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January 2, 1973

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Pharmacological studies on a possible role of central noradrenaline neurons in respiratory control

In studies on central noradrenaline vasodepressor mechanisms (Bolme & Fuxe, 1971; Bolme, Corrodi & Fuxe, 1972, 1973) it was discovered that drugs increasing noradrenaline receptor activity in the central nervous system can decrease the respiratory frequency of anaesthetized rats. A short report of the pharmacological evidence suggesting the existence of a noradrenaline mechanism in the neural control of respiration is now given.

Male Sprague-Dawley rats (200-250 g) in groups of 5–6 animals were anaesthetized with 1–1·25% fluothane in oxygen. The body temperature was regularly controlled and if necessary adjusted with a heating lamp. The drug treatments used were: (1) The central noradrenaline receptor stimulating agent, clonidine, (Andén, Corrodi & others, 1970; Bolme & Fuxe, 1971; Schmitt, Schmitt & Fenard, 1971) was given in a dose of 10 μg kg^{-1} (i.v.); (2). Another drug 2,6-dichlorobenzylidene aminoguanidine acetate (DCBAG, Wy 8678, Wyeth Laboratories) also recently shown to be a central noradrenaline receptor stimulating agent (Bolme, Corrodi & Fuxe, 1972, 1973), was given in a dose of 50 μg kg^{-1} (i.v.); (3) L-dopa was given in a dose of 150 mg kg^{-1} (i.p.) 60 min after treatment with a peripheral dopadecarboxylase inhibitor, 1-α-(3,4-dihydroxybenzyl) α-hydrazinopropionic acid (MK 486; 100 mg kg^{-1}, i.p.; Porter, Watson & others, 1962; Bartholini & Pletscher, 1969). This treatment results in increased central dopamine and noradrenaline activity (see Henning & Rubenson, 1970; Rubenson, 1971).

The results are summarized in Table 1. Clonidine caused a 15–20% decrease of respiration rate 5–10 min after the injection. The rate was restored after 30–60 min. DCBAG caused a 30% decrease of the rate, which lasted for 30 min. After 60 min the rate was almost restored to its preinjection value. The combined MK 486-dopa treatment also resulted in a decrease of respiration rate, which was about 20% and started after 15 min. After 60 min the rate was almost back to normal.

The three drug treatments have one thing in common—that they cause increases in central noradrenaline receptor activity. It is therefore possible that a central noradrenaline receptor stimulation is responsible for the decrease of respiration frequency observed. In view of this, a central noradrenergic mechanism may also exist in the neural control of respiration of unanaesthetized rats. This possibility becomes even

Table 1. *Effects of drugs increasing noradrenaline receptor activity on respiration rate.* 5–6 rats have been tested with each drug treatment. The mean values are given and expressed in breaths per 30s. S.e. ranges from 1–3 breaths per 30s. In parentheses the percentage decrease from control value is given.

Treatment	Dose	Control	Respiration rate Min after injection				
			5′	10′	15′	30′	60′
Clonidine	10μg kg^{-1} i.v.	42	34 (19)	35 (17)	39 (7)	43 (—)	47 (—)
DCBAG	50 μg kg^{-1} i.v.	54	38 (29)	38 (29)	37 (32)	42 (22)	50 (7)
L-Dopa after pretreatment with MK 486 (100 mg kg^{-1}, i.p.)	150 mg kg^{-1} i.p.	36			29 (19)	30 (17)	34 (6)

more likely from the existing assumption that locus coeruleus, which consists of noradrenaline cell bodies (Dahlström & Fuxe, 1964), could be the pneumotaxic centre, *i.e.* the neural substrate for inhibitory respiratory activity (Baxter & Olszewski, 1955; Johnson & Russel, 1952). Thus, after bilateral lesion of the locus coeruleus apneustic respiration is obtained with maximal inspiratory depths. It should also be underlined that the nucleus tractus solitarius which probably is the relay station for vagal respiratory reflexes (see Oberholzer & Tofani, 1960), is densely innervated by noradrenaline nerve terminals (Fuxe, 1965), some of which may originate from the locus coeruleus area (Loizou, 1969; Olson & Fuxe, 1972). Therefore, on the basis of the available morphological and the present pharmacological evidence, the hypothesis is made that a central inhibitory noradrenergic mechanism may exist to control respiration rate, *e.g.* at the level of the nucleus tractus solitarius.

This work has been supported by a grant (B73-04X-715-08A) from the Swedish Medical Research Council and by Grants from the Karolinska Institute.

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January 4, 1973

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