J. Pharm. Pharmacol. 1981, 33: 226–231
Received October 6, 1980

0022–3573/81/040226–06 $02.50/0

A hypertensive response to baclofen in the nucleus tractus solitarii in rats

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The hypertension and tachycardia after intraperitoneal administration of baclofen, 5 mg kg^{-1}, to conscious rats was prevented by a midcollicular decerebration but not by a brain transection rostral to the hypothalamus. In conscious rats, local application of baclofen (50 ng) into the region of the nucleus tractus solitarii (NTS) caused a consistent pressor response while injections into the hypothalamus, n. fastiguus, nn. amygdala, nn. dorsalis raphe or n. locus coreuleus did not. The cardiovascular effects of NTS injections of baclofen in anaesthetized animals were variable. The reflex heart rate reduction to noradrenaline (0·5 μg i.v.) was prevented by administration of baclofen i.v. as well as locally into the NTS. It is concluded that baclofen causes elevation of blood pressure in the NTS, and that this structure is a possible locus of action for systemically administered baclofen in producing hypertension.

One of the lipophilic derivatives of γ-aminobutyric acid (GABA) that penetrates the blood brain barrier better than the parent compound is baclofen (β-*p*-chlorophenyl-GABA, Faigle & Keberle 1972). This agent has proved useful in alleviation of spasticity in man (Birkmayer 1972). It has been used to directly or indirectly activate GABA mechanisms but available evidence indicates that baclofen does not depress neuronal activity by activation of GABA receptors (Mao & Costa 1978).

Previously we have reported that systemic administration of baclofen in the conscious rat causes a sustained hypertension and tachycardia by a central mechanism of action, whereas in the anaesthetized rat baclofen decreases blood pressure (Persson & Henning 1979, 1980a). Similar results have been reported by Chahl & Walker (1980), who, however, using a different mode of anaesthesia and rat strain, observed a biphasic blood pressure response to baclofen in anaesthetized animals. The baclofen-induced blood pressure increase is probably unrelated to GABA mechanisms (Persson & Henning 1980b).

The aim of the present study was to investigate the brain structures from which baclofen elicits its cardiovascular effects. By employing brain lesions and local application of drugs it is shown that the nucleus tractus solitarii (NTS) is a possible locus of action for baclofen.

METHODS

Male Sprague-Dawley rats (250–300 g) were used. Mean arterial blood pressure and heart rate were measured through in-dwelling arterial catheters (a. carotis, Portex Tubing, PP 50) connected to Statham P23Dc transducers writing on a Grass Polygraph (Trolin 1975). Intravenous catheters were implanted into the right jugular vein.

For microinjections into the area of the NTS of anaesthetized animals the rats were mounted in a stereotaxic apparatus and the head flexed to an angle of 45° forward. After a midline incision through the dorsal neck muscles and opening of the atlanto-occipital membrane the dorsal surface of the lower brain stem was visualized upon completion of a limited cranial occipitotomy. Microinjections were given through a stainless steel cannula (outer diameter 0·20 mm) in a volume of 0·5 μl, which was delivered in 10 s with a Hamilton syringe. With microscopy, the obex was demarcated as a stereotaxic zero. If not otherwise indicated, the coordinates, relative to the obex, for NTS injections were: anterior 0·5 mm, lateral 0·5 mm and 0·5 mm below the surface of the medulla.

For intracerebral injections to conscious animals the rats were mounted in a stereotaxic apparatus and stainless steel guiding cannulae were implanted 24–48 h before circulatory experiments. The guides were placed on the dura and attached to the skull with dental cement and screws. The coordinates for proper cannula positions were extrapolated from the atlases of König & Klippel (1963), Pellegrino & Cushman (1967) and Palkovits & Jacobowitz (1974). The reference zero points were: anterior-posterior (A)—the demarcation between the frontal lobe and the olfactorian bulb (when using König & Klippel),

