by biogenic amines administered intraventricularly. *Br. J. Pharmac.*, **35**, 362-363P.

SPARKES, C.G. & SPENCER, P.S.J. (1971). Antinociceptive activity of morphine after injection of biogenic amines in the cerebral ventricles of the conscious rat. *Br. J. Pharmac.*, **42**, 230-341.

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.

References

ACHESON, G.H. & PEREIRA, S.A. (1946). The blocking effect of tetraethylammonium ion on the superior cervical ganglion of the cat. *J. Pharmac. exp. Ther.*, 87, 273-280.

GILLESPIE, J.S. (1972). The rat anococcygeus muscle and its response to nerve stimulation and to some drugs. *Br. J. Pharmac.*, 45, 404-416.

KOKETSU, K. (1958). Action of tetraethylammonium chloride on neuromuscular transmission in frogs. *Amer. J. Physiol.*, 193, 213-218.

TASAKI, I. & HAGIWARA, S. (1957). Demonstration of two stable potential states in the squid giant axon under tetraethylammonium chloride. *J. Gen. Physiol.*, 40, 859-885.

THOENEN, H., HAEFELY, W. & STAEHELIN, H. (1967). Potentiation by tetraethylammonium of the response of the cat spleen to post-ganglionic sympathetic nerve stimulation. *J. Pharmac. exp. Ther.*, 157, 532-540.

Comparison of the effects of mescaline, noradrenaline and 5-hydroxytryptamine on single cortical neurones

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Previously we have reported that single cortical neurones can respond either with excitation or with depression to microelectrophoretic application of mescaline, and that these responses can be antagonized by the β-adrenoceptor antagonist, sotalol, and the 5-hydroxytryptamine antagonist, methysergide (Bradshaw, Roberts & Szabadi, 1971). In the present communication we report the results of some further studies in which we attempted to identify the receptor at which mescaline acts on cortical neurones.

Single spontaneously active neurones were studied in the somatosensory cortex of cats anaesthetized with halothane. Drugs were applied from 5-barrelled micropipettes by microelectrophoresis.

Of 199 cells yielding consistent responses to mescaline, 159 were excited, 34 were depressed, and 6 responded in a biphasic fashion (depression followed by excitation). Responses to mescaline were compared with responses to noradrenaline and 5-hydroxytryptamine on 66 cells. Fifty-one of these cells responded in the same direction to all three agonists. The remaining 15 cells responded in the same direction to noradrenaline and mescaline and in the opposite direction to 5-hydroxytryptamine. When responses to mescaline were compared with responses to noradrenaline and 5-hydroxytryptamine using a range of ejecting current intensities mescaline appeared to be less potent than the other amines.

Desensitization to the excitatory effects of mescaline was observed on 12 cells. Following desensitization to mescaline, neurones were found to be less sensitive to noradrenaline. This cross-desensitization was usually not specific, however, since responses to acetylcholine were also reduced.

The effect of mescaline on responses to noradrenaline and 5-hydroxytryptamine was also studied on 5 cells which did not respond to mescaline. The simultaneous application of mescaline resulted in antagonism of excitatory responses to noradrenaline and 5-hydroxytryptamine.

We have investigated the effects of sotalol (17 cells) and methysergide (20 cells) on responses to mescaline. We have found that sotalol and methysergide reversibly antagonized responses to mescaline. This antagonism was specific inasmuch as responses to acetylcholine were not affected. However, neither antagonist was able to discriminate between the actions of mescaline, noradreanline and 5-hydroxytryptamine.

These results suggest that mescaline may act at receptors similar to those activated by noradrenaline and 5-hydroxytryptamine on cortical neurones. However, although the correlation studies suggest that mescaline acts at noradrenaline receptors, it is not clear from the antagonist studies using sotalol and methysergide whether noradrenaline and 5-hydroxytryptamine act at the same or at different receptor sites. The apparently lower potency of mescaline might be due to a lower transport number of mescaline. However the observation that on some cells mescaline had very little agonistic effect yet was able to antagonize responses to noradrenaline and 5-hydroxytryptamine suggests that the lower potency of mescaline might be due to a lower intrinsic activity of this drug.

Reference

BRADSHAW, C.M., ROBERTS, M.H.T. & SZABADI, E. (1971). The effect of mescaline on single cortical neurones. *Br. J. Pharmac.*, 43, 871-873.