Protective Effects of I₁-Antihypertensive Agent Moxonidine against Neurogenic Cardiac Arrhythmias in Halothane-Anesthetized Rabbits

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ABSTRACT
Numerous studies have addressed the antihypertensive properties of I₁-imidazoline receptor agonists such as moxonidine, but very few authors examined their cardiac antiarrhythmic potency. Due to the important role of the sympathetic nervous system in the genesis of neurogenic cardiac arrhythmias, we investigated the antiarrhythmic effects of moxonidine and compared them to those of propranolol in an experimental model of neurogenic arrhythmias. Chronic bipolar electrodes were implanted within the posterior hypothalamus of six halothane-anesthetized rabbits. Every 15 days, after three 10-min-interval control electrical stimulations, we compared the effects of randomized i.v. administrations of moxonidine (25 μg/kg), propranolol (0.5 mg/kg), and saline (0.9% NaCl) on mean arterial pressure (MAP), heart rate (HR), and ECG during 2.5 h with six stimulations every 20 min. We observed that: 1) in control conditions, intrahypothalamic stimulation increased MAP (ΔMAP = 17 ± 2 mm Hg) and HR (ΔHR = 60 ± 1 beats/min), and triggered extrasystoles (number of extrasystoles = 55 ± 2) and abnormal complexes (number of abnormal ECG complexes = 37 ± 1), which occurred with a 6.4 ± 0.4-s delay and 33 ± 1-s duration; 2) moxonidine and propranolol induced almost equihiptensive (ΔMAP = −12 ± 2 and −10 ± 2 mm Hg) and pronounced bradycardic effects (ΔHR = −47 ± 10 and −78 ± 9 beats/min, respectively). Arrhythmias were significantly reduced by moxonidine and propranolol: Δnumber of extrasystoles = −83 and −98%; Δnumber of abnormal ECG complexes = −33 and −79%; Δdelay = +65 and +188%; Δduration = −35 and −58%, respectively. Our results show that moxonidine presents an antiarrhythmic potency comparable to that of propranolol that should be predominantly related to their central action. However, additional studies are required to determine whether these antiarrhythmic effects are of central and/or peripheral origin.

The antihypertensive properties of clonidine (Schmitt, 1977), rilmenidine (Sannajust and Head, 1994), and moxonidine (Ernsberger et al., 1993) have been largely described, but very few authors determined the cardiac antiarrhythmic properties of these compounds. These centrally acting anti-hypertensive agents were originally considered as preferential agonists of presynaptic α₂-adrenoceptors and developed to inhibit the activity of the sympathetic nervous system. In addition, it is well established that the sympathetic nervous system plays an important role in the genesis of certain types of arrhythmias (Manning and de van Cotten, 1962; Hayashi et al., 1991). Therefore, imidazoline compounds, which interact via imidazoline receptors (IRs) and α₂-adrenoceptors with the activity of ortho- and parasympathetic nervous systems, may present cardiac interests in therapeutics.

Since the first studies from Lathers et al. (1978) and Helke et al. (1979), it has been clearly confirmed that the central nervous system contributes to the antiarrhythmic side effects of numerous antihypertensive agents such as β-blockers and ganglionic blocking agents, as well as α₂-adrenoceptor agonists. Subsequently, Thomas and Tripathi (1986), then Hayashi et al. (1991), showed that α₂-adrenoceptors were involved in the central control of neurogenic arrhythmias and that hyperactivation of the adrenergic tone is a triggering factor of several cardiac rhythm disorders (e.g., ventricular, junctional, and atrial arrhythmias). However, their mechanism of action, initially related to stimulation of central α₂-adrenoceptors (Schmitt, 1977), was brought under review by various studies (Bousquet et al., 1984; Ernsberger et al., 1990), leading to the concept of the existence of the new class of IRs. It has been suggested that IRs, mainly located in the rostral ventrolateral medulla oblongata, are involved in the central regulation of arterial blood pressure (BP), and that stimulation of these receptors induces a sympathoinhibitory effect with direct impact on the heart, kidneys, and vasculature (Göthert and Molderings, 1992).

