CENTRAL ADRENERGIC NEURONS AND THE CONTROL OF BLOOD PRESSURE

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EVIDENCE that central adrenergic neurons are involved in the cardiovascular control stems mainly from two types of observations. Firstly, some hypotensive drugs, in particular α-methyldopa and clonidine reduce peripheral sympathetic tone and lower blood pressure predominantly by an interaction with central adrenergic structures (SCHMITT and SCHMITT, 1970; RUBENSON, 1971; SCHMITT *et al.*, 1971; HEISE and KRONEBERG, 1972; FINCH and HAEUSLER, 1973; HAEUSLER, 1973a). Secondly, in experimental hypertension changes in the turnover of hypothalamic, bulbar or spinal norepinephrine seem to occur (CHALMERS and WURTMAN, 1971; NAKAMURA *et al.*, 1971a,b) and destruction of central adrenergic neurons interferes with the initiation of experimental hypertension (HAEUSLER *et al.*, 1972). In all probability central adrenergic neurons are involved in the peripheral sympathetic activation which follows electrical stimulation of the posterior hypothalamus (PRZUNTEK *et al.*, 1971; PRZUNTEK and PHILIPPU, 1973). The present report deals with the possible existence of another central adrenergic system which seems to be intimately related to the baroreceptor reflex arc.

In cats anaesthetised with urethane electrical stimulation of the posterior hypothalamus causes an increase in peripheral sympathetic nerve activity—recorded from the preganglionic splanchnic and a postganglionic renal sympathetic nerve—and an elevation of blood pressure and heart rate (Fig. 1, panel 1). The original recording from the oscilloscope screen (Fig. 1, panel 1) shows that the stimulation-induced augmentation of sympathetic nerve activity is characterised by a strong initial burst, followed by a phase of inhibition and a final stabilisation of the discharges at a reduced level.

Previous experiments (HAEUSLER, 1973a) have shown that the phase of inhibition in the stimulation-induced discharge pattern is due to the counterregulation by the depressor baroreceptor reflex which is activated by the rapid rise in blood pressure during hypothalamic stimulation. For instance, the phase of inhibition disappears after an artificial lowering of the blood pressure by bleeding and it is readily re-introduced after re-infusion of the blood and re-elevation of the blood pressure. Furthermore, cutting the buffer nerves (both vagus and sinus nerves) irreversibly converts the normal stimulation-induced discharge pattern containing an inhibitory phase into a continuous firing.

If hypothalamic stimulation meets an already activated depressor baroreceptor reflex, the phase of inhibition is also absent. Panel 2 of Fig. 1 shows that electrical stimulation of both sinus nerves virtually abolished spontaneous sympathetic nerve activity; additional hypothalamic stimulation resulted in a continuous low amplitude firing without an inhibitory phase (Fig. 1, panel 3). Therefore, the phase of inhibition in the discharge pattern during hypothalamic stimulation can be considered as a