bregma or lambda, lateral (L)—midline and depth (D)—the dura. The coordinates were in mm: ant. hypothalamus—A 6·8, L 1·8 angled 10°, D 7·7; post. hypothalamus—A 9·2, L 1·8 angled 10°, D 7·6; n. raphe dorsalis—A 12·6, L 2 angled 21°, D 5·4; n. fastiguus—A 10·6 (from bregma), L 0·8, D 4·7; locus coeruleus—A 2·5 (from lambda), L 1·1, D 5·5; nn. amygdala—A between −7·8 and 8·4, L 3·3, D 7·2; NTS—A 13·2 (from lambda) angled 13°, L 1 angled 5°, D 7·1. Microinjections were given through a stainless steel cannula (outer diameter 0·35 mm) in a volume of 0·5 μl.

Lesions of the NTS, hypothalamus, locus coeruleus (LC) and the area surrounding the 3rd ventricle were performed with a monopolar electrode consisting of a stainless steel wire coated with Teflon, except for the tip (0·2 mm). Lesions were made by passing an anodal dc current of 5–15 mA for 1–10 s. Coordinates for electrode placement were the same as for the microinjections and for the 3rd ventricle 0·5 mm caudal to bregma in the midline and 7·5 mm below the surface of the brain (Buggy et al 1977).

At the termination of the experiments involving microinjections or electrolytic lesions the animals were perfused with 10% formaldehyde through the heart and the brains were placed in formaldehyde, frozen and sectioned every 50 μM for histological confirmation of brain lesions and cannula tip positions.

For decerebrations at the midcollicular level the skull was opened immediately caudal to the sutura lambdoidea and for transections rostral to the hypothalamus (prehypothalamic section) the skull was opened on both sides of the sutura sagittalis just rostral to the sutura lambdoidea 2 days before circulatory experiments. The brain transections were performed with a blunt spatula (Trolin 1975) under ether anaesthesia 3 h before circulatory experiments. Upon termination of the experiments the brains were removed and the completeness of the transections were checked macroscopically.

Drugs. The following drugs were used: γ-aminobutyric acid (GABA, Sigma, St Louis, U.S.A.), (±)β-*p*-chlorophenyl-GABA (Lioresal, baclofen, courtesy of Ciba-Geigy, Mölndal, Sweden), (+)-bicuculline HCl (Sigma), muscimol (courtesy of Synthélabo, Paris, France), noradrenaline bitartrate (Sigma), 2-carboxy-3-carboxymethyl-4-isopropenyl-pyrrolidine (kainic acid, Sigma) and papaverine (ACO, Solna, Sweden).

Statistics. Significance of differences were calculated by analysis of variance with one or two independent criteria for classification, followed by *t*-test (two-tailed tests were used).

RESULTS

Cardiovascular effects of intraperitoneal baclofen following brain transections

After a midcollicular brain transection, which, in keeping with previous work, slightly affected blood pressure and heart rate (Henning et al 1972), the hypertensive response to baclofen was completely prevented (Fig. 1). The blood pressure was even reduced compared with pretreatment levels ($P < 0·05$ at 60 min after injection). In contrast, a transection rostral to the hypothalamus, if anything, augmented the baclofen-induced blood pressure elevation (Fig. 1).

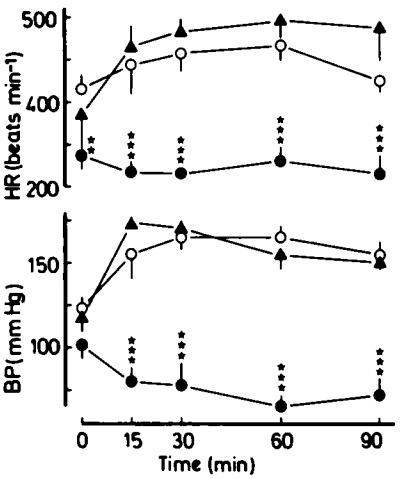

FIG. 1. Cardiovascular effects of baclofen, 5 mg kg^{-1} i.p., in rats with brain transections at the midcollicular level (●, n = 6) and rostral to the hypothalamus (▲, n = 5). The values are means with s.e.m. of arterial blood pressure (mm Hg, lower ordinate) and heart rate (beats min^{-1}, upper ordinate). Abscissa: time (min). The decerebrations were performed under ether anaesthesia 3 h before circulatory experiments. In controls (○, n = 3) only the skull was opened. Asterisks indicate significances of differences from control rats. $^{**}P < 0·025$, $^{***}P < 0·005$.