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ABBREVIATIONS: IR, imidazoline receptor; AC, abnormal ECG complex; NbAC, number of abnormal ECG complexes; BP, blood pressure; ES, extrasystoles; HR, heart rate; IHR, initial heart rate; IMAP, initial mean arterial pressure; MAP, mean arterial pressure; NbES, number of extrasystoles; SHR, maximal heart rate under hypothalamic stimulation; SMAP, maximal mean arterial pressure under hypothalamic stimulation.
In the light of this concept of IR, we planned to examine the antiarrhythmic properties of one of the most selective $\beta_1$ subtype of IR agonist, moxonidine. Its effects have been previously studied in conscious Sprague-Dawley rats with acute coronary occlusion without reperfusion, or when anesthetized, with reperfusion (Lepran and Papp, 1994). These authors showed that a preventive i.v. treatment with moxonidine significantly reduced both ischemic and reperfusion arrhythmias. Furthermore, a recent study reported potent antiarrhythmic effects of moxonidine on ouabain-induced cardiac arrhythmias in guinea pigs (Mest et al., 1995).

The role of the central and autonomic nervous systems in cardiac diseases has been clearly demonstrated in experimental and clinical studies (Randall et al., 1976; Burch, 1978). Historically, the hypothalamus has been recognized as one of the major structures involved in the cardiovascular responses induced by emotion and stress, and observed during defense reaction in both animals and humans. Electrical stimulation of various diencephalic structures has been shown to induce extrasystoles (ES), ventricular tachycardias, and other types of arrhythmias in rabbits (Evans, 1976; Zhou et al., 1994), cats (Fuster and Weinberg, 1960; Manning and de van Cotten, 1962; Evans and Gillis, 1978), dogs (Verrier et al., 1975), or rats (Morpurgo, 1968). From such studies, we have chosen to electrically stimulate the posterior hypothalamus of halothane-anesthetized rabbits to obtain a reproducible experimental model of cardiac neurogenic arrhythmias.

Propranolol, a Vaughan-Williams (1984) class-II antiarrhythmic agent, belongs to the series of $\beta_1/\beta_2$-blockers. It exerts a membrane stabilizing effect, by specifically increasing the electrical stability of the myocardium, and is devoid of partial adrenoceptor agonist properties. Moreover, Huang (1969) showed that propranolol (0.1–4 mg/kg i.v.), 5 min postinjection, prevents the development of cardiac arrhythmias triggered by intrahypothalamic electrical stimulation in anesthetized cat, and these effects can persist from ~20 to 30 min. In Wistar rats, Elghozi et al. (1979) demonstrated that after i.v. injection, propranolol diffuses into hypothalamus and medullary structures. The retention by nuclei involved after i.v. injection, propranolol diffuses into hypothalamic surface with three post screws (RRA-S1; Dentatus S.A., Hagersten, Sweden) and dental cement (Texton; SS-White, Gloucester, UK).

Experimental Protocol. During each experiment, the electrode of stimulation was connected to a main stimulator (Physiowor TR; Alvar, Bordeaux, France) associated with two high-frequency isolation units. The stimulator delivered two successive 1-ms rectangular pulses from opposite polarity, with amplitude stimulation from 6 to 12 V and frequency from 20 to 120 Hz. These latter parameters were varying in function of delay between surgical implantation and experimental series and degree of anesthesia. This stimulator was programmed by another stimulator (Stimulator-T; Hugo Sachs Electronic, Hugstetten, Germany) which, by means of a time switch, delivered impulse trains for 30 s every 10, 20, or 45 min. The bipolar electrode was subsequently connected to two outputs of the two high-frequency links in series with the center connected to the negative pole and the shaft to the positive pole. Stimulation was monitored by a scope (THS 720A; Tektronix S.A., Les Ulis, France) mounted in parallel with the circuit, enabling accurate adjustment of voltage stimulation and maintenance of a constant amplitude throughout the duration of experimentation.

The arterial catheter was connected to a direct BP transducer and systolic BP, diastolic BP, heart rate (HR), and the ECG biopotentials were continuously recorded on a physiograph (Desk...
Cardiac Antiarrhythmic Properties of Moxonidine in Rabbits

Model DMP-4B; NARCO, Roucaire S.A., Vélizy-Villacoublay, France.

After a 20-min control period (C1) for which the hemodynamic and ECG parameters were stable, the animals were subjected to three control (S1, S2, S3) intrahypothalamic electrical stimulations (30-s duration with a 10-min interval). After a 10-min recovery period, each animal received an i.v. bolus injection of one of the three randomized treatments (saline, moxonidine, propranolol). Fifteen minutes after administration of the drug, four intrahypothalamic stimulations (S4, S5, S6, S7) separated by 20 min were applied. Finally, to determine the kinetics of antiarrhythmic effects of each treatment, S7 was followed 45 min later, by two additional postadministration stimulations (S8 and S9) 20 min apart. A second control recording period (C2) was performed to assess the reproducibility and stability of the experimental conditions.

