J. Pharm. Pharmacol. 1980, 32: 417–422 Received November 9, 1979

Central cardiovascular and biochemical effects of baclofen in the conscious rat

BENGT PERSSON* AND MATTS HENNING

Department of Pharmacology, University of Göteborg, S-400 33 Göteborg, Sweden

Baclofen (β-*p*-chlorophenyl-GABA, 1·25–10 mg kg^{-1} i.p.) elicited dose-dependent increases in blood pressure and heart rate in conscious rats. Similar responses were observed after intracisternal or intracerebroventricular injections of baclofen 0·125–1 μg kg^{-1}. Baclofen i.p. was largely ineffective after spinal transection at C7. Pretreatment with phenoxybenzamine, bethanidine or hexamethonium antagonized the cardiovascular effects of i.p. baclofen. These actions were significantly attenuated after catecholamine depletion and synthesis inhibition by means of α-methyl-*m*-tyrosine and α-methyl-*p*-tyrosine. The responses to baclofen were not affected by bilateral adrenal demedullation but abolished by pentobarbitone anaesthesia. Hence, the cardiovascular effects of baclofen are probably evoked from central nervous structures and mediated via the sympathetic nervous system. In doses corresponding to those used in the circulatory studies i.p. baclofen increased endogenous concentrations of brain DA and decreased DA utilization but only slightly affected brain NA concentrations and utilization.

The GABA analogue γ-hydroxybutyric acid (GHBA) increases rat brain dopamine (Stock et al 1973; Walters et al 1973), increases noradrenaline turnover (Gomes et al 1976a) and decreases GABA utilization (Pericic et al 1978). In addition, GHBA has profound cardiovascular effects in the rat (Gomes et al 1976a) and this observation prompted us to study the circulatory effects of other GABA analogues which exert biochemical effects (Andén & Wachtel 1977; Bernasconi & Martin 1978) similar to GHBA. Baclofen (*p*-chlorophenyl-GABA) is a lipophilic GABA derivative that passes the blood brain barrier (Faigle & Keberle 1972) and has been useful in alleviating spasticity in man (Birkmayer 1972) by a central action (Carlidge et al 1974). Baclofen has been reported to lower blood pressure in man (Pinto et al 1972) and anaesthetized animals (Suzuki & Murayama 1975; Sweet et al 1979).

We present evidence that administration of even small doses of baclofen to conscious rats results in profound circulatory changes (hypertension and tachycardia) which are caused by a central nervous action. Some of the results including Fig. 1 have been published in a preliminary communication (Persson & Henning 1979).

METHODS

Male Sprague-Dawley rats (200–270 g) were used. Mean arterial blood pressure was recorded in conscious unrestrained animals through in-dwelling catheters connected to Statham P23Dc transducers writing on a Grass Polygraph and intravenous catheters were implanted as described by Trolin (1975).

Intracisternal catheters (i.ci., cisterna cerebellomedullaris) were implanted according to Gomes et al (1979) and intracerebroventricular catheters (i.c.v., lateral ventricles) according to Biswas & Carlsson (1977a).

Intraperitoneal injections were given at a volume of 10 ml kg^{-1} and intravenous injections at a volume of 2 ml kg^{-1}. Intracisternal injections consisted of 2–4 μl followed by 6–8 μl 0·9% NaCl (saline) and injections into each of the lateral ventricles consisted of 2–4 μl followed by 6–8 μl saline given at a rate of 10 μl min^{-1}. In one group of animals adrenal demedullation was performed according to Farris & Griffith (1949), the animals being allowed to recover for two weeks with a free access to saline before circulatory experiments. In some rats the spinal cord was transected at the C7 under diethylether anaesthesia. In animals subjected to 'acute spinalization' arterial catheters were implanted the day before and circulatory experiments performed several hours after the transection. Animals for 'chronic spinalization' were kept for two weeks after the transection before implantation of catheters and circulatory experiments. During the first week manual bladder emptying was necessary before bladder reflexes had developed.

