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COMMUNICATIONS

Cardiovascular effects of intracerebroventricular injections of baclofen in the conscious rabbit

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Baclofen [β-(4-chlorophenyl)-γ-aminobutyric acid] is a lipophilic analogue of γ-aminobutyric acid (GABA) that penetrates the blood brain barrier. It is effective in the treatment of spasticities of spinal origin. During trials with baclofen in spastic patients, Pinto et al (1972) described hypotensive side effects. In the anaesthetized cat, Stanovnik et al (1978), Olpe et al (1978) and Sweet et al (1979) reported a hypotensive effect of intravenous and intracisternal baclofen. Recently, we observed a marked hypotensive and bradycardic effect of baclofen in the anaesthetized cat. The origin of this action appeared to be located mainly within the forebrain and may be related to the inhibition of glutamate release (Bousquet et al 1981). However, Persson & Henning (1980) observed that baclofen administered intraperitoneally or intracisternally to the conscious rat produced a sustained hypertension and tachycardia reversed by pentobarbitone anaesthesia.

We have investigated the central cardiovascular actions of baclofen in the conscious rabbit and present evidence that the drugs direct intracerebroventricular (i.c.v.) administration into the central nervous system results in a marked hypotension and bradycardia.

Material and methods

Normotensive male rabbits, 2 to 3·5 kg, were used. The central ear artery was cannulated under local anaesthesia (lignocaine 1%) with a polyethylene catheter filled with 0·9% NaCl to which heparin had been added (saline). This catheter was connected to a Statham P23 Db strain gauge transducer and arterial pressure was recorded on a Minipolygraph Gilson (module ICS_3). Mean arterial pressure (MAP) was calculated with the formula: MAP = diastolic pressure + one third pulse pressure, in mm Hg.

The heart rate (HR) was determined by counting directly from the pressure tracings. An indwelling 26G stainless needle was inserted into the marginal ear vein to provide a route for intravenous injection.

For administration of drug solutions in the central nervous system, a 22G stainless needle was inserted into the right cerebral lateral ventricle of the animal under local anaesthesia (posterior 3 mm from the sutura bregma, lateral 4 mm from the sutura sagitalis, depth 5 mm) according to the stereotaxic atlas from Monnier & Gangloff (1961). The cannula was fixed to the skull with dental cement, it was thus permanent.

Each conscious animal was then left undisturbed in an appropriate box for 1 h. Once basal recordings of MAP and HR were obtained, an initial control amount of saline (100 μl) was injected i.c.v. into the lateral ventricle.

Baclofen ((±)-baclofen, Lioresal, Ciba-Geigy) dissolved in saline was similarly administered in 100 μl. At the end of the experiments, Evans blue solution was injected into the lateral ventricle to check that the solution had diffused into all the cerebral cavities and into the subarachnoid space.

Results are expressed as means ± s.e.m. Changes from base line MAP and HR were analysed for statistical significance with Student's paired *t*-test. $P < 0.05$ was set as the threshold of statistical significance.

Results

Intracerebroventricular injections of (±)*-baclofen.* (±)-Baclofen was injected into the lateral ventricle at

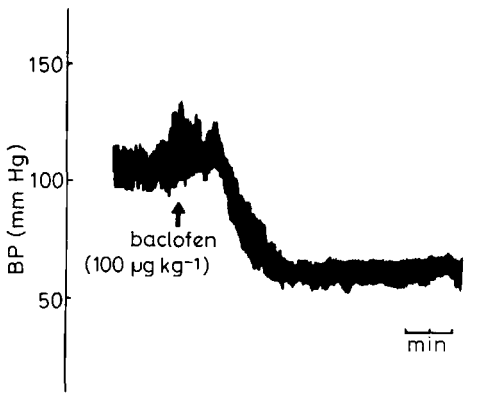

FIG. 1. Conscious rabbit 3·2 kg. Hypotensive effect of an intracerebroventricular injection (100 μl) of a total dose of 100 μg kg^{-1} (±)-baclofen.

