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Central hypotensive effect of γ-aminobutyric acid in anaesthetized dogs

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γ-Aminobutyric acid (GABA) is widely distributed in the central nervous system (Berl & Waelsh 1958) and is known to produce hypotension when injected intravenously (Elliot & Hobbiger 1959; Stanton 1963) or intracisternally in rabbits (Takahashi et al 1959). Dhumal et al (1976) have reported that GABA regulates body temperature through release of putative transmitters. It is likely that GABA may have a role in centrally mediated regulation of blood pressure.

In the present study the effects of intraventricularly administered GABA were examined on the blood pressure of anaesthetized dogs. An attempt has also been made to elucidate the mechanism by which GABA affects the blood pressure. Mongrel dogs (6–10 kg, either sex) were anaesthetized with intravenous pentobarbitone sodium (30 mg kg^{-1}) and carotid blood pressure recorded. The details of perfusion of the cerebral ventricles from ventricular to aqueductal cannula and the intraventricular injections of drugs have been reported elsewhere (Dhumal et al 1974).

Optimal hypotensive effects were obtained with a 1 mg dose of GABA injected in volume of 0·5 ml. The reduction in blood pressure (mean ± s.e.) was 30 mm ± 3 mm Hg (n = 7) and the effect lasted for 10–15 min. Repeated administration of the same dose produced a smaller decrease in blood pressure than first. Intraventricular injection of 0·5 ml of artificial CSF had no effect on blood pressure.

In three experiments, noradrenaline (NA) 500 ng or adrenaline (A) 1 μg, administered intraventricularly also produced hypotension. Perfusion of the ventricles with phentolamine (20 μg ml^{-1}) for 30 min did not produce any effect on blood pressure, but it reduced the hypotensive effects of A and NA completely, and of GABA by about 50% (Fig. 1b). In the present experiments, administration of cocaine 1 mg, intraventricularly before injection of GABA, resulted in a loss of the hypotensive response to GABA (Fig. 1c).

The NA content in cerebrospinal fluid (c.s.f.) was estimated as described by Dhumal et al (1974). In these experiments, cocaine (1 mg) intraventricularly, increased the amount of NA in the cerebral effluent. When NA (500 ng) was injected, after cocaine, there was a significant ($P < 0.001$) increase in content of NA in the c.s.f. compared with the NA content in the effluent after i.c.v. NA (500 ng) injection alone; this indicated a block of the uptake of exogenously injected and endogenously released NA by cocaine.

The release of NA after GABA was, however, significantly ($P < 0.001$) less after cocaine (Fig. 2). Pretreatment with reserpine (0·3 mg kg^{-1} i.m., 72 h before) also abolished the hypotensive response of GABA and reversed it to a hypertensive response which was not studied further. In four experiments, where ventricles were perfused with calcium-free artificial c.s.f. containing sodium edetate (0·37 mg ml^{-1})

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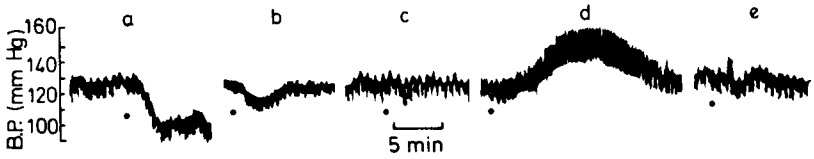

FIG. 1. Arterial blood pressure response obtained from separate dogs anaesthetized with pentobarbitone sodium (30 mg kg^{-1} i.v.). Responses to GABA (1 mg) i.c.v. (○) were studied after various pretreatments (a) control hypotensive response of GABA; (b) after perfusion with artificial cerebrospinal fluid containing phentolamine (20 μg ml^{-1}) at a rate of 0·4–0·5 ml min^{-1} from the ventricular to the aqueductal cannulae for 30 min. Hypotensive response is inhibited; (c) after pretreatment with cocaine (1 mg) i.c.v., hypotensive response is inhibited; (d) in reserpinized dog, hypotensive response is converted into a hypertensive response; (e) ventricles perfused with calcium-free solution resulted in a loss of hypotensive response.

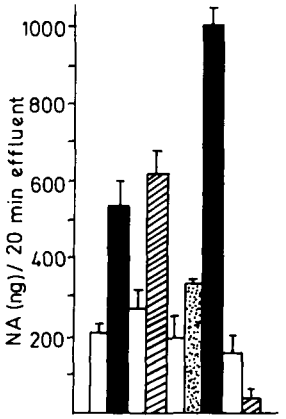

FIG. 2. NA content (in ng) in the effluents, during perfusion of the cerebral ventricles from left lateral ventricular to aqueductal cannulae with artificial c.s.f., in dogs under pentobarbitone sodium anaesthesia. Effluents from the perfused ventricles were collected in 20 min samples. The bars depict the NA content (in ng) of the control effluent (open); NA effluent, collected immediately after injecting 500 ng NA intraventricularly (solid); GABA effluent, collected immediately after injecting 1 mg GABA intraventricularly (Diagonally hatched); and cocaine effluent, collected immediately after intraventricular injection of 1 mg cocaine (stippled); vertical lines indicate s.e. of means (n = 5).

for 1 h, GABA (1 mg) had no effect of blood pressure. The ventricles were then perfused with normal artificial c.s.f., but there was no restoration of the hypotensive action of GABA.

These results indicate that GABA, when administered intraventricularly can produce a hypotensive response which can be modified by derangement of adrenergic neuron function by drugs like reserpine and cocaine. Thus, pre-treatment of dogs with reserpine by a dose schedule which is known to produce a marked depletion of central catecholamines (Dhumal et al 1974) almost completely prevented the hypotensive effect of GABA and cocaine pretreatment produced antagonism of the GABA effect. This suggests that intact central adrenergic neurons are a pre-requisite for the central hypotensive actions of GABA and that a mechanism involving uptake into central adrenergic neurons is essential.

During perfusion with phentolamine, an α-adrenoceptor blocking agent, the effect of GABA was blocked. This result is in accord with the reported hypotensive effect of intraventricularly injected or endogenously released adrenaline and noradrenaline being mediated by α-adrenoceptors (Day & Roach 1974; Finch et al 1975).

Calcium is necessary for the release of NA (Phillippu et al 1970; Dhumal et al 1974). During perfusion with calcium-free solution, GABA failed to have any effect on blood pressure, indicating that NA release by GABA is calcium-mediated and further supporting the role of NA release in mediating GABA-induced hypotension.

In the present study the administration of GABA into the cerebral ventricles leads to an increased release of NA, and it is proposed that the hypotensive effect of GABA is due to release of endogenous NA. This assumption is supported by the fact that GABA was found to release NA from rat hypothalamic slices (Yessian & Arakelian 1970) and by a finding that intraventricular injection of GABA in dogs produced hypothermia due to the release of NA (Dhumal et al 1974).

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