On each experimental day, separated by a 2-week wash-out period, the animals were subjected to arterial and venous ear catheterization. After propofol-induced anesthesia, the animals were connected via an endotracheal cannula to the halothane-anesthesia maintenance system and placed prone by using a foam. The preparative procedures for stimulation and recording of hemodynamic and ECG parameters were conducted as previously described.

At the end of the experimental series, each animal was sacrificed by an overdose of sodium pentobarbital (Sanofi Santé Animale Laboratories, Libourne, France) and subjected to an intracarotid infusion of 200 ml of saline (NaCl 0.9%) followed by 150 ml of a 10% formalin solution. Then, the implanted electrode was taken out of the brain and the midbrain was removed for fixation in 10% formalin. After fixation, the brains were cut in 10-μm sections to verify the intrahypothalamic stimulation sites identified according to the stereotaxic landmarks based on the atlas of Urban and Richard (1972) (see Fig. 1).

Drugs. Moxonidine or 4-chloro-N-(4,5-dihydro-1H-imidazol-2-yl)-6-methoxy-2-methyl-5-pyrimidine, kindly supplied by Solvay-Pharma (Suresnes, France), was administered at the dose of 25 μg/kg i.v. Propranolol or dl-(1-isopropylamino)-3-(α-naphthylxoy)-2-propanol HCl was purchased from Sigma Chemical Company (L’Isle d’Abeau, France) and administered i.v. at a dose of 500 μg/kg.

Sterile saline (NaCl 0.9%), moxonidine (25 μg/kg), and propranolol (500 μg/kg) were administered i.v. under a constant 250-μl volume and followed by a 400-μl injection of sterile saline.

Data Analysis. Systolic BP, diastolic BP, HR, and ECG values continuously recorded on the chart physiograph were manually measured off-line. The maximal values of mean arterial pressure (MAP) and HR induced by each hypothalamic electrical stimulation (SMAP and SHR, respectively) were determined at the peak value observed during the 30-s stimulation and after the 2-min periods; they were then compared with MAP and HR initial values (IMAP and IHR, respectively) measured over the minute preceding each stimulation.

Arrhythmias of atrial or ventricular origins presented several kinds of forms: isolated or by bursts of bigeminy, atrial or ventricular tachycardias, torsades de pointes, auriculoventricular blocks, and the QRS and T waves alterations (Fig. 2). They were quantified by: 1) the number of extrasystoles (NbES) as premature atrial or ventricular complexes; 2) the number of abnormal ECG complexes (NbAC), consisting of ECG disorders of repolarization or conduction type. Disorders of repolarization were based on reference standard values reported by Kossakowski and Kuczynski (1973) in anesthetized rabbits. In our experimental conditions, the values observed in lead II were: magnitude of T wave: 0.1 ± 0.02 mV, QT interval: 80 ± 6 ms and broad QRS interval: 40 ± 4 ms. Abnormal values observed in magnitude of T wave (range: 0.17–0.3 mV), QT interval (range: 100–160 ms), and broad QRS interval (range: 60–100 ms) were therefore considered as abnormal ECG complexes (ACs). In addition, the deeply inverted T waves, as well as cardiac auriculoventricular blocks have also been quantified as AC; 3) the delay (d) of initiation of arrhythmias after the onset of hypothalamic electrical stimulation; and 4) the total duration (D) of arrhythmias for each period of stimulation.

The hypotensive and bradycardic effects of moxonidine and propranolol were measured during the first 15 min after injection and
Fig. 2. Representative traces showing the effects of hypothalamic stimulation on arterial blood pressure (ABP) and ECG leads II and III in one halothane-anesthetized rabbit in: control condition, during the first stimulation (66 Hz, 7 V) (A); during the fourth stimulation, 15 min after moxonidine (25 µg/kg i.v.) and 15 days later in the same rabbit (B); during the third control stimulation (100 Hz, 10 V) (C); and during the fourth stimulation, 15 min after propranolol (500 µg/kg i.v.) (D). Time scale indicates the delay (seconds) after the onset of stimulation. A, typical ventricular ES and two bursts of ventricular tachycardia [global parameters of arrhythmias were 117 ES, 46 AC, onset delay of arrhythmia (d) = 8 s, duration of arrhythmia (D) = 36 s] associated to a fall in ABP after an initial hypertension. B, antiarrhythmic action of moxonidine characterized by a suppression of ventricular tachycardia, decrease in NbES (22), NbAC (45), and arrhythmias duration (d = 12 s, D = 30 s). C, similar succession of various ectopic beats (86 ES, 42 AC, d = 7 s, D = 39 s) to (A). D, pronounced inhibition of arrhythmias after propranolol (0 ES, 2 AC, d = 16 s, D = 2 s).
successively during the minute preceding each intrahypothalamic stimulation (S4, S5, S6, S7, S8, and S9).

