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OSIYEMI, F. O. & SMITH, R. L. (1972). *Fifth Int. Congr. Pharmac.*, Abstract No. 1039.

Analgesia produced by clonidine in mice and rats

The functional role of noradrenaline in the central nervous system is contradictory. Activation of the noradrenaline neurons may be required to meet situations e.g. involving defence and attack behaviour (for review see Fuxe, Hökfelt & Ungerstedt, 1970). It is not clear whether this is a consequence of a stimulant or an inhibitory function. Clonidine (2-(2,6-dichlorophenylamino)-2-imidazoline HCl), a central noradrenaline receptor stimulating agent, has been shown to possess a sedative effect in man (Brüner & Klein, 1968) and in animals (Delbarre & Schmitt, 1971, 1973; Holman, Shillito & Vogt, 1971). Administration of dihydroxyphenylserine, which is directly decarboxylated to noradrenaline in the brain, produces sleep in the rat (Vogt, 1973). Bolme & Fuxe (1973) have recently suggested that a central inhibitory noradrenergic mechanism exists to control the respiratory rate. Since considerable evidence suggests that central monoaminergic mechanisms play a role in opiate analgesia (for review see Way & Shen, 1971), the effects of clonidine on the threshold for nociceptive stimulation have been investigated in mice and rats.

Male Sprague-Dawley rats (130–190 g) and male NMRI mice (18–20 g) were allowed free access to water but no food 16 h before the test. Nociceptive stimulation was as described by Paalzow (1969a, b) and Paalzow & Paalzow (1973a). By standardized electrical stimulation of the tail of the animals, the changes in the threshold for vocalization were followed in mice, while in rats the threshold for motor response (spinal reflex), vocalization and vocalization afterdischarge (vocalization after withdrawal of stimulus) were studied. The electrodes (injection needles No. 20) were placed and retained intracutaneously in the middle section of the tail. In each animal the individual thresholds were determined before administration of the drug and graded in volts. After injection of the drug, the different thresholds were registered at 15 min intervals and the graded response expressed as a percentage of the pretreatment threshold voltage. For the 100 rats used, the average control thresholds were: motor response $1{\cdot}38 \pm 0{\cdot}03$ V; vocalization $2{\cdot}11 \pm 0{\cdot}08$ V; vocalization afterdischarge $3{\cdot}94 \pm 0{\cdot}14$ V. In mice the corresponding threshold for vocalization was $4{\cdot}26 \pm 0{\cdot}18$V ($n = 45$). The normal thresholds (placebo) of the three responses to nociceptive stimulation remain stable for 3 h or more (Paalzow, 1969a, b; Paalzow & Paalzow, 1973a).

Fig. 1A shows that after subcutanous administration of clonidine to rats there was a dose-dependent increase of the thresholds for vocalization and vocalization after discharge. Clonidine was more potent in the elevation of the threshold for vocalization afterdischarge. An analysis of regression gave significant slopes ($P < 0{\cdot}001$) for the dose-response lines and an analysis of variance showed no significant departure from regression ($P > 0{\cdot}05$).

The threshold for motor response was unaffected by the clonidine treatment in doses from 80–1250 μg kg^{-1}. At a dose of 10 mg kg^{-1} the threshold for a motor response was increased by about 100% during the first 30 min after administration, but at this high

