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Cardiovascular Effects of Intracerebroventricular Injections of (±)-Nebivolol and its Enantiomers—a Comparison with those of Metoprolol in the Rat

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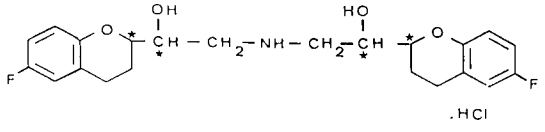
Abstract—The cardiovascular effects of (±)-nebivolol, a potent β_1-adrenoceptor antagonist, and its enantiomers, (+)-nebivolol (SRRR) and (−)-nebivolol (RSSS) in normotensive anaesthetized rats, have been investigated using metoprolol as a reference substance. The drugs decreased blood pressure and heart rate immediately after i.c.v. injection. These effects paralleled the β-blocking potencies ((+)- > (±)- > (−)-nebivolol). Metoprolol induced a weaker hypotension than (±)-nebivolol, and a long-lasting reduction in stroke volume. As reported after i.v. administration, (±)-nebivolol and isomers by the i.c.v. route decreased peripheral vascular resistance following i.c.v. administration while metoprolol increased it. These effects are centrally mediated since cardiovascular responses to isoprenaline i.v. remained unchanged.

(±)-Nebivolol is a potent and selective β_1-adrenoceptor antagonist (Van de Water et al 1988a). It is a racemic mixture of two enantiomers: (+)-nebivolol (SRRR) and (−)-nebivolol (RSSS) (Fig. 1). These three compounds have different β_1-adrenoceptor blocking potencies: (+)-nebivolol > (±)-nebivolol > (−)-nebivolol, as has been shown in-vitro and in-vivo (Pauwels et al 1988; Van de Water et al 1988a; Heimburger et al 1989). (±)-Nebivolol is a highly lipophilic compound devoid of intrinsic sympathomimetic activity (Janssens et al 1989). Despite its lipophilicity, the absence of CNS stimulant or sedative activity, even at high doses, was demonstrated by a battery of tests (Janssen Research Foundation, Investigator's brochure). However, the long-term effects can differ from acute effects and it is still possible that (±)-nebivolol could penetrate the CNS during chronic treatment. The presence of the β-blocker in the brain could result in a direct action on the central cardiovascular control system.

The aim of the present study was to investigate the cardiovascular effects of (±)-nebivolol and its enantiomers, when injected i.c.v. Metoprolol was chosen as a reference compound because it has the same profile as nebivolol: selective β_1-blocking activity with similar potency and no intrinsic sympathomimetic activity, and similar lipophilicity (Van Zwieten & Timmermans 1979; Woods & Robinson 1981; Van de Water et al 1988b).



(+)-Nebivolol	S	R	R	R
(-)-Nebivolol	R	S	S	S

FIG. 1. Structure of nebivolol showing the four asymetric carbons. (±)-Nebivolol is the racemic mixture of the two enantiomers: (+)-nebivolol (SRRR) and (−)-nebivolol (RSSS).

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Materials and Methods

Male Sprague-Dawley rats (Charles River France), 280–320 g, were anaesthetized with pentobarbitone sodium (60 mg kg^{-1}, i.p.).

First study

In four groups of rats (n = 7–10), femoral arterial blood pressure and heart rate (HR) derived from the pulsatile arterial pressure were simultaneously recorded (Narco system). The cardiac output (CO) was measured by a thermodilution technique (Cardiotherm 500, Colombus, OH). Mean arterial blood pressure (MABP) was determined graphically.

Peripheral vascular resistance (PVR) in pressure resistance units (PRU) was obtained from the ratio of blood pressure to cardiac output as formulated by Green et al (1964).

Stroke volume (SV) was calculated from CO and HR.

As previously described (Cohen et al 1979), the parameters were measured three times at 3 min intervals in order to test their stability. Then 10 μL of drug solution ((±)-, (+)-, (−)-nebivolol or metoprolol) was injected slowly into the lateral cerebral ventricle according to the technique described by Noble et al (1967). Blood pressure, heart rate and cardiac output were subsequently measured every 5 min for 30 min.

Five control rats received 10 μL of solvent i.c.v., and MABP and HR were observed over 30 min.