Cardiovascular effects of baclofen following lesions of different brain structures or intracerebral microinjections

Since baclofen rapidly causes hypertension after intracerebroventricular injections (Persson & Henning 1980a), we administered baclofen into various brain structures that are located in the vicinity of the ventricular system and from which electrical or pharmacological stimulation are known to evoke

Table 1. Cardiovascular effects of baclofen given bilaterally (2 × 50 ng) into various brain structures in conscious rats (A) or of baclofen, 5 mg kg^{-1} i.p., after brain lesions (B). Local injections were given 24–36 h after implantation of guide cannulas and baclofen i.p. was given 7–9 days after brain lesions. The means with s.e.m. of blood pressure and heart rate are shown at various times after the injection. Asterisks in A indicate significance of differences from own basal levels and in B significant difference between l. coeruleus and post. hypothalamus group. (a) injection sites in the n. ant. hypothalamus; (b) injection sites in the n. post. hypothalamus; (c) injection sites along a caudal-rostral axis in the amygdala complex; (d) midline injection, 50 ng; (e) large lesions including the entire ant. hypothalamus; (f) discrete lesions, mainly of the n. post. hypothalamus; (g) lesions of the tissue surrounding the antero-lateral parts of the 3rd ventricle (c.f. Buggy et al 1977).

	Sites for injections or lesions	No. of rats	Mean blood pressure (mmHg) / Mean heart rate (beats min^{-1}) basal	15 min	30 min
A.	ant. hypothalamus (a)	4	114 ± 5	129 ± 10	128 ± 10
			387 ± 12	418 ± 4	369 ± 19
	post. hypothalamus (b)	3	118 ± 9	117 ± 15	115 ± 13
			387 ± 22	362 ± 22	345 ± 33
	n. fastiguus	4	115 ± 12	124 ± 11	121 ± 13
			381 ± 22	352 ± 31	366 ± 16
	n. locus coeruleus	3	118 ± 3	130 ± 9	131 ± 7
			426 ± 27	410 ± 31	423 ± 41
	nn. amygdala (c)	4	110 ± 3	108 ± 2	116 ± 3
			420 ± 20	400 ± 25	425 ± 25
	nn. raphe dorsalis (d)	4	110 ± 3	112 ± 6	129 ± 9**
			407 ± 28	385 ± 18	446 ± 26
	n. tractus solitarii	3	123 ± 3	177 ± 3***	167 ± 4***
			380 ± 0	380 ± 5	377 ± 2
B.	ant. hypothalamus (e)	2	107 ± 2	132 ± 2	145 ± 0
			412 ± 37	425 ± 25	450 ± 100
	post. hypothalamus (f)	3	108 ± 2	136 ± 4	152 ± 2
			425 ± 18	396 ± 15	430 ± 22
	n. locus coeruleus	5	106 ± 5	147 ± 12	166 ± 5
			347 ± 14*	402 ± 31	470 ± 14
	3rd ventricle (g)	3	115 ± 3	153 ± 6	168 ± 9
			402 ± 13	407 ± 30	413 ± 7

pressor responses (for reviews see Korner 1971; Chalaresu et al 1975). As can be seen from Table 1, only when applied into the NTS region did baclofen rapidly and consistently cause hypertension.

Small bilateral lesions of different parts of the hypothalamus and the locus coeruleus or destruction of the area surrounding the anterolateral part of the 3rd ventricle did not influence the cardiovascular actions of i.p. baclofen (Table 1).