* Correspondence.

Table 1. Effects on the mean arterial pressure (MAP) and heart rate (HR) of successive doses of (±)-baclofen administered intracerebroventricularly to conscious rabbits at 10 min intervals. Measures were made 5 min after each injection (maximal effects). Mean values ± s.e.m. are given. Number of experiments = 7.

	Control	Vehicle	Baclofen (μg kg^{-1}) 10	20	70
MAP (mm Hg)	110 ± 6	109 ± 7	113 ± 5	116 ± 7	57 ± 6**
HR (beats min^{-1})	228 ± 9	230 ± 10	213 ± 3	210 ± 5	197 ± 16*

* $P < 0.05$.
** $P < 0.001$.

increasing doses of 10, 20 and 70 μg kg^{-1} at intervals of 10 min to 7 conscious rabbits. The drug produced a significant and sustained fall in MAP associated with a reduction in heart rate, which was maximal 3 min after injection of the 70 μg kg^{-1} dose (i.e. a total dose of 100 μg kg^{-1}; Table 1, Fig. 1). At this time, the average decrease in MAP was 47 ± 4% ($P < 0.001$) and the drop in HR was 12 ± 6·5% ($P < 0.05$). These effects lasted for at least 1 h. After baclofen (100 μg kg^{-1} i.c.v.), the rabbits were sedated and akinetic. The i.c.v. injection of saline did not produce any significant cardiovascular effect.

Intravenous injections of (±)-baclofen. In another 3 conscious rabbits, (±)-baclofen administered intravenously in successive doses (10, 50, 100, 500, 1000 and 5000 μg kg^{-1}) at intervals of 15 min produced no significant cardiovascular modification. However, at the dose of 500 μg kg^{-1} and above, the rabbits displayed sedation and akinesia.

Discussion

According to Persson & Henning (1980), (±)-baclofen administered centrally produced sustained hypertension and tachycardia of central origin in the rat, whereas Stanovnik et al (1978), Sweet et al (1979) and Olpe et al (1978) observed opposite effects in the anaesthetized cat. A possible explanation for this discrepancy might be an influence of the barbiturate anaesthesia on the central cardiovascular responses to (±)-baclofen, since Persson & Henning (1980) reported that pentobarbitone pretreatment reversed the cardiovascular effects of intraperitoneal baclofen.

The present study confirms this hypothesis, at least in the rabbit, since (±)-baclofen administered centrally at low doses similar to those used by Persson & Henning (1980) produced no hypertension or tachycardia in the unanaesthetized animal. However, higher doses produced marked hypotension and bradycardia when injected intracerebroventricularly. These effects were clearly of central origin since there was no effect when baclofen was administered systematically even at high doses. This result differs from those of Chahl & Walker (1980) and Lalley (1980) in the rat and cat respectively. These authors observed a biphasic blood pressure effect of baclofen administered intravenously: i.e., an initial hypotension followed by a lasting increase in blood pressure. Persson (1981) observed that direct application of baclofen into the nucleus tractus solitarii of the rat elicited hypertension and trachycardia. These considerations led Persson (1981) to suggest that, at least in the unanaesthetized rat, the vasopressive and tachycardic effect of baclofen administered either centrally or peripherally may be mediated by a preferential inhibition of the nucleus tractus solitarii which is the primary relay area for arterial baroreceptor afferents (Miura & Reis 1969). Since we never observed any hypertension or tachycardia after baclofen administration in the conscious rabbit, we can suggest either interspecies differences in the organization of the central regulation of blood pressure or different sensitivities of the central neuronal structures to baclofen between the rat and the rabbit.

One possible explanation for the observed hypotensive effect of baclofen is that it inhibits some rostral vasopressive structures in the rabbit as well as in the cat (Bousquet et al 1981).

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