Results

Anatomical Verification of Electrode Implantation Sites. The accuracy of intrahypothalamic stimulation sites was checked by measuring the intensity and amplitude of the stimulation-induced arrhythmic responses and post-mortem histological verifications. Brain sections of six rabbits showed three stimulation sites (see Fig. 1) mainly located within the posterior (A14.5, L0.5, H +2 to H +3), dorsal (A15, L0.5 to L1, H +1 to H +3) hypothalamic areas, and the dorsomedial hypothalamic (A15.5, L0.5 to L0.8, H +1 to H +2) nucleus, according to the atlas of Urban and Richard (1972).

Initial Cardiovascular Parameters. In six halothane-anesthetized rabbits, basal average MAP and HR values determined during the minute preceding the three control stimulations (S1, S2, S3) were 61 ± 1 mm Hg and 305 ± 4 beats/min, respectively (n = 54). There was no significant difference in IMAP and IHR values between the three (moxidined-, propranolol-, and saline-) treated groups of animals.

Control intrahypothalamic stimulations (n = 54) induced a significant (P < .001) increase (28%) in MAP evaluated by the difference measured between SMAP and IMAP of +17 ± 2 mm Hg. The stimulation produced a significant (P < .001) tachycardic (20%) effect determined by the difference between SHR and IHR (ΔHR = +60 ± 1 beats/min) (Fig. 2). The mean values for control group are presented in Table 1. No significant difference during control hypothalamic stimulations was observed between the three groups of measured values (n = 18).

Cardiovascular Effects of Substances. The maximal hypertensive and bradycardic effects of each substance were determined during the 15 min after i.v. bolus injection. Moxididine (25 μg/kg) significantly (P < .01) lowered MAP: 49 ± 5 versus 61 ± 4 mm Hg (ΔMAP = −12 ± 2 mm Hg) and was almost equi-hypotensive: 46 ± 4 versus 56 ± 4 mm Hg (ΔMAP = −10 ± 2 mm Hg) to propranolol (500 μg/kg). In contrast, propranolol produced a significant (P < .01) decrease (25%) of resting HR: 234 ± 9 versus 312 ± 9 bpm (ΔHR = −78 ± 9 bpm). This effect was more pronounced after propranolol than moxonidine treatment (16%): 253 ± 8 versus 300 ± 15 beats/min (ΔHR = −47 ± 10 beats/min) (Fig. 3).

Data in Fig. 4 indicate that 1 min before each stimulation (S4, S5, S6, S7, S8, and S9) after injection, each treatment significantly (P < .05) lowered MAP in comparison with the mean IMAP recorded before each control stimulations (S1, S2, and S3). Moxididine exerted an hypotensive effect: 52 ± 5 versus 62 ± 3 mm Hg (ΔIMAP = −15%), which became significant (P < .05) only 2 h after injection whereas those of propranolol: 47 ± 5 versus 56 ± 3 mm Hg (ΔIMAP = −16%) appeared significant (P < .01) from 55 to 75 min after the injection. The hypotensive action was short-lived (20 min) for propranolol as well as for moxonidine. Propranolol induced a significant (P < .01) decrease in IHR: 219 ± 10 versus 309 ± 11 beats/min (ΔIHR = −29%) compared with the mean IHR observed before each of the control stimulations (S1, S2, S3) and to the saline-treated group: 300 ± 10 versus 307 ± 10 beats/min (ΔIHR = −2%) and moxonidine treated-group: 280 ± 21 versus 299 ± 17 beats/min (ΔIHR = −6%). This decrease appeared 15 min postinjection and persisted beyond the 140 min of recording.