The synthesis of dopamine (DA) and noradrenaline (NA) was studied by determining the accumula-

* Correspondence. Department of Pharmacology, Fack, S-400 33 Göteborg, Sweden.

tion of dopa during 30 min following inhibition of the dopa decarboxylase by a supramaximal dose of 3-hydroxybenzylhydrazine (NSD 1015, 100 mg kg^{-1} i.p.; Carlsson et al 1972). The utilization of DA and NA was determined by the disappearance of the amines during 4 h following inhibition of the tyrosine hydroxylase by a supramaximal dose of DL-α-methyl-*p*-tyrosine methylester (250 mg kg^{-1} i.p.; Spector et al 1965; Andén et al 1966). The rats were decapitated and the brains rapidly dissected on an ice-cold plate. With the primary aim of studying NA metabolism, the brain parts were: cortex, cerebellum, medulla oblongata—pons and mesencephalon-diencephalon—striatum. In some experiments cortex and cerebellum were taken together and in addition hypothalami were dissected and pooled two and two. The tissues were homogenized in 0·4 M perchloric acid. After cation exchange chromatography and oxidation, dopa, NA and DA were determined spectrofluorimetrically (Bertler et al 1958; Atack & Magnusson 1970; Kehr et al 1972).

Drugs. The following drugs were used: baclofen (β-*p*-chlorophenyl-GABA, Lioresal, CIBA-Geigy, Sweden), 3-hydroxybenzylhydrazine HCl (NSD 1015, synthesized in this department), DL-α-methyl-*p*-tyrosine methylester HCl (AMPT, H 44/68, Hässle, Sweden), clonidine HCl (Boehringer Ingelheim, Sweden), pentobarbitone (sodium form, Mebumal Vet., ACO, Sweden), DL-α-methyl-*m*-tyrosine (AMMT, Regis Chem., U.S.A.), phenoxybenzamine HCl (SKF, U.S.A.), hexamethonium HCl (Fluka) and bethanidine sulphate (Wellcome, England). Phenoxybenzamine was dissolved in a few drops of glacial acetic acid with 5·5% glucose added to volume. Pentobarbitone and bethanidine were commercially available solutions. Other drugs were dissolved in saline.

Statistics. Statistical differences were calculated by analysis of variance with one or two independent criteria for classification, followed by Student's *t*-test (Davies 1949).

RESULTS

Cardiovascular responses to baclofen in intact rats

Intraperitoneal injection of baclofen (1·25–10 mg kg^{-1}) resulted within 10–20 min in a dose-dependent increase in blood pressure and heart rate lasting 2–5 h (Fig. 1). In many rats there was an initial transient hypotension (not shown). Intravenous injections gave similar results (4 rats, data not shown). After baclofen the rats were slightly atactic, displayed a low spontaneous motility but were

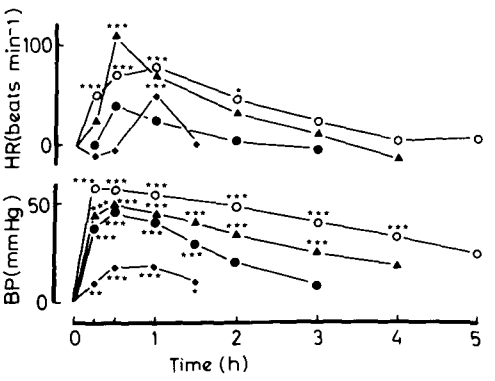

FIG. 1. Cardiovascular effects of intraperitoneal baclofen in the conscious rat. The values are changes in mean arterial blood pressure (mm Hg, lower ordinate) and heart rate (beats min^{-1}, upper ordinate) from basal level (time 0). Abscissa: time (h). Basal levels are indicated within brackets as: b.p. mm Hg/HR beats min^{-1}. ○ 10 mg kg^{-1} (113/361), n = 5. ▲ 5 mg kg^{-1} (110/379), n = 7. ● 2·5 mg kg^{-1} (113/358), n = 5. ◆ 1·25 mg kg^{-1} (112/354), n = 6. * indicate significant differences from basal level. * $P < 0·05$, ** $P < 0·025$, *** $P < 0·005$.

hyperresponsive to exogenous stimuli. High doses (15–40 mg kg^{-1} i.p.) were tested in 6 rats. After an intensive hypertension there followed a period of variable cardiovascular responses; however, hypotension was never observed.