Second study

In a second series of experiments, MABP and HR were recorded as described above. The pudenial vein was cannulated (PE 50) for drug injections. The responses to i.v. injection of angiotensin, phenylephrine and isoprenaline were compared before and after the β-blocker i.c.v. injection.

I.v. injections

In 2 groups of rats, cardiovascular parameters were observed

before and after solvent (n = 7) or (±)-nebivolol (n = 9) i.v. injection. In addition, responses to isoprenaline were compared before and after i.v. treatment.

Drugs and doses

Drug solutions were prepared daily. Each i.c.v. injection was in a fixed volume of 10 μL. (±)-Nebivolol, (±)-[R*[S*[S*(S*)]]]-α,α'[iminobis(methylene)] bi [6-fluoro-3,4-dihydro-2H-1-benzopyran-2-methanol] hydrochloride, and its enantiomers (+)-nebivolol (SRRR) and (−)-nebivolol (RSSS) (Janssen, Beerse, Belgium) were dissolved in polyethlene glycol (PEG 300). The dose injected was 0·05 μmol.

When injected i.v., nebivolol was prepared in a solution of 2% w/v PEG 300 in 2% w/v (−)-tartaric acid, with gentle heating (0·05 μmol in 200 μL solution) (Bowden & Marchione 1989).

Metoprolol, (±)-1-[4-(2-methoxyethyl)phenoxy]-3-[(1-methylethyl)amino]-2-propanol tartrate (Astra, France), (0·075 μmol) was dissolved in a sterile saline solution (NaCl 0·9%).

Bolus administration of the following drugs was via the pudendal vein in a volume of 1 mL kg^{-1}: angiotensin (Hypertensin, Ciba-Geigy), 0·5 μg kg^{-1}; phenylephrine hydrochloride (Sigma), 3 μg kg^{-1}; isoprenaline hydrochloride (Isuprel, Winthrop), 3 μg kg^{-1}.

Data analysis

Results are expressed as mean ± s.e.m. Drug effects were expressed as percentage change of initial pretreatment values shown in Table 1, and were evaluated by the two-tailed Student's paired *t*-test.

Drug effects 10 min after injection were compared using analysis of variance. Pair-wise comparisons were made using the least significant difference (LSD) Fisher's test (Woolson 1987).

Results

Cardiovascular parameters

Initial values of cardiovascular parameters are shown in Table 1. I.c.v. injection of PEG 300 (10 μL) had no effect on MABP or HR (88 ± 4 - 87 ± 5 mmHg, 352 ± 10 - 340 ± 12 beats min^{-1} maximal fluctuations).

Time-dependent changes in MABP induced by i.c.v. injection of β-blocking drugs are shown in Fig. 2a. The i.c.v. injection of nebivolol and its enantiomers evoked an immediate decrease in MABP, reaching a maximum within 5 min. This decrease was still statistically significant 30 min after (±)-nebivolol and (+)-nebivolol injection, while (−)-nebivolol, was without effect at 20 min (Fig. 2a). Lastly, MABP was not affected by metoprolol injection.

All compounds significantly decreased HR a few minutes after i.c.v. administration; maximal bradycardia occurred between 5 and 10 min (Fig. 2b).

CO was significantly decreased by the four drugs (Fig. 2c). The maximal changes induced by metoprolol, (±)-nebivolol, and (−)-nebivolol were not significantly different from each other. On the contrary, differences appeared in the time course of the depressive effect; 10 min after i.c.v. administration of nebivolol and enantiomers, CO began to recover, while metoprolol caused a sustained decrease (20%) which persisted during the whole experiment.

Metoprolol increased PVR during the whole experiment (Fig. 2d). (±)-Nebivolol and its enantiomers had an opposite effect: PVR was significantly decreased by (±)-nebivolol and (+)-nebivolol, slightly and not significantly reduced by (−)-nebivolol. This effect disappeared 5 min after (±)-nebivolol, 20 min after (+)-nebivolol administration.

SV was significantly decreased by (±)-nebivolol and its enantiomers, but this effect did not last more than 5 min.

Maximal responses to metoprolol and nebivolol were not significantly different; however, the effect of metoprolol was longer lasting (Fig. 2e).