The stimulation-induced hypertensive effect was significantly (P < .01) lowered by moxonidine: SMAP = 67 ± 4 versus 75 ± 3 mm Hg (ΔSMAP = −11%) from 35 to 55 min postinjection. Propranolol similarly prevented the SMAP increase: 69 ± 3 versus 77 ± 6 mm Hg (ΔSMAP = −10%) but this significant (P < .05) effect only appeared 35 min postinjection. Moxididine significantly (P < .05) decreased SHR: 324 ± 9 versus 388 ± 28 beats/min (ΔSHR = −16%) 15 min after injection; this effect lasted 60 min. Fifteen minutes after injection, propranolol induced a significant (P < .001) decrease in SHR: 230 ± 8 versus 351 ± 15 beats/min (ΔSHR = −34%), which persisted throughout the duration of recording.

Effects of Control Intrahypothalamic Stimulation on ECG Parameters. The control intrahypothalamic stimulations (S1, S2, and S3) induced for all animals cardiac arrhythmias that were mainly characterized by sinusal or

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<th>Stimulation</th>
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<th>NbES</th>
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<td>S1</td>
<td>0</td>
<td>18 ± 6</td>
<td>38 ± 10**</td>
<td>51 ± 9</td>
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<td>7.7 ± 1.3</td>
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<td>S2</td>
<td>10</td>
<td>19 ± 6**</td>
<td>48 ± 16*</td>
<td>52 ± 10</td>
<td>37 ± 4</td>
<td>6.3 ± 0.7</td>
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<td>S3</td>
<td>20</td>
<td>19 ± 4**</td>
<td>58 ± 17*</td>
<td>53 ± 10</td>
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<td>S4</td>
<td>45</td>
<td>20 ± 7*</td>
<td>64 ± 22*</td>
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<td>S5</td>
<td>65</td>
<td>20 ± 5**</td>
<td>56 ± 16**</td>
<td>45 ± 8</td>
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<td>6.4 ± 0.8</td>
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<td>S6</td>
<td>85</td>
<td>19 ± 6**</td>
<td>52 ± 9*</td>
<td>45 ± 11</td>
<td>34 ± 5</td>
<td>6.3 ± 0.7</td>
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<td>S7</td>
<td>105</td>
<td>19 ± 7*</td>
<td>48 ± 10**</td>
<td>49 ± 8</td>
<td>36 ± 7</td>
<td>7.4 ± 1.2</td>
<td>33.8 ± 3.9</td>
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<td>S8</td>
<td>150</td>
<td>20 ± 5**</td>
<td>56 ± 14**</td>
<td>58 ± 9</td>
<td>32 ± 4</td>
<td>5.4 ± 0.7</td>
<td>36.3 ± 3.0</td>
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<td>S9</td>
<td>170</td>
<td>19 ± 6*</td>
<td>40 ± 12*</td>
<td>50 ± 7</td>
<td>31 ± 7</td>
<td>6.2 ± 0.7</td>
<td>32.8 ± 2.9</td>
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—, saline injection 30 min after the first stimulation; ΔMAP, difference between SMAP and IMAP; ΔHR, difference between SHR and IHR; d, delay of arrhythmias onset after the start of each stimulation; D, total duration of arrhythmias for each stimulation. Significance of the differences: * P < .05; ** P < .01 (Student’s t test for paired variables).
ventricular ES for whom mean number (NbES) was 55 ± 2 (see Fig. 2 and Table 1 for control group). There was no significant difference in NbES between each treated (saline, moxonidine, propranolol) group of measured values (n = 18). Stimulation induced the emergence of NbAC characterized by broadened QRS intervals, increased T wave, QT lengthening with sometimes torsades de pointes, ST segment depression or elevation, and auriculoventricular conduction disorders, eventually blocks. The mean NbAC observed in animals was 37 ± 1 (Fig. 5). The average delay of arrhythmia onset after poststimulation initiation observed in animals was 6.4 ± 0.4 s, and the mean duration of arrhythmia measured from the first AC extended to 33.1 ± 1.4 s (Fig. 6). All parameters did not present any significant difference between saline, moxonidine, and propranolol treatments.

