pellet was discarded and the supernatant centrifuged at 100,000 *g* for 30 min. The final pellet was resuspended in Krebs-Henseleit bicarbonate incubation medium without phosphate and containing 1.24 $\times 10^{-4}$M EDTA, 5×10^{-5}M pargyline and 1.14×10^{-3}M ascorbic acid) to a final protein concentration of 3–5 mg/ml. Aliquots (3 ml.) of this suspension were incubated at 37° under O_2–CO_2 (95 : 5) with 25 μc [^{32}P] orthophosphate. Phospholipids were extracted by the method of Hokin & Hokin (1958) and the incorporation of ^{32}P was measured by liquid scintillation counting.

The effect of NA on ^{32}P incorporation is shown in Fig. 1. NA caused a significant decrease in the incorporation of ^{32}P at 5 min ($P<0.05$) and a significant increase at 30, 60 and 120 min ($P<0.001$). Thymoxamine, which blocks peripheral α-receptors (Birmingham & Szolcsanyi, 1965) inhibited the stimulatory effect of NA on ^{32}P incorporation at 4×10^{-5} g/ml. The β-receptor blocking agent, propranolol (4×10^{-5} g/ml.), itself increased incorporation of ^{32}P into phospholipids and so potentiated the effect of noradrenaline. The possible significance of these findings will be discussed.

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Analgesic activity after intracerebral injection in the mouse

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It has been reported that the sympathomimetic agent, adrenaline (Leimdorfer & Metzner, 1949), and the parasympathomimetic, oxotremorine (Haslett, 1963), possess analgesic activity. Consequently, these and related compounds have been examined for analgesic activity in the mouse following their intracerebral injection (Brittain & Handley, 1967).

Analgesic activity was determined in A_2G albino male mice, using the hot-plate method of Woolfe & Macdonald (1944). ED50 values were determined 15 min after intracerebral injection, the criterion of analgesia being a response time at least twice that in control mice. When tested in this way, morphine had an ED50 of 0.07 (0.05–0.10) μg/mouse. Oxotremorine was equipotent with morphine, while both noradrenaline and adrenaline were 1/5 as active, and dopamine was 1/100 as active as morphine. Acetylcholine was only weakly active, although its activity was increased 20-fold by physostigmine (20 μg/kg subcutaneously). Intracerebral injections of histamine, 5-hydroxytryptamine, amphetamine and angiotensin were almost completely inactive. Subcutaneous injections of noradrenaline were completely inactive.

Next, an examination was made of the effects of noradrenaline and oxotremorine in the presence of other drugs. Atropine (0.8–2.0 mg/kg subcutaneously) significantly reduced the analgesic activity of both noradrenaline and oxotremorine, while

atropine methyl nitrate (2 mg/kg) was inactive. Phentolamine (2 mg/kg, subcutaneously) had variable effects, but 1 μg intracerebrally significantly antagonized only the effect of noradrenaline. Phenoxybenzamine (10–25 mg/kg, subcutaneously) also only antagonized noradrenaline. Physostigmine (20 μg/kg, subcutaneously) caused marked potentiation of not only oxotremorine but also noradrenaline, yet nialamide (20 mg/kg, subcutaneously) and tranylcypromine (2 mg/kg, subcutaneously) potentiated only noradrenaline. With the exception of high doses of physostigmine, none of these drugs given alone significantly affected the hot-plate response times of mice.

These results provide evidence that both adrenergic and cholinergic mechanisms may be involved in producing analgesia in the mouse. The effects of various drugs on the analgesic action of noradrenaline and oxotremorine suggest that both mechanisms may be involved in the same pathway, an adrenergic synapse preceding a cholinergic one. There is evidence (Livingston, 1959) for the existence of descending cortico-reticulo-spinal pathways possessing an inhibitory effect on conduction in sensory afferents, and it is tentatively suggested that analgesia may be produced in the mouse by activation of these or similar pathways.

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Modification of morphine analgesia in the rat by biogenic amines administered intraventricularly

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Based on a method described by Hayden, Johnson & Maickel (1966), a technique has been developed to inject drugs directly into the cerebral ventricles of the conscious rat. A cannula guide of 20 gauge stainless steel tubing was set into a Perspex block, 6.35 mm × 7 mm × 6 mm deep, so that it protruded under the block by 5 mm. Under halothane anaesthesia, the block was fixed to the skulls of 250–300 g albino rats using stainless steel screws and dental acrylic cement. By placing the guide through the skull at a point 2.5 mm lateral and 0.9 mm caudal to the bregma, a 5 mm cannula (modified 26 gauge hypodermic needle) could be passed directly into the lateral ventricle of the rat. Intraventricular injections were made after recovery from anaesthetic (24 hr later and up to 28 days after operation).

Previous studies suggest that there is a relation between morphine analgesia and tissue levels of certain biogenic amines (see, for example, Sigg, Caprio & Schneider,