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Reduced Hemodynamic Responses to Physical and Mental Stress Under Low-Dose Rilmenidine in Healthy Subjects

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Summary. **Activation of the sympathetic nervous system plays a major role in the pathogenesis and prognosis of cardiovascular diseases. Rilmenidine is an I_1-imidazoline receptor agonist that reduces blood pressure by modulation of central sympathetic activity, but the effects of low-dose rilmenidine on the hemodynamic responses to physiological maneuvers that increase adrenergic drive is not known. To assess the effects of low-dose rilmenidine on the hemodynamic responses to stress, 32 healthy subjects (20–56 years old) underwent acute physical exercise ($n = 15$, individualized ramp protocol on treadmill) and mental stress ($n = 17$, word color Stroop and mental arithmetics tests) two hours after the oral administration of 0.5 mg of rilmenidine (RIL) or placebo (PLA) following a randomized, double-blind, placebo controlled crossover study. No subject complained of any side effect. Rilmenidine reduced peak exercise heart rate (PLA: 187 ± 7; RIL: 181 ± 9 bpm; $P = 0.003$), but did not modify peak aerobic power (VO_{2max} — PLA: 41.7 ± 6.2; RIL: 42.3 ± 6.7 ml/kg/min; $P = 0.26$). During mental stress, rilmenidine inhibited the peak systolic (PLA: 123 ± 10; RIL: 114 ± 8 mmHg; $P = 0.02$) and diastolic (PLA: 86 ± 7; RIL: 81 ± 7 mmHg; $P < 0.05$) blood pressure responses. In conclusion, rilmenidine reduced the hemodynamic response to physical and mental stress stimuli without limiting exercise capacity. These results support the concept that rilmenidine, at a dose lower than the ones recommended to treat hypertension, reduced the myocardial oxygen demand to stress and may carry potential clinical impact.**

Key words: **rilmenidine, exercise test, mental stress, sympathetic activity**

Introduction

Chronic activation of the sympathetic nervous system (SNS) is a pathophysiological feature shared by many cardiovascular diseases such as arterial hypertension, heart failure and myocardial ischemia [1]. Increased SNS activity contributes to cardiovascular remodeling, including left ventricular and vascular smooth muscle hypertrophy [2,3], as well as to the occurrence of life threatening ventricular tachyarrhythmias [4]. Therefore, the imbalance of the autonomic nervous system, characterized by increased sympathetic drive and reduced vagal activity, is considered to be an independent and powerful risk factor for adverse cardiovascular events, including sudden death [5]. Accordingly, the pharmacological modulation of the effect of increased sympathetic activity with β-blockers [6] as well as the increase of the vagal tone using muscarinic agonists [7] or reversible cholinesterase inhibitors such as pyridostigmine [8,9] elicit potential cardioprotective effects.

The SNS activity can also be modulated by drugs acting directly on the neural source of the mechanism, i.e., the central nervous system (CNS). In this context, first generation centrally acting antihypertensive drugs such as clonidine have long been used in the treatment of essential arterial hypertension [10], as an effective central sympatholytic agent. Clonidine is known to inhibit the activity of sympathoexcitatory neurons in the ventrolateral medulla acting upon alpha$_2$-adrenoceptors [10], resulting in a reduction of the activity of sympathetic preganglionic neurons and the consequent modulation of peripheral sympathetic activity. Nevertheless, the antihypertensive effect of this class of drugs was frequently accompanied by important central side effects such as sedation and dry mouth, resulting in a loss of interest in

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its clinical use [10]. Since then, the existence of specific binding sites to these drugs characterized by their lack of sensitivity to catecholamines has been demonstrated in the CNS: the nonadrenergic I_1-imidazoline receptors [11–14]. The dissociation of the pharmacological mechanisms involved in the hypotensive effect [11,12,15] of clonidine-like drugs from the one responsible for their sedative action [11,16] was also established. As a result, a second generation of centrally acting antihypertensive drugs has been developed. In this context, rilmenidine has proved to be safe and effective in the treatment of mild to moderate (stage I) arterial hypertension without significant sedative effects at the dose of 1–2 mg once daily [17–20].