**Effects of Administration of i.v. Drugs on Arrhythmias.** Moxonidine (25 µg/kg i.v.) induced a persistent (140 min after injection) and significant (P < .01) decrease in NbES: 10 ± 4 versus 59 ± 6 (ΔNbES = −83%) 15 min postinjection (see Table 2 and Fig. 5). Comparatively, propranolol (500 µg/kg i.v.) markedly (P < .01) decreased NbES: 2 ± 1 versus 53 ± 5 (ΔNbES = −98%) triggered by stimulation in animals; this effect began 15 min after injection and persisted until the end of the experiment. Moxonidine induced a significant (P < .05) decrease in NbAC: 28 ± 2 versus 37 ± 2 (ΔNbAC = −33%) 75 min after i.v. injection. Propranolol significantly (P < .01) decreased the NbAC induced by stimulation: 14 ± 5 versus 37 ± 2 (ΔNbAC = −79%) 15 min after injection and this effect lasted throughout the duration of recording. The effects of propranolol were significantly (P < .05) more pronounced (ΔNbES = −15%; ΔNbAC = −46%) than those of moxonidine (Table 2). There were no significant effects on NbES and NbAC in the saline-treated group (Table 1).

Moxonidine treatment significantly (P < .01) prolonged the average delay of onset of arrhythmia emergence as shown in Fig. 6 and Table 2. The maximal mean delay value was 12 ± 1 versus 7 ± 1 s (Δd = +65%). This effect started 15 min postinjection and lasted 60 min. In contrast, propranolol did not significantly increase the delay of arrhythmias: 13 ± 4 versus 6 ± 1 s (Δd = +188%). Fifteen to fifty-five min after injection, moxonidine significantly (P < .01) decreased the duration of arrhythmias: 22 ± 2 versus 34 ± 2 s (ΔD = −35%). This effect was then attenuated but became significant (P < .01; ΔD = −23%) at the end of the experiment (140 min). Propranolol significantly (P < .01) reduced the duration of arrhythmias triggered by stimulations: 15 ± 5 versus 35 ± 2 s (ΔD = −58%) but this effect, appearing 15 min after injection, lasted only for 40 min. The comparison of moxonidine and propranolol antiarrhythmic actions did not show any significant difference (Table 2), and saline injection did not modify the delay and duration of arrhythmias.

**Discussion**

The major finding of this study is that the most selective I1 subtype of IR antihypertensive agent, moxonidine, could not only prevent increases in MAP and HR induced by electrical intrahypothalamic stimulation, but also exert potent antiarrhythmic properties. These cardioprotective effects of moxonidine have been demonstrated by using an halothane-anesthetized rabbit arrhythmia model with posterior intrahypothalamic electrical stimulations. Such conditions produced significant hypertensive and tachycardic effects associated with neurogenic cardiac arrhythmias predominantly characterized by premature and ectopic beats, auriculoventricular blocks, and repolarization disorders.

First, we found that an i.v. dose of 25 µg/kg of moxonidine induced, during the 15 min after the injection, significant but moderate decreases in MAP and HR, which were similar to those observed after administration of an i.v. dose of 500 µg/kg of propranolol (class II β-blocking agent of reference). Thus, if moxonidine and propranolol were still equihypotensive, this effect was then attenuated but became significant (P < .01; ΔD = −23%) at the end of the experiment (140 min). Propranolol significantly (P < .01) reduced the duration of arrhythmias triggered by stimulations: 15 ± 5 versus 35 ± 2 s (ΔD = −58%) but this effect, appearing 15 min after injection, lasted only for 40 min. The comparison of moxonidine and propranolol antiarrhythmic actions did not show any significant difference (Table 2), and saline injection did not modify the delay and duration of arrhythmias.

This study performed under long-lasting halothane anes-
thesia confirmed the cardiodepressive and arrhythmogenic actions of this anesthetic agent as previously reported by Maze and Smith (1983), Tranquilli et al. (1986), and Hayashi et al. (1993) in anesthetized dogs. Halothane lowered basal MAP (60 ± 1 versus 71 ± 4 mm Hg) and accelerated HR levels (305 ± 4 versus 180 ± 10 beats/min) in comparison with conscious rabbits (Sannajust and Head, 1994). In addition, it is well established that halothane (as chloroform) sensitizes the heart to arrhythmogenic effects of adrenaline, and this property is currently used in experimental animal models of arrhythmias (Caillard and Louis, 1980). Because the intrahypothalamic electrical stimulations are responsible for an elevation in sympathetic tone and adrenaline release from adrenal glands (Stoddard-Apter et al., 1983), halothane potentiated the cardiac arrhythmias in our experimental model. Moreover, it has been shown that the sympathetic nervous system and adrenergic neuromediators (e.g., noradrenaline and adrenaline) are directly involved in the BP and HR increases induced by posterior intrahypothalamic stimulation in anesthetized and conscious cats (Singewald and Philippu, 1996). However, the genesis of cardiac arrhythmias of central origin may be related to a parasympathetic nervous system activation as demonstrated by Manning and de van Cotten (1962) in anesthetized cats. Similarly, the marked bradycardia obtained by Zhou et al. (1994) during electrical stimulation of lateral hypothalamus in isoflurane-anesthetized rabbits confirmed the important role of cardiac vagal innervation in the genesis of arrhythmias.