Cardiovascular effects of baclofen following NTS injections

Unilateral administration of baclofen into the region of the NTS of conscious rats caused a dose-dependent increase in blood pressure (Fig. 2). The heart rate changes were variable. Post mortem examinations revealed that less effective injections were located more than 1 mm outside the coordinates for NTS as given in methods. Bilateral injections were more effective than unilateral ones (Table 1). The animals did not display any overt motor disturbances. In a few rats NTS injections of noradrenaline (NA, 1–5 μg) caused a slight bradycardia and hypotension lasting 15–30 min.

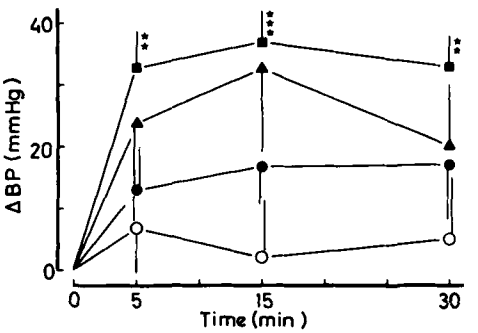

FIG. 2. Cardiovascular effects of unilateral injections (0·5 μl) of baclofen into the left NTS of conscious rats. The values are changes with s.e.m. in arterial blood pressure (mm Hg) from basal level (time 0). Abscissa: time (min). Basal levels of blood pressure are indicated within brackets. ○ saline (115 ± 9), n = 5. ● baclofen, 10 ng (110 ± 8), n = 4. ▲ baclofen 25 ng (107 ± 9), n = 5. ■ baclofen, 50 ng (123 ± 3), n = 5. Asterisks indicate significances of differences from group treated with saline. $^{**}P < 0{\cdot}025$, $^{***}P < 0{\cdot}005$. Heart rate changes were variable and insignificant.

In rats anaesthetized with chloral hydrate the cardiovascular response to microinjections of baclofen (2 × 50 ng) into the NTS were variable. In most rats a slight hypertension and tachycardia were seen (from 95 ± 4 to 111 ± 4 mmHg and from 330 ± 17 to 352 ± 19 beats min^{-1}, respectively, at 5 min, n = 14). As was evident from injections of 0·9% NaCl (saline) into the NTS the cardiovascular responses were sensitive to the injection volume and depth of anaesthesia (from 101 ± 10 to 103 ± 3 mmHg and from 305 ± 31 to 296 ± 31 beats min^{-1}, respectively, at 5 min, n = 5). However, administration of NA (5 μg) and kainic acid (4 ng) at this site consistently reduced blood pressure with around 15 and 50 mmHg respectively, while muscimol (10 ng), GABA (30 μg) and bicuculline (50 ng) had insignificant effects on blood pressure and heart rate.

Since the cardiovascular effects of baclofen are longlasting, another approach was to administer baclofen during ether anaesthesia and measure blood pressure and heart rate subsequent to termination of anaesthesia. As can be seen in Fig. 3,

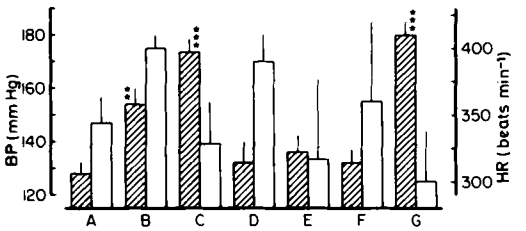

FIG. 3. Cardiovascular effects of baclofen given bilaterally into different sites in the area of the NTS. The injections were made during ether anaesthesia and the values are means with s.e.m. of arterial blood pressure (mm Hg), hatched column, left ordinate) and heart rate (beats min, open column, right ordinate) 15 min after termination of anaesthesia (and injection). NTS refers to a point 0·5 mm anterior and 0·5 mm lateral to the obex. A. saline into the NTS, n = 5. B. baclofen 10 ng into the NTS, n = 4. C. baclofen 50 ng into the NTS, n = 5. D. baclofen 50 ng, 2 mm lat. to the NTS, n = 3. E. baclofen 50 ng, 2 mm caudal to the NTS, n = 3. F. baclofen 50 ng, 2 mm rostral to the NTS, n = 3. G. bilateral electrolytic lesions of the NTS, n = 2. $^{**}P < 0·025$ and $^{***}P < 0·005$ denote significant differences from rats treated with saline.