Changes in cardiovascular responses

Cardiovascular responses (MABP and HR) to i.v. injection of angiotensin, phenylephrine and isoprenaline were tested before and after i.c.v. injection of (±)-, (+)-nebivolol and, (−)-nebivolol (0·05 μmol) and metoprolol (0·075 μmol).

Angiotensin-induced hypertension and reflex bradycardia were unchanged after (±)-nebivolol i.c.v. The administration of (+)-nebivolol resulted in a greater hypertensive response to angiotensin (from 40 ± 4 to 54 ± 3 mmHg), without modification of bradycardia, while (−)-nebivolol reduced reflex bradycardia (from −61 ± 3 to −6 ± 16 beats min^{-1}) without change in MABP response. Metoprolol decreased both vascular (from 45 ± 6 to 26 ± 8 mmHg) and cardiac (from −39 ± 11 to −3 ± 5 beats min^{-1}) responses to angiotensin. Per cent variations are shown in Fig. 3.

Phenylephrine-induced hypertension and reflex bradycardia were not changed after (±)-nebivolol i.c.v. In the (+)-nebivolol treated group, hypertensive response increased significantly from 54 ± 4 to 70 ± 3 mmHg and reflex bradycardia decreased from −97 ± 18 to −46 ± 8 beats min^{-1}. (−)-Nebivolol did not change pressive and cardiac effects of phenylephrine; on the contrary, metoprolol reduced the increase in MABP (from 82 ± 2 to 72 ± 2 mmHg) without change in reflex bradycardia.

Cardiovascular effects of isoprenaline were unchanged after i.c.v. injection of (±)-nebivolol and (+)-nebivolol, whereas after (−)-nebivolol, hypotension was decreased (from −52 ± 4 to −40 ± 3 mmHg) as was tachycardia (from 60 ± 13 to 21 ± 6 beats min^{-1}). Lastly metoprolol did not alter the decrease in MABP and tachycardia was increased

Table 1. Initial pretreatment values (mean ± s.e.m.) of cardiovascular parameters.

β-blockers	μmol	n	MABP mmHg	HR beats min^{-1}	CO mL min^{-1} kg^{-1}	PVR PRU × 10^3	SV mL × 10^3
(±)-Nebivolol	0·05	10	86 ± 5	378 ± 10	229 ± 14	391 ± 39	606 ± 35
(+)-Nebivolol	0·05	7	92 ± 5	366 ± 13	207 ± 19	459 ± 33	562 ± 39
(−)-Nebivolol	0·05	7	96 ± 8	358 ± 16	212 ± 16	458 ± 24	596 ± 50
Metoprolol	0·075	8	101 ± 6	386 ± 18	239 ± 8	421 ± 18	626 ± 28