The choice of moxonidine and propranolol doses used was based on preliminary studies performed in our laboratory and by others (Lepran and Papp, 1994) for which we observed that low doses (10–20 μg/kg i.v.) of moxonidine induced slight antiarrhythmic effects, whereas a higher dose (30 μg/kg i.v.) exerts pronounced and long-lasting bradycardic effects. Furthermore, we found that doses higher than 50 μg/kg i.v. could sometimes provoke respiratory or cardiac arrests in some animals. The dose of propranolol (500 μg/kg) was chosen to be equihypotensive with moxonidine.

In our experiments, the stimulation of specific posterior and dorsal hypothalamic areas (as shown in Fig. 1) produced hypertension and tachycardia, which suggest the involvement of the sympathetic nervous system in the genesis of...

Fig. 4. Effects of i.v. administration of moxonidine (●, MOX, 25 μg/kg), propranolol (□, PRO, 500 μg/kg), and saline (○, SAL) on IMAP and IHR before stimulations, or SMAP and SHR in six anesthetized rabbits. Initial data represent mean values measured during the minute preceding each stimulation (S1, S2, S3, S4, S5, S6, S7, S8, and S9) and data under stimulation represent mean values measured during the 30 s of each hypothalamic stimulation at the maximum of variation. Time is indicated after the first stimulation according to the protocol used, and dotted lines represent i.v. injection (30 min after the start of the experiment). Vertical bars show S.E. values, *P < .05, **P < .01, ***P < .001 versus before propranolol injection; †P < .05, ††P < .01, †††P < .001 versus before moxonidine injection.
these neurogenic cardiac arrhythmias. This sympathetic hyperactivity could be antagonized by central stimulation of: 1) β-adrenoceptors, as demonstrated by the effects of propranolol in the anesthetized cat with hypothalamic electrical stimulation (Huang, 1969); 2) α₂-adrenoceptors, which are stimulated by clonidine in the ouabain-induced guinea pig arrhythmia model (Thomas and Tripathi, 1986); and 3) I₁ subtype of IRs predominantly stimulated by moxonidine in the same model (Mest et al., 1995). In addition, the hypotensive action of these compounds represents an additional benefit in the prevention of the stimulation-induced BP increases that involve cardiac baroreflex mechanisms responsible for arrhythmias (Evans and Gillis, 1978).

However, if the hypotensive effect of moxonidine in the conscious (Head and Burke, 1991) and anesthetized rabbit has been initially attributed to the stimulation of α₂-adrenoceptors (Arnaud et al., 1988), additional studies demonstrated that the sympathoinhibitory action of moxonidine (Ernsberger et al., 1993; Chan et al., 1996) is more related to stimulation of I₁ subtype of IRs mainly located within the rostral ventrolateral medulla oblongata (Haxhiu et al., 1994). Moreover, Chan et al. (1996) showed that the i.v. moxonidine-induced hypotension was antagonized with efaroxan (a mixed I₁-IRs and α₂-adrenoceptor antagonist) given intracisternally but not with 2-methoxyidazoxan (one of the most selective α₂-adrenoceptor antagonists). Therefore, these findings suggest that the antihypertensive action of moxonidine is preferentially mediated via stimulation of central I₁ subtype of IRs.

