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

C. G. SPARKES* and P. S. J. SPENCER, *Department of Pharmacy, The University of Aston, Birmingham 4*

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,

1958 ; Takagi, Takashima & Kimura, 1964 ; Rudzik & Mennear, 1965). The ability to inject drugs directly into the brains of conscious rats has permitted a re-examination of the role of these amines in morphine analgesia.

A nociceptive response was induced in rats by a foot-pressure method similar to that described by Randall & Selitto (1957), using a commercially available apparatus (Arnold R. Horwell, Ltd.). A constantly increasing pressure was applied to the dorsal surface of the hind paw, the actual load applied being recorded when the animal made its first escape attempt.

When given alone, intraventricularly, noradrenaline (NA), 10–80 μg, or 5-hydroxytryptamine (5-HT), 5–20 μg, did not alter the minimum load at which the animal responded. When 20 μg of NA was injected intraventricularly 30 min after morphine (8 mg/kg subcutaneously) the analgesic action of morphine was abolished. In contrast, when 5-HT was given after the morphine, it substantially prolonged the analgesic effect.

In a second series of experiments, the rats were pretreated with reserpine (5 mg/kg intraperitoneally) 16 hr before the injection of morphine (8 mg/kg subcutaneously). The analgesic action of morphine was completely abolished. Intraventricular NA (20 μg) failed to restore the morphine effect ; rather there was some evidence that it induced an increased sensitivity to the nociceptive stimulus. Intraventricular 5-HT (5 μg) restored the effect of morphine in reserpinized rats to the level observed in morphine-treated control rats. In the absence of morphine, intraventricular injections of NA or 5-HT did not alter the response of reserpinized animals.

All these experiments were repeated giving the amines peripherally. Intravenous injections or infusions of either NA or 5-HT failed to modify the analgesic effect of morphine.

It is concluded that the previously observed antagonism of morphine analgesia in rats by reserpine is related to the depletion of central stores of 5-HT ; the antagonism of morphine by intraventricular NA requires further study.

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Post-operative pain in the assessment of analgesics in man

R. C. HILL* and P. TURNER, *Department of Clinical Pharmacology, Medical Professorial Unit, St. Bartholomew's Hospital, London E.C.1*

Post-operative pain has been used to assess potential analgesic compounds (Beecher, 1957 ; Lasagna, 1964). We have tested a number of oral analgesics against post-operative pain to evaluate the sensitivity and usefulness of the method for the assessment of potential analgesic compounds. Patients aged between 20 and