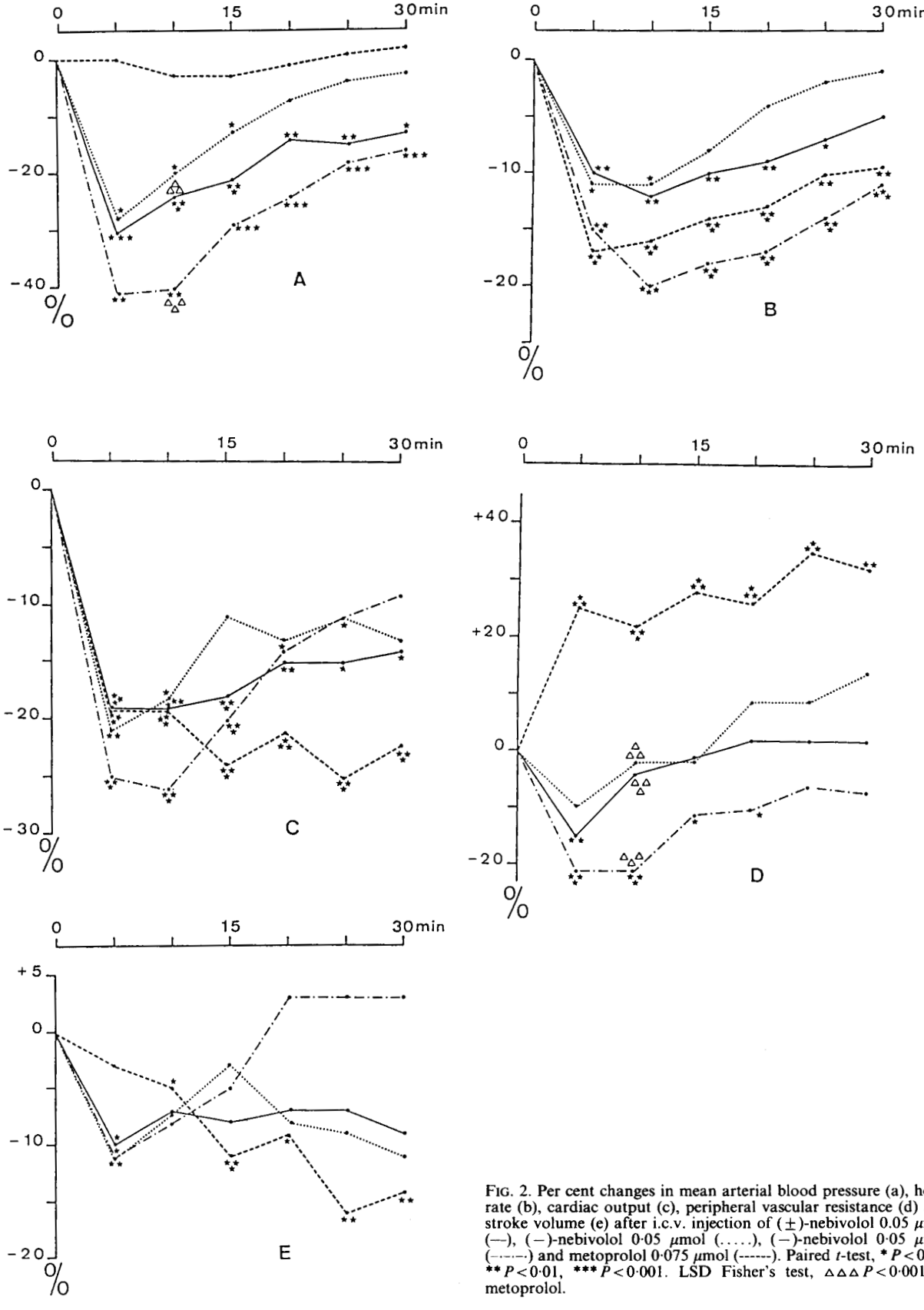

FIG. 2. Per cent changes in mean arterial blood pressure (a), heart rate (b), cardiac output (c), peripheral vascular resistance (d) and stroke volume (e) after i.c.v. injection of (±)-nebivolol 0.05 μmol (—), (−)-nebivolol 0·05 μmol (.....), (−)-nebivolol 0·05 μmol (-·-·-) and metoprolol 0·075 μmol (------). Paired *t*-test, * $P<0.05$, ** $P<0.01$, *** $P<0.001$. LSD Fisher's test, △△△ $P<0.001$ vs metoprolol.