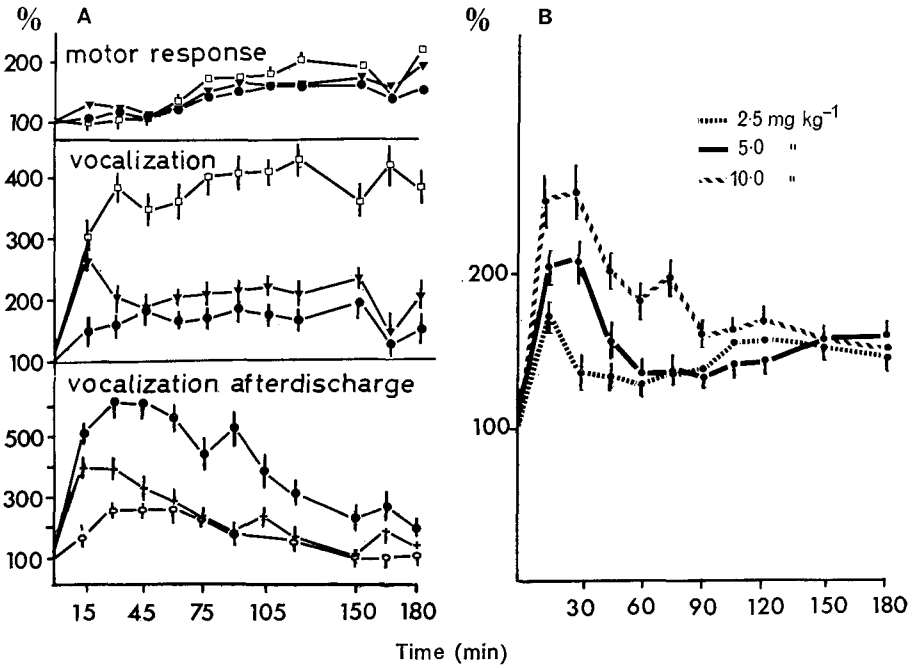

FIG. 1. A. The dose effect of clonidine on the thresholds for motor response, vocalization and vocalization afterdischarge. Each point represents the mean from 20 rats. Clonidine (μg kg^{-1}) 79 (○), 157 (+), 313 (●), 625 (▼) and 1250 (□).

B. The dose effect of clonidine on the threshold for vocalization in mice. Each point represents the mean ± s.e. from 15 mice.

dose level clonidine induced in the rats sedation, marked exophthalmos, horripilation and tremor. Doses higher than 1·25 μg kg^{-1} of clonidine produced a levelling off of the effects on the threshold for vocalization with a maximal increase of about 200–300%.

In mice clonidine was also able to increase the threshold for vocalization but the dose required was higher than for rats. The time course is shown in Fig. 1B. An analysis of regression gave a significant slope ($P < 0{\cdot}001$) for the dose-response curve and no significant departure from regression ($< 0{\cdot}05$).

In earlier investigations in mice, morphine- and salicylate-induced elevation of the threshold for vocalization seemed to be related to an increased turnover of noradrenaline rather than to that of dopamine (Paalzow & Paalzow, 1971; Paalzow, 1973). In rats, where a dissociation of the reactions into vocalization and vocalization afterdischarge is possible, morphine and pentazocine effectively increased both these thresholds. Turnover studies of regions of the rat brain have shown that the increases are not only dependent on the activity in noradrenaline neurons in the brain stem, but also on the activity of dopaminergic neurons in the telencephalic cortex (Paalzow, Paalzow & Stalby, 1972, 1974). Furthermore, an increased sensitivity to nociceptive stimulation produced by theophylline can be related to a decreased turnover of dopamine in the telencephalon (Paalzow & Paalzow, 1974). From these studies it was concluded that an increased turnover of noradrenaline in the brain stem and dopamine in the telencephalon are of importance for analgesia. This increased turnover of noradrenaline can be a consequence of an inhibitory function of this catecholamine in lower brain stem structures, since it has been reported that the responses to nociceptive stimulation (vocalization and vocalization afterdischarge) are abolished after

transection at a level of medulla oblongata-pons (Carroll & Lim, 1960; Hoffmeister & Kroneberg, 1966; Weller & Sulman, 1970).

Clonidine is considered to stimulate noradrenaline receptors and the increase of the thresholds for vocalization and vocalization afterdischarge found [in doses of clonidine relating to those able to produce central noradrenaline receptor stimulation (Andén, Corrodi & others, 1970; Persson & Waldeck, 1970)] can therefore be related to a stimulation preferably in the lower brain stem structures. However, such a relation has to be further evaluated, since biochemical experiments have shown that, apart from noradrenaline, clonidine decreases the 5-HT turnover (Andén & others, 1970) a transmitter which also has been implicated in morphine analgesia (for review see Way & Shen, 1971).

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