10 ng of baclofen given bilaterally into the NTS significantly increased blood pressure 15 min after termination of anaesthesia compared with saline injections. Administration of baclofen, 50 ng, in areas outside the intermediate part of the NTS were less effective. For comparison, the cardiovascular effects of bilateral lesions of the NTS are included.

Effects of baclofen on baroreceptor reflexes

Since the intermediate part of the NTS appears to be the major relay station for afferent baroreceptor neurons (Cottle 1964), we examined the effects of baclofen on baroreceptor reflexes. These reflexes, evoked by infusion of NA and papaverine, were tested in rats before and after administration of baclofen. Before treatment with baclofen injections of NA, 0·5 μg i.v., or papaverine, 0·5 mg kg^{-1} i.v., elicited reflex bradycardia or tachycardia, respectively. After administration of baclofen, 5 mg kg^{-1} i.v., these responses were absent or in some cases reversed (Fig. 4).

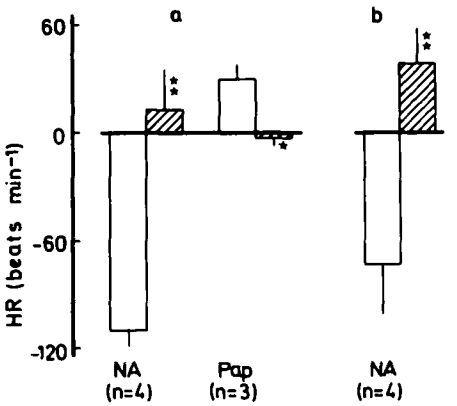

FIG. 4. Changes with s.e.m. in heart rate in rats first injected with saline (open column) and then with baclofen (hatched columns). Heart rate changes were induced by hypotension after i.v. administration of papaverine, 0·5 mg kg^{-1}, or by blood pressure elevation following i.v. administration of NA, 0·5 μg. In A saline and baclofen (5 mg kg^{-1}) were given i.v. In B saline was first given bilaterally into the NTS (0·5 μl) during ether anaesthesia and heart rate changes induced 15 min after termination of the anaesthesia. The rats were subsequently reanaesthetized and the procedure repeated but with local administration of baclofen, 100 ng. Asterisks indicate significances of differences from values obtained after injection of saline. $^{*}P < 0·05$, $^{***}P < 0·025$.

In other experiments NA, 0·5 μg, was infused after termination of ether anaesthesia, during which saline had been given bilaterally into the NTS. Thirty min later the procedure was repeated but with bilateral injections of baclofen, 100 ng. As can be seen from Fig. 4 the reflex bradycardia elicited by NA after saline injections was prevented by injections of baclofen into the NTS.

DISCUSSION

The hypertensive response to baclofen was completely prevented by a midcollicular decerebration but, if anything, augmented by a transection rostral

to the hypothalamus. This would indicate that the hypertension after baclofen is elicited either from structures between the transection levels or from more caudal structures that are dependent on the integrity of midbrain pathways for mediation of pressor responses, much as the pressor response to a lesion of the NTS is prevented by a decerebration (Doba & Reis 1973). When applied to structures which are adjacent to the ventricular system caudal to the hypothalamus and which have been implicated in cardiovascular control, baclofen only administered into the NTS region consistently and rapidly produced a pressor response. This effect was not unspecific since saline injections did not elevate blood pressure in a similar manner and, e.g. administration of NA at this site reduced blood pressure as previously reported (Zandberg et al 1979). Consideration of the ability of baclofen to diffuse from the injection site (cf Waldmeier et al 1979), suggests that structures adjacent to the NTS, such as the paramedian nucleus, could be responsible for the effects of baclofen in this region. However, kainic acid injected into the same site produced hypotension, a response that has been reported to emanate from the NTS (Talman et al 1980). In addition, the cardiovascular effects of local administration of baclofen into the NTS region resemble those of bilateral NTS lesions in several respects. They were sensitive to anaesthesia, the most effective region involved was close to the obex, and there was no consistent tachycardia (cf. Doba & Reis 1973; De Jong et al 1977).