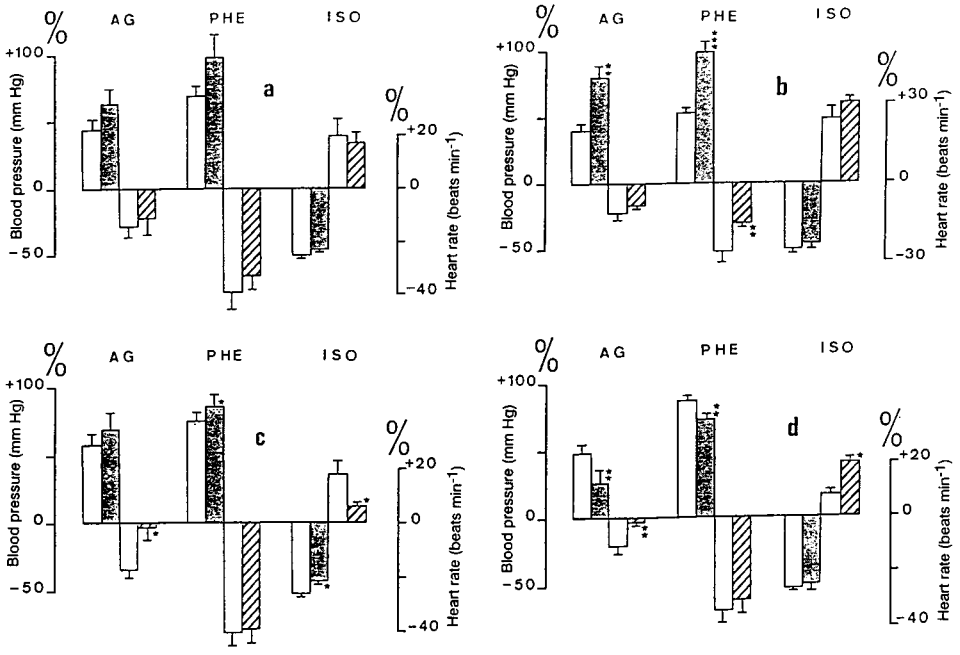

FIG. 3. Per cent changes in cardiovascular responses to i.v. injection of angiotensin (AG) 0·5 μg kg^{-1}, phenylephrine (PHE) 3 μg kg^{-1}, isoprenaline (ISO) 3 μg kg^{-1} after i.c.v. injection of (±)-nebivolol 0·05 μmol (a), (+)-nebivolol 0·05 μmol (b), (−)-nebivolol 0·05 μmol (c) and metoprolol 0·075 μmol (d). Open bars are control values. Paired t-test * $P<0.05$, ** $P<0.01$, *** $P<0.001$.

proportionally (Fig. 3d), but was not significantly different in absolute values (48 ± 7 and 63 ± 7 beats min^{-1}).

I.v. injections

Cardiovascular parameters were unchanged after solvent injection. (±)-Nebivolol i.v. (0·05 μmol) did not change MABP, CO, PVR or SV. HR was slowly and slightly reduced by about 7%, 15 min after i.v. injection, but this was not a statistically significant change. The tachycardic effect of isoprenaline was unchanged (12% increase before and after nebivolol).

Discussion

(±)-Nebivolol has been described as a very selective antagonist of β_1-adrenoceptors in the rat, with the same β_1-blocking potency as atenolol but less potent than pindolol or propranolol (Van de Water et al 1988a). (±)-Nebivolol has a high lipophilicity (log P = 3·84 vs propranolol 3·7) (data from Janssen investigator's brochure 1988). Numerous investigations have shown that highly lipid-soluble β-adrenoceptor blocking molecules easily cross the blood–brain barrier, suggesting that nebivolol could have a direct effect on central cardiovascular control.

For many years, β-adrenoceptor blocking drugs have been studied in our laboratory, and many (including alprenolol, pindolol, propranolol, practolol and atenolol) have been studied following i.c.v. injection at different doses. We have noted that the maximal effect is generally obtained when the drop in MABP reaches about 40% (Wepierre et al 1978). After preliminary studies using (±)-nebivolol, we chose a dose of 0·05 μmol, which causes a hypotension of 32% (data not shown), and we considered that it was a sub-maximal effect. Furthermore, (±)-nebivolol has a β-blocking potency between (+)- and (−)-nebivolol (Van de Water et al 1988b) and these two enantiomers were therefore injected at the same dose.

Nebivolol has often been compared with atenolol (Van de Water et al 1988a, b; De Clerck et al 1989). However, we chose metoprolol as a reference compound because its pharmacological properties are similar to those of atenolol, but is also lipophilic (Van Zwieten & Timmermans 1979; Woods & Robinson 1981). An equiactive dose was used (0·075 μmol).

The central activity of β-blockers on MABP is generally reported as hypotensive (Kelliher & Buckley 1970; Klevans et al 1976; Cohen et al 1979) sometimes following a transient rise in MABP in the dog (Srivastava et al 1973), the cat (Day & Roach 1974) and the rat (Sweet et al 1976; Burris et al 1984, 1985). Some authors reported that hypotension was related to β-adrenoceptor blocking activity (Garvey & Ram 1975; Sharma et al 1979). Involvement of local anaesthetic activity has been suggested (Zawoiski 1980). However, we have shown that β-blocking drugs without local anaesthetic properties, practolol and atenolol, are able to induce a hypotensive effect when their penetration into the brain is enhanced after blood–brain barrier opening (Davy et al 1986). With this experimental procedure, hypotension induced by β-blockers is only dependent on their specific activity.