Following intracisternal injections (0·125–1·0 μg) the cardiovascular responses were essentially similar to those observed after i.p. administration, i.e. hypertension and tachycardia developing 10–15 min after the injection and lasting for several hours depending on the dose (Fig. 2). There were no significant differences between intracisternal injections (0·5 μg, n = 5) and intracerebroventricular injections (lat. ventricles, 0·5 μg × 2, n = 15). Shortly after the injection, especially by the lat. ventricles, the rats displayed stereotype behaviour such as gnawing or eating. Coinciding with the development of hypertension the animals appeared more rigid with extended limbs, arched back and occasional myoclonic jerks. Convulsions were never observed. After about 30 min the animals were relaxed and atactic. Sometimes the rigid myoclonic behaviour was absent but the cardiovascular responses were the same. As with high doses given i.p., high doses given intracisternally (10–20 μg) resulted in an initial hypertensive response followed by a period of fluctuating blood pressure.

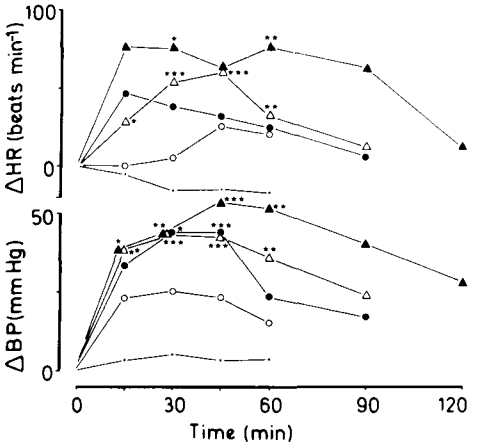

FIG. 2. Cardiovascular effects of intracisternal injections of baclofen in conscious rats. The values are changes in mean arterial blood pressure (mm Hg, lower ordinate) and heart rate (beats min^{-1}, upper ordinate) from basal level (time 0). Abscissa: time (min). Basal levels are indicated within brackets as: b.p. mm Hg/HR beats min^{-1}. • saline (116/350), n = 4. ○ 0·125 μg kg^{-1} (105/345), n = 4. ● 0·250 μg (106/330), n = 4. △ 0·5 μg (106/371), n = 5. ▲ 1·0 μg (106/325), n = 3. * indicate significant differences from saline * $P < 0.05$, ** $P < 0.025$, *** $P < 0.005$.

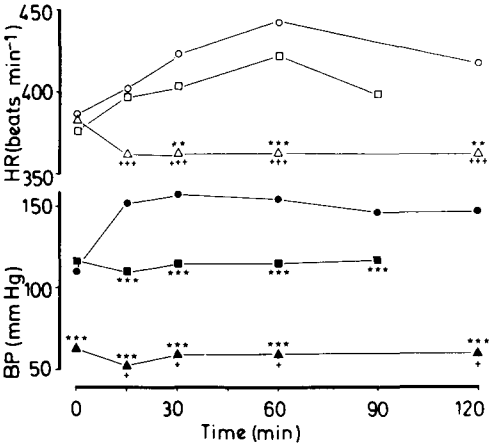

FIG. 3. Cardiovascular effects of intraperitoneal baclofen (5 mg kg^{-1}) in intact conscious rats (circles, n = 7) and in conscious rats 2 h (triangles, n = 6) and 2 weeks (squares, n = 6), respectively, after a high spinal transection. The values are mean arterial blood pressure (mm Hg, solid symbols, lower ordinate) and heart rate (beats min^{-1}, open symbols, upper ordinate). Abscissa: time (min). * indicates significant differences from intact rats. † indicate significant differences from own basal level (spinal rats). † $P < 0.05$, ** $P < 0.025$, ††† and *** $P < 0.005$.

Cardiovascular responses to i.p. baclofen after spinal transection

Two h after a spinal transection the blood pressure and heart rate were reduced (63 ± 2 mm Hg, 384 ± 20 beats min^{-1}). Despite this, baclofen (5 mg kg^{-1} i.p.) resulted in a slight but significant further reduction of both heart rate and blood pressure (Fig. 3). When given 4 h after baclofen, clonidine (0·1 mg kg^{-1} i.v.) raised blood pressure from 60 ± 2 to 153 ± 5 mm Hg (not shown).

The effects of baclofen were also examined in a group of chronically spinalized rats. Two weeks after the spinalization the blood pressure had returned to normal. The hypertension observed after baclofen in intact rats was completely prevented (Fig. 3) while the heart rate was slightly increased.