The NTS plays an essential role in the central neuronal integration of cardiovascular activity. The intermediate part of this brain nucleus, located at the level of the obex, serves as a primary relay area for arterial baroreceptor afferents (Cottle 1964; Crill & Reis 1969; Miura & Reis 1969). Hypertension induced by NTS lesions is presumably due to removal of an inhibitory drive from systemic baroreceptors. Possibly, the cardiovascular actions to local administration of baclofen into the NTS region are due to a similar mechanism. This was supported by the observation that baclofen injected into the NTS seemed to interfere with baroreceptor reflexes.

Thus, local application of baclofen into the NTS region elicits hypertension, possibly by inhibition of baroreceptor reflexes. Whether these effects are relevant to the hypertension induced by systemic administration of baclofen is less clear. Although the various brain structures other than the NTS tested in the present experiments are not likely to be responsible for the cardiovascular effects of i.p. baclofen, there are obviously other possible sites from which baclofen can evoke an increased sympathetic outflow. However, several observations indicate that the hypertension following i.p. administration of baclofen might be linked to the pressor response of baclofen injections into the NTS. Intraperitoneal administration of baclofen interfered with baroreceptor reflexes in a manner similar to that of local baclofen application. After both modes of administration the pressor response was sensitive to anaesthesia. Pretreatment with diazepam, which is known to largely prevent pressor responses to diencephalic but not to stimulation of hindbrain areas (Antonaccio & Halley 1975), only slightly attenuates the cardiovascular effects to i.p. baclofen (Persson & Henning, to be published). Furthermore, the elevation of blood pressure following i.p. baclofen was abolished by decerebration, as is the hypertension induced by NTS lesions. Finally, following intracerebroventricular administration of baclofen, injections into the cisterna cerebellomedullaris were more effective than injections into the lateral ventricles (Persson & Henning 1980a). Consequently, the NTS is possibly the site from which systemically administered baclofen evokes hypertension.

The mechanism(s) of action of baclofen has so far defied pharmacological classification. However, in support of previous data (Persson & Henning 1980b) the hypertension to baclofen is probably unrelated to GABA mechanisms since local administration of GABA or bicuculline into the NTS had insignificant cardiovascular effects (cf. DiMicco et al 1979; Talman et al 1980). Furthermore, both the hypertensive effects of baclofen in conscious rats and the hypotension to baclofen in anaesthetized rats seem to reside with the (−)-isomer of baclofen (Persson & Henning, submitted, Olpe et al 1978). Since most of the biological activity of baclofen, such as depression of spinal reflexes (Olpe et al 1978) is specific for the (−)-isomer whereas interference by baclofen with GABA mechanisms, e.g. GABA-dependent rotation (Waddington & Cross 1979) resides with both (+)- and (−)-baclofen, these observations again suggest a non-gabaergic mechanism for the hypertensive effects of baclofen.

In view of the observations that baclofen in a physiological dose-range reduces transmitter release from nerve terminals in the spinal cord and cuneate nucleus (Fox et al 1976; Pierau & Zimmerman 1973), where L-glutamate probably is the transmitter (Krnjević 1974), it has been suggested that baclofen

interferes with glutamate neurotransmission. Subsequent studies have shown that baclofen, specifically the (−)-isomer, depresses the release of glutamate from tissue slices (Potaschner 1978; Johnston et al 1980). Since L-glutamate appears to be the major transmitter of baroreceptor afferents in the NTS (Talman et al 1980; Perrone et al 1980), our observed pressor response to baclofen in the NTS region might be related to the ability of baclofen to depress glutamate release.

Acknowledgements

This work was supported by the Swedish Medical Research Council (proj. No. 2863) and the Medical Faculty, University of Göteborg. For assisting in the histological work Drs Sven Ahlenius and Lennart Svensson are gratefully acknowledged.

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