The four components induced bradycardia, as we reported with most of the β-adrenoceptor blocking drugs when centrally injected. The effect of nebivolol and enantiomers was related to their β-adrenoceptor blocking potency as previously reported with other drugs (Day et al 1976; Wepierre et al 1978; Cohen et al 1979; Burris et al 1985; Pearson et al 1989).

We injected the same dose of (±)-nebivolol (0·05 μmol) i.v. to verify that the effects observed on MABP and heart rate are centrally mediated. This treatment induced no change in cardiovascular parameters and did not modify isoprenaline response.

We have shown that (±)-nebivolol and its enantiomers induce a decrease of the PVR while metoprolol increases it. The same observation was reported after a peripheral treatment in the dog. Although the mechanism of the vasodilation is still unknown (Janssens et al 1989), it may contribute to the hypotensive effect. Schneider et al (1990) have studied the mechanism of the decrease in peripheral vascular resistance in the pithed rat. They investigated the β_1-adrenoceptor selectivity of (±)-nebivolol and they demonstrated it is devoid of interaction with α-, β_2-, 5-HT_2- and anigotensin II-receptors, it does not inhibit Ca^{2+} influx, converting enzyme activity or sympathetic neurotransmission, and does not cause direct vasodilatation. They suggest that this vasodilatory property peculiar to this β-adrenoceptor blocking drug, does not originate in conventional peripheral mechanisms. From the present experiments, a central mechanism could be considered, and thereby would be a specific feature for this molecule; while bradycardia and decrease in CO following metoprolol treatment do not result in a hypotension, it was shown that (±)-nebivolol lowers arterial blood pressure without cardiac depressive efect.

Cardiovascular responses to hypertensive agents were not modified by (±)-nebivolol, were increased by (+)-nebivolol, and were decreased by metoprolol. This could be connected with the activity of each drug upon PVR: the more PVR is decreased, the more the response to vasoconstrictors is increased.

(±)-Nebivolol and its enantiomers (i.c.v.) did not modify cardiovascular responses to isoprenaline (i.v.). After metoprolol (i.c.v.), isoprenaline-induced tachycardia was increased proportionally, since at the time of the isoprenaline injection, the heart rate was significantly lower after metoprolol treatment than before it. The heart rate reached the same levels and these results show that metoprolol at this dose, did not modify the isoprenaline-induced tachycardia.

Therefore the effects of i.c.v. treatments are clearly centrally mediated.

The decrease in the hypotensive effect of isoprenaline after (−)-nebivolol injection is unexpected, since it is the weaker β-adrenoceptor blocking compound (Van de Water et al 1988b). This may be related to the data expression shown as a percentage, since the maximal levels of hypotension and tachycardia induced by isoprenaline are the same before and after treatment.

Baroreflex sensitivity is lowered by β-blocking drugs. However, this is especially true after chronic treatment, whereas short-time administration is without effect (Prichard & Owens 1980). The cardiovascular responses to angiotensin and phenylephrine demonstrate that i.c.v. administration of (±)-nebivolol and metoprolol did not change baroreflex sensitivity. It is interesting to note that central mechanisms controlling arterial pressure are not disturbed.

In conclusion, when injected by the i.c.v. route, the cardiovascular effects of (±)-nebivolol are different from those of metoprolol, despite their comparable pharmacological properties. (±)-Nebivolol and enantiomers lower mean arterial pressure mainly by a decrease in vascular peripheral resistance; β-blocking properties seem to be involved since the rank order of potency is the same as that of β-blocking activity: (+)-nebivolol > (±)-nebivolol > (−)-nebivolol.

Unlike other β-adrenoceptor antagonists, (±)-nebivolol lowers arterial blood pressure and peripheral vascular resistance, whether centrally or peripherally injected. (±)-Nebivolol is active centrally at a very low dose which was inactive peripherally. Therefore, if a central activity of (±)-nebivolol is involved, because of its lipophilicity, it could contribute to the peripheral antihypertensive effect of this compound.

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