Cardiovascular responses to i.p. baclofen after sympatholytic treatments

By administering drugs that interfere with the sympathetic nervous system we aimed to test the importance of the sympathetic nervous system for the cardiovascular actions of baclofen. After phenoxybenzamine pretreatment (10 mg kg^{-1} i.p., 15 h before and 5 mg kg^{-1}, 3 h before circulatory experiments) the blood pressure and heart rate were almost normal, though a substantial α-adrenoceptor blockade as assessed by the effect of 1 μg of NA i.v. still prevailed. Following phenoxybenzamine baclofen (5 mg kg^{-1}) elicited a slight hypotensive response while having no effect on heart rate (Fig. 4). When given 30 min after baclofen (5 mg kg^{-1}) bethanidine (10 mg kg^{-1} i.v.) normalized the elevated blood pressure within 20 min (from 165 ± 12 to 128 ± 3, n = 4). Similarly, hexamethonium (15 mg kg^{-1} i.p.) completely antagonized the hypertension and tachycardia induced by baclofen (5 mg kg^{-1}, Fig. 4). Neither catecholamine depletion by means of AMMT (400 mg kg^{-1} i.p., 27 and 15 h before baclofen) nor synthesis inhibition by means of AMPT (250 mg kg^{-1} i.p., 3 h before baclofen) significantly affected the cardiovascular responses to baclofen (5 mg kg^{-1}) except for an initial and late attenuation of the responses respectively. However, a significant attenuation for the entire observation period occurred when the two pretreatments were combined (Fig. 4). Two weeks after adrenal demedullation the cardiovascular response to baclofen (5 mg kg^{-1}) was largely unaffected (Fig. 4).

Cardiovascular responses to i.p. and i.c.v. baclofen in anaesthetized rats

Following pentobarbitone pretreatment (50 mg kg^{-1} i.p. 30 min before baclofen) intraperitoneal baclofen

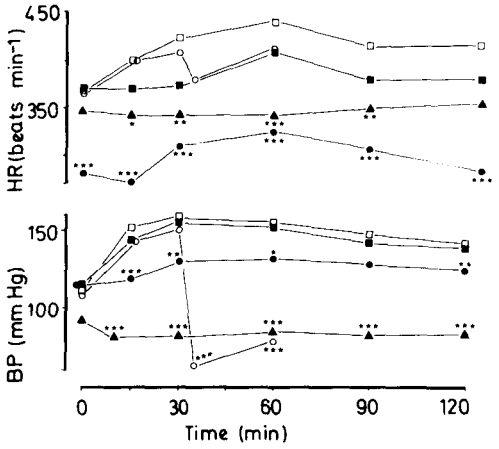

FIG. 4. Cardiovascular effects of intraperitoneal baclofen (5 mg kg^{-1}, time 0) after different sympatholytic treatments. The values are means of arterial blood pressure (mm Hg, lower ordinate) and heart rate (beats min^{-1}, upper ordinate). Abscissa: time (min). □ no pretreatment, n = 7. ■ adrenal demedullation, n = 5. △ phenoxybenzamine (10 mg kg^{-1} i.p. 15 h before and 5 mg kg^{-1} i.p. 3 h before baclofen), n = 6. ● AMMT (400 mg kg^{-1} i.p. 27 and 15 h before baclofen) and AMPT (250 mg kg^{-1} i.p. 3 h before baclofen), n = 4. ○ hexamethonium (15 mg kg^{-1} i.p. 30 min after baclofen), n = 5. * indicates significant differences from no pretreatment group. * $P < 0.05$, ** $P < 0.025$, *** $P < 0.005$.

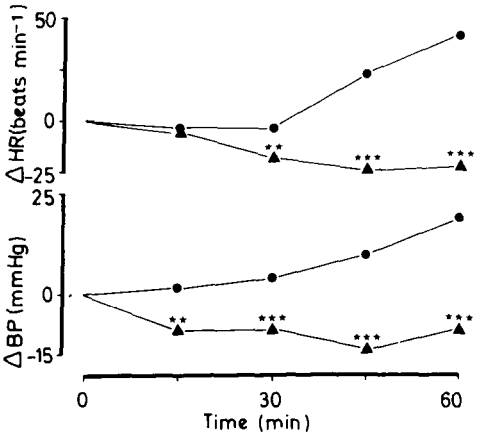

FIG. 5. Cardiovascular effects of intraperitoneal baclofen (5 mg kg^{-1}, time 0) 30 min after pentobarbitone (50 mg kg^{-1} i.p.). The values are changes in mean arterial blood pressure (mm Hg, lower ordinate) and heart rate (beats min^{-1}, upper ordinate) from basal level (time 0). The basal levels are indicated within brackets as: b.p. mm Hg/HR beats min^{-1}. ▲ pentobarbitone and baclofen (82/340), n = 4. ● pentobarbitone (94/387), n = 8. * indicates significant differences from group treated with only pentobarbitone. ** $P < 0.025$, *** $P < 0.005$.