The antiarrhythmic effects of moxonidine observed in our study confirm those previously reported by Lepran and Papp (1994). These authors observed pronounced antiarrhythmic properties of moxonidine when administered i.v. (10–100 μg/kg) during the acute phase of experimental myocardial infarction to conscious coronary artery-ligated rats and, when anesthetized, subjected to reperfusion arrhythmias. In addition, Mest et al. (1995) demonstrated that moxonidine (100–400 μg/kg i.v.) dose dependently increased the threshold for ouabain-induced arrhythmias in guinea pigs. They have shown that moxonidine was 2-fold more effective than clonidine and as effective as propranolol at a 10-fold higher dose. Our experiments show that moxonidine at a relatively
**TABLE 2**

Comparative maximal antiarrhythmic effects of moxonidine (MOX, 25 µg/kg i.v.) and propranolol (PRO, 500 µg/kg i.v.) in six halothane-anesthetized rabbits

<table>
<thead>
<tr>
<th>% Relative Effect</th>
<th>NbES</th>
<th>NbAC</th>
<th>d</th>
<th>D</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOX versus before injection</td>
<td>-83**</td>
<td>-33*</td>
<td>+65**</td>
<td>-35*</td>
</tr>
<tr>
<td>MOX versus saline</td>
<td>-81*</td>
<td>-25</td>
<td>+81***</td>
<td>-31*</td>
</tr>
<tr>
<td>PRO versus before injection</td>
<td>-98**</td>
<td>-79**</td>
<td>+18 -</td>
<td>58**</td>
</tr>
<tr>
<td>PRO versus saline</td>
<td>-96**</td>
<td>-81*</td>
<td>+155</td>
<td>-55*</td>
</tr>
<tr>
<td>PRO versus MOX</td>
<td>-92*</td>
<td>-74*</td>
<td>+72</td>
<td>-39</td>
</tr>
</tbody>
</table>

d, delay of arrhythmias onset after the start of stimulation; D, total duration of arrhythmias for each stimulation.

*p < .05; **p < .01; ***p < .001 (Contrast method comparison).

low dose (25 µg/kg i.v.) and propranolol used at a 20-fold higher dose markedly decreased NbES and NbAC in anesthetized rabbits, and confirm previous data reported by Mest et al. (1995). In addition, these authors observed that the antiarrhythmic action of moxonidine was completely prevented with an i.v. pretreatment with efaroxan and was partially suppressed by a pretreatment with idazoxan (a mixed ligand of I1 and I2 subtypes of IR and an α2-adrenoceptor antagonist). Small doses (10 and 100 nM) of moxonidine and propranolol inhibited the appearance of ES induced by application of aconitine in isolated preparations of guinea pig atria. In contrast, a relatively high dose (1 µM) of moxonidine was revealed to be ineffective in this model. Mest et al. (1995) suggested that this biphasic action reflects a peripherally mediated effect (only appearing at low doses) without any arrhythmogenic effect (at high doses). Our experimental model of neurogenic arrhythmias, like ouabain infusion-induced arrhythmia model, is characterized by an elevation of sympathetic tone, which could be antagonized by stimulation of the I1 subtype of IR (Schäfer et al., 1995).

Furthermore, the chronic implantation of intrahypothalamic bipolar electrodes in our normotensive rabbits allowed us to establish a within animal statistical design, each animal being its own control. Such an experimental model presents the advantages of performing long-lasting experiments and determining the kinetics of action of drugs (such as moxonidine and propranolol), which present prolonged antiarrhythmic potency (see Table 2). Our results showed that the effects of propranolol peaked 35 min postinjection and persisted for more than 2 h, except for the delay of onset and duration of arrhythmias (1 h only). Maximal antiarrhythmic effects of moxonidine were obtained 15 min after injection and, in some cases, exceeded the duration of the experiments (140 min). We observed that the kinetics of the antiarrhythmic action of moxonidine and propranolol was comparable despite the difference in concentration. Likewise, the direct cardiac and central effects, the propranolol-induced bradycardia, are known to contribute to its antiarrhythmic properties. Thus, moxonidine presents a slight bradycardic action at the dose used but no direct cardiac effect, showing that its antiarrhythmic properties, as well as those of propranolol, are probably of central origin (Mest et al., 1995).

In conclusion, the results of this study demonstrate that moxonidine, one of the most selective central I1 subtype of IR antihypertensive agents, presents a dual therapeutic potency. A low dose (25 µg/kg) of moxonidine inducing moderate hypotension and pronounced bradycardia when administered i.v. to halothane-anesthetized normotensive rabbits, can prevent neurogenic cardiac arrhythmias resulting from repeated posterior hypothalamic electrical stimulations. The pronounced and long-lasting reductions in NbES, NbAC, and duration of arrhythmias obtained after moxonidine were comparable to those observed with propranolol treatment, a reference class II antiarrhythmic agent. However, additional studies are required to determine whether these antiarrhythmic effects are of central and/or peripheral origin.

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**References**


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