In addition to its antihypertensive effect, rilmenidine also presents antiarrhythmic and anti-ischemic properties of central origin [10]. In fact, rilmenidine is able to diminish centrally induced severe ventricular tachyarrhythmias through the inhibition of sympathetic activity—acting upon central imidazoline receptors—in different experimental models using rabbits [21,22] and dogs [23,24]. Moreover, it has already been demonstrated that sub-hypotensive doses of rilmenidine inhibit myocardial ischemia and ventricular arrhythmias resulting from the association of global myocardial ischemia with central sympathetic overactivity in rabbits [25].

Increased sympathetic activity usually occurs during mental and physical stress increasing the risk of death, myocardial ischemia and arrhythmias in subjects suffering from coronary heart disease [26]. Therefore, drugs able to counteract augmented sympathetic activity are potentially useful in this clinical scenario. Panfilov et al. [27] compared the effects of rilmenidine and atenolol in hypertensive patients during physical and mental stress and found that these drugs exert comparable antihypertensive effects both at rest and during mental stress and dynamic exercise. However it is not known whether rilmenidine, at a dose lower than the ones recommended for the treatment of hypertension, could inhibit the hemodynamic response to stress. This information could have relevant clinical implications since it would be possible to reduce the hemodynamic responses to stress-induced sympathetic overactivity, thus protecting patients with coronary artery disease from myocardial ischemia, regardless of their blood pressure status.

Therefore, the main purpose of the present study was to investigate the effects of the oral administration of a single low dose of rilmenidine on the hemodynamic responses induced by maximal physical exercise and mental stress in healthy volunteers.

Methods

Thirty-two apparently healthy volunteers were selected for the study among our laboratory staff and medical students of our University campus after clinical examination had excluded the presence of diseases, use of medications, or inability to complete an exercise test of maximal intensity. Subjects were randomly divided in two groups: mental stress test ($n = 17$; 6 male; age = 20–52 years) and exercise test ($n = 15$; 7 male; age = 23–56 years). Each group underwent a randomized, double-blind, placebo-controlled and crossover design where the effects of rilmenidine on the hemodynamic responses to the tests were studied. Each study day was separated from the next one by at least a 48 h period for drug washout.

The investigation complied with the principles outlined in the Declaration of Helsinki and was approved by the institutional research ethics committee on human research. All volunteers gave written informed consent to participate in the study after full explanation of the procedures and their potential risks. They were instructed to avoid alcohol, beverages containing caffeine, and strenuous physical activity on the day before the experiments.

Mental stress protocol

Each volunteer of the mental stress group was submitted to mental stress tests (Stroop color and arithmetical) in two different mornings, 2 h after the oral ingestion of rilmenidine (0.5 mg) or placebo. This dose of rilmenidine corresponds to half of the lowest one recommended to treat arterial hypertension [17], which is not able to induce a significant fall in arterial pressure of hypertensive patients after a single oral administration [28]. Experiment days were separated by at least 48 h. Heart rate was continuously monitored during each test (Polar Advantage, Finland) and arterial blood pressure (measured with cuff sphygmomanometer) was recorded three times at baseline before the mental stress test and each 30 sec during the test and its recovery phase.

After a 30 min rest in a quiet room, each volunteer was submitted to the Stroop Color Test [29]. During three minutes, each subject was shown changing pictures on a personal computer screen (60 pictures/minute). Each picture displays the name of one color, which is written in letters of a non-matching color; simultaneously the name of another non-matching color is heard aloud in earphones. The volunteer is requested to say the color of the letters that appeared on the screen. After this test, the subject remained seated for 6 min and started the second test (arithmetical test). During the arithmetical test, 4 different pictures (1 picture/3 min), showing three columns of numbers each, are presented to the patient, who has to sum up the numbers in each column and say the results. Simultaneously, different numbers are heard loudly in earphones.

Exercise test protocol

Each subject underwent, on three different days, to a maximal exercise test on a treadmill (KT10200; Inbramed, Brazil) according to an individualized ramp protocol, where the initial and final work rates were set to achieve estimated test duration of 8–12 min, considering the age and physical activity habits of each volunteer. The first day was used for adaptation to the equipment and to determine exercise tolerance. During the other two days, the exercise test was performed according to

the same protocol, two hours after the oral administration of either rilmenidine (0.5 mg) or placebo.