(5 mg kg^{-1}) resulted in a significant reduction of blood pressure and heart rate compared with pentobarbitone controls (Fig. 5). After the same pretreatment intracerebroventricular baclofen (0·5 μg × 2, n = 4) caused an initial blood pressure reduction ($P < 0.05$ at 15 min compared with pentobarbitone controls) while having no effect on heart rate (data not shown).

Biochemical effects of i.p. baclofen

Four h after baclofen (1·25–5 mg kg^{-1}) there was a slight and dose-dependent increase in DA concentrations in the complex containing the striatum (Table 1). Baclofen, 5 mg kg^{-1}, significantly decreased DA utilization in the same brain regions (Table 2).

In a dose of 1·25 mg kg^{-1} baclofen significantly increased endogenous NA levels in most brain parts analysed while 2·5 and 5 mg kg^{-1} were largely ineffective (Table 1). A dose of 5 mg kg^{-1} did not change the utilization of NA (Table 2). There was a tendency to decreased dopa synthesis in NA-dominated brain parts (Table 3).

DISCUSSION

Our results show that baclofen causes a dose-dependent increase in arterial blood pressure and heart rate after i.p. or i.v. administration. These responses are probably of central nervous origin since they are completely prevented by spinal transections and since closely similar responses are

Table 1. Concentrations of dopamine (DA) and noradrenaline (NA) in different parts of rat brain 4 h following different doses of intraperitoneal baclofen. The values are means of 5–6 animals (ng g^{-1}) with s.e.m. * Indicate significant differences from saline group. * $P < 0.05$, ** $P < 0.025$, *** $P < 0.005$.

Dose	Cortex		Cerebellum		Med. + pons		Rest + striatum	
mg kg^{-1}	DA	NA	DA	NA	DA	NA	DA	NA
NaCl	45 ± 1	281 ± 13	26 ± 8	114 ± 1	60 ± 8	698 ± 8	1518 ± 74	648 ± 53
1.25	92 ± 21	315 ± 17	23 ± 8	171 ± 14**	53 ± 10	825 ± 46*	1775 ± 155	921 ± 33***
2·5	87 ± 28	212 ± 20*	86 ± 55	113 ± 1	104 ± 51	730 ± 39	1935 ± 141**	717 ± 56
5·0	74 ± 15	242 ± 18	28 ± 8	124 ± 10	79 ± 11	676 ± 16	2316 ± 172***	838 ± 41

Table 2. Concentrations of dopamine (DA) and noradrenaline (NA) in different parts of rat brain following baclofen (5 mg kg^{-1} i.p., 4 h) with or without DL-α-methyltyrosine methylester (AMPT, 250 mg kg^{-1} i.p., 4 h). The values are means of 4 rats (ng g^{-1}) with s.e.m. (hypothalami were pooled in pairs). * Indicates significant difference ($P < 0.05$) from group treated with only AMPT.

Treatment	Cortex + cer. DA	Cortex + cer. NA	Med. + pons. DA	Med. + pons. NA	Hypothalamus DA	Hypothalamus NA	Rest + striatum DA	Rest + striatum NA
AMPT	40 ± 5	48 ± 9	0	185 ± 15	267 ± 0	1665 ± 652	524 ± 40	213 ± 28
Baclofen + AMPT	84 ± 13	76 ± 9	48 ± 8	183 ± 38	685 ± 148	1140 ± 64	731 ± 26*	153 ± 7

Table 3. Effects of baclofen (5 mg kg^{-1} i.p., 45 min) on the accumulation of DOPA induced by 3-hydroxybenzylhydrazine (NSD 1015, 100 mg kg^{-1} i.p., 30 min) in different parts of rat brain. The values are means of 4 rats (ng g^{-1}) with s.e.m. (hypothalami were pooled in pairs). * indicates significant difference ($P < 0.05$) from group treated with only NSD 1015.