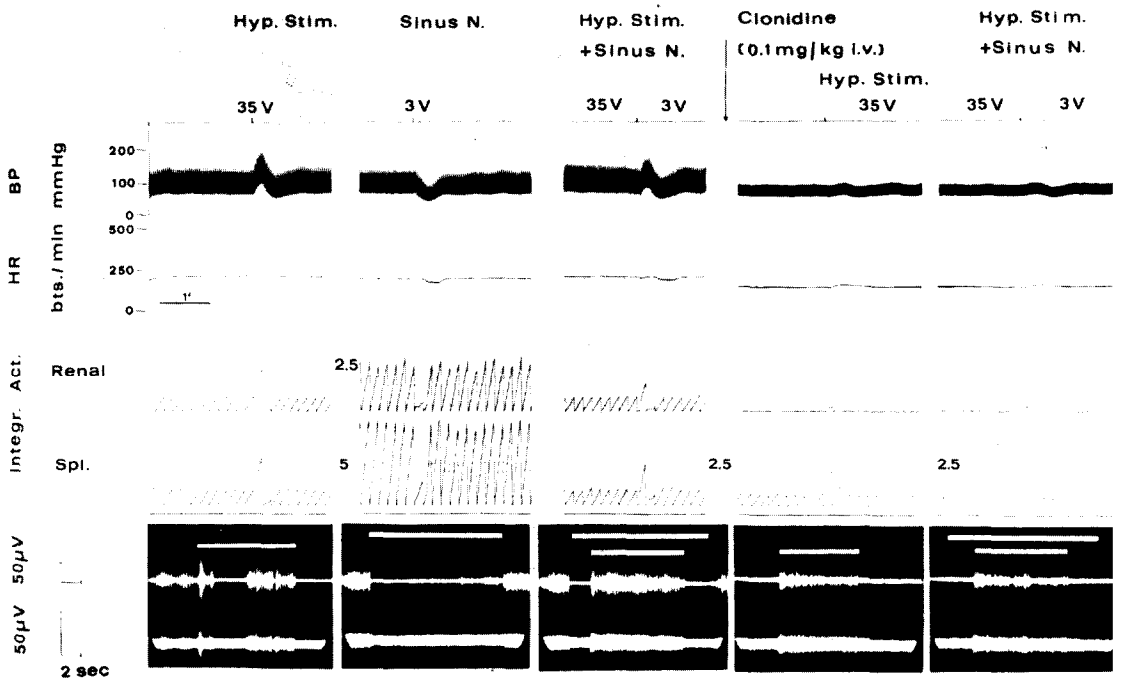

FIG. 1.—Cat, urethane anaesthesia (0·9 g/kg i.p.). Similarity between the effect of clonidine (0·1 mg/kg i.v.) and that of bilateral sinus nerve stimulation. The four channels of the record paper show from top to bottom blood pressure, heart rate, integrated electrical activity of a postganglionic renal sympathetic nerve and the right sympathetic preganglionic splanchnic nerve in arbitrary units. Below each panel the original oscilloscope recordings show the effect of the electrical stimulation of the posterior hypothalamus on the discharges in the renal (upper trace) and splanchnic (lower trace) sympathetic nerves. The upper white horizontal bar in the oscilloscope recordings indicates the duration (14 sec) of bilateral sinus nerve stimulation, the lower bar the duration (10 sec) of hypothalamic stimulation. The voltage and rate of stimulation of the posterior hypothalamus were 35 V and 60 Hz, those for stimulation of the sinus nerves were 3 V and 32 Hz. The sensitivity of the integrators was increased by a factor of 2·5 or 5 in the panels 2, 4 and 5 as shown by the numbers on the left-hand side of these panels. The intervals between the panels were 5–6 min each, except the interval between the panels 3 and 4 which was 30 min. From: HAEUSLER, G.: Activation of the Central Pathway of the Baroreceptor Reflex, a Possible Mechanism of the Hypotensive Action of Clonidine. *Naunyn-Schmiedeberg's Arch. Pharmacol.* **278,** 231–246 (1973). Berlin-Heidelberg-New York: Springer.

reliable criterion for an inhibition of peripheral sympathetic nerve activity by the counterregulating depressor baroreceptor reflex. This holds also true for the peripheral sympathetic activation which is achieved by electrical stimulation of the anterior part of the fastigial nucleus of the cerebellum (HAEUSLER, 1973a).

Intravenous administration of clonidine to cats is followed by a decrease in spontaneous sympathetic nerve activity, blood pressure and heart rate. Hypothalamic stimulation after clonidine causes a similar discharge pattern in the peripheral sympathetic nerves as does combined stimulation of the sinus nerves and the posterior hypothalamus (compare panels 3 and 4 of Fig. 1). This discharge pattern is not further modified by additional stimulation of the sinus nerves (Fig. 1, panel 5).

Thus, clonidine induced a state which closely resembles that of an activation of the depressor baroreceptor reflex. In view of the well-known property of clonidine to stimulate α-adrenoceptors the possibility was considered that the central part of the baroreceptor reflex arc is under the influence of adrenergic neurons.

Support for this hypothesis was provided by experiments in rats. The fall in blood pressure due to the stimulation of the baroreceptor fibres of the carotid sinus was inhibited in a dose-dependent manner by the intraventricular injection of the α-adrenoceptor blocking agents phentolamine, phenoxybenzamine and piperoxan (HAEUSLER, 1973b).

Thus, the intraventricular injection of three α-adrenoceptor blocking agents from different chemical classes prevents the activation of the depressor baroreceptor reflex. Such an activation is, however, induced by the α-stimulating agent clonidine. Both observations support each other and make it highly probable that the central part of the baroreceptor reflex arc either contains adrenergic neurons or is profoundly modulated by such neurons.

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