Treatment	Cortex + cer.	Med. + pons	Hypothalamus	Rest + striatum
NSD 1015	96 ± 5	183 ± 12	353 ± 98	442 ± 23
Baclofen + NSD	67 ± 8*	141 ± 17*	308 ± 19	366 ± 23

observed when baclofen is administered into the central nervous system by i.ci. or i.c.v. injections in doses 10^{-4} times lower than those effective systemically. The elevation of blood pressure seen after baclofen appears to be caused mainly by vasoconstriction and to a less extent by an increase in cardiac output. The heart rate responses were more variable than the blood pressure and, at times, some rats were observed to have normal or low heart rate while the blood pressure was still high. Furthermore, we have observed that reduction of the heart rate by β-adrenoceptor blocking agents does not affect the hypertension after baclofen.

The cardiovascular responses to baclofen were prevented by several procedures known to interfere with the functional integrity of the sympathetic system, i.e. α-adrenoceptor blockade, adrenergic neuron blockade and ganglionic blockade. These results emphasize the significance of the sympathetic nervous system in mediating the response to baclofen. In addition, a combined pretreatment with AMMT which is known to deplete granular stores of NA (Andén 1964) and AMPT which effectively inhibits NA biosynthesis (Spector et al 1965) largely prevented the cardiovascular responses to baclofen. Adrenal catecholamines probably contribute little since adrenal demedullation did not significantly influence the response.

In rats anaesthetized with pentobarbitone, baclofen administration failed to exert any excitatory cardiovascular effects and actually produced hypotension and bradycardia, particularly after intraperitoneal administration. Hypotensive responses have previously been observed in anaesthetized animals (see introduction). We also observed a transient hypotension after i.p. injections to conscious rats and there was a tendency to a lowered blood pressure after baclofen in spinal rats or after phenoxybenzamine pretreatment. Judging from these observations, it appears that baclofen may possess both hypertensive and hypotensive properties, the latter being unmasked by e.g. anaesthesia. This phenomenon can also be exemplified with other drugs such as oxotremorine (Weinstock et al 1979) or morphine (Gomes et al 1976b, c) where centrally mediated excitatory cardiovascular effects are prevented by anaesthesia. However, anaesthesia may also modify the effect of baclofen by enhancing its hypotensive action, as seems to be the case for clonidine (Zandberg & de Jong 1977). The experiments reported so far show that baclofen, like GHBA (Gomes et al 1976a), increases arterial blood pressure and heart rate through a central nervous action. Since GHBA influences central catecholamine mechanisms and, in particular, increases NA utilization, and since this effect may be related to its cardiovascular effects (unpublished results from this laboratory) the possible effects of baclofen treatment on central NA turnover are of considerable interest. Previous studies show that baclofen, in addition to increasing brain DA concentrations (Andén & Wachtel 1977), if anything, tends to decrease endogenous concentrations of NA and increase NA utilization. However, the doses of baclofen used by Andén & Wachtel (1977) were much larger than those that influenced cardiovascular functions in the present study. The results obtained here with DA agree with other investigations (Andén & Wachtel 1978; Waldmeier & Fehr 1978): there is a slight increase in endogenous brain DA concentrations, largely attributable to a decreased utilization. After baclofen at 5 mg kg^{-1}, there were no indications of an increased NA turnover in terms of changes in endogenous concentra-

tions or utilization. There was a tendency to a decrease in dopa synthesis in most brain parts analysed, probably analogous to the previous findings of a decrease in DA synthesis in the striatum after small doses of baclofen (Carlsson et al 1977). If increased NA turnover is taken as a reflection of increased neuronal firing rate in NA neurons (Svensson et al 1975) our results do not indicate that central NA neurons are involved in the mediation of the cardiovascular actions of baclofen. Interestingly, the smallest dose of baclofen used (1·25 mg kg^{-1}) significantly increased brain NA concentrations; a similar tendency has previously been observed after small doses of GABA (Biswas & Carlsson 1977b).

In summarizing these results we find that baclofen elicits a pronounced hypertension and tachycardia which are evoked from central nervous structures and mediated via the sympathetic nervous system. In the same dose range baclofen increases brain DA concentrations but has little effect on central NA mechanisms. The possible relationship between the functional and biochemical effects of these drugs will require further analysis.

Acknowledgements

This work was supported by the Swedish Medical Research Council (project No. 2863) and the Medical Faculty, University of Göteborg. The technical assistance of Mrs Anna Sandahl and Mrs Inger Oscarsson is gratefully acknowledged.

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