The 12 lead ECG was continuously monitored throughout the exercise test (with Mason-Likar electrode placement; Cardiosmart ST®, Medical systems, USA). ECG tracings and arterial blood pressure (measured with a cuff sphygmomanometer) were recorded before the exercise test and every two minutes during exercise and recovery phase. Oxygen consumption (VO_2), carbon dioxide production (VCO_2), and minute ventilation (VE) were derived on-line from expiratory gases and pulmonary ventilation determined automatically at 20 sec interval (TEEM 100®, Aerosport, Ann Arbor, Michigan, USA). Anaerobic threshold was identified by two experienced evaluators by the combination of the following methods: (1) Point of upward inflection of the ventilation vs. time curve; (2) Beginning of a consistent increase in the ventilatory equivalent for O_2 (VE/VO_2) without a concomitant increase in the ventilatory equivalent for carbon dioxide (VE/VCO_2); and (3) Beginning of an increase in expired oxygen fraction. Ventilatory threshold was considered to be the point identified by at least two of these three criteria. There was no case where each one of the criteria identified different thresholds.

Statistical analysis

All obtained variables were normally distributed. Two-way analysis of variance, where drug and moment were the main factors, followed by Bonferroni *post-hoc* test, was applied to compare the hemodynamic responses to mental stress and exercise. Paired *t* tests were used to compare variables at peak exercise after rilmenidine or placebo. Results are presented as mean (SE) and statistical significance was set at $P < 0.05$.

Results

Rilmenidine was well tolerated by the volunteers, and none of them complained of any side effect. At rest, rilmenidine induced a significant fall in systolic blood pressure (from 107 ± 8 to 103 ± 7 mmHg, $P = 0.014$) but not in diastolic blood pressure (from 68 ± 5 to 70 ± 5 mmHg, $P = 0.217$), heart rate (from 81 ± 7 to 75 ± 7 bpm, $P = 0.371$) or rate-pressure product (from 8.7 ± 0.9 to 7.7 ± 0.8 mmHg.bpm.10^{-3}, $P = 0.144$).

Under placebo, both mental stress tests were effective in producing increases in heart rate (Stroop color: baseline 75 ± 7 bpm and peak 84 ± 10 bpm; $P = 0.01$; arithmetics: baseline 75 ± 6 bpm and peak 83 ± 11 bpm; $P = 0.01$; Fig. 1), in systolic blood pressure (Stroop color: baseline 108 ± 8 mmHg and peak 123 ± 10 mmHg; $P < 0.001$; arithmetics: baseline 109 ± 8 mmHg and peak 122 ± 13 mmHg; $P < 0.001$; Fig. 1), and in diastolic blood pressure (Stroop color: baseline 74 ± 6 mmHg and peak 86 ± 7 mmHg; $P < 0.001$; arithmetics: baseline 78 ± 6 mmHg and peak 86 ± 7 mmHg; $P = 0.003$). Although mental stress also produced significant systolic blood pressure response under the effect of rilmenidine (Fig. 1), the values were lower than with placebo. Peak diastolic blood pressure was also lower under rilmenidine (Stroop color 81 ± 7 mmHg; arithmetics 86 ± 7 mmHg) than under placebo (Stroop color: 86 ± 7 mmHg, $P = 0.046$; arithmetics: 79 ± 7 mmHg, $P = 0.003$). Concerning the heart rate response (Fig. 1), the values were higher than baseline only at the third minute into the arithmetics under rilmenidine, whereas under placebo heart rate was elevated throughout the test.

There was no difference between exercise tolerance after rilmenidine (RIL) and placebo (PLA) (VO_{2max} - PLA: 41.7 ± 6.2 ml/kg· $min^{-1;}$ RIL: 42.3 ± 6.7 ml/kg· $min^{-1;}$ $P = 0.26$), but peak exercise was achieved with lower heart rate (RIL: 181 ± 9 bpm vs PLA: 187 ± 7 bpm; $P = 0.003$), systolic blood pressure (RIL: 147 ± 16 mmHg vs PLA 166 ± 15 mmHg; $P = 0.003$) and, consequently, rate-pressure product (RIL: 26.5 ± 3.2 mmHg· bpm.10^{-3} vs PLA: 31.1 ± 3.1 mmHg· bpm· $10^{-3;}$ $P = 0.001$) after rilmenidine. The peak hemodynamic responses to exercise are depicted in Fig. 2.

Discussion

The present results show that rilmenidine, at a single oral dose corresponding to half of the lowest recommended one to treat arterial hypertension, inhibits the increase in blood pressure and heart rate during mental stress and dynamic exercise in healthy subjects. These results support the concept that I_1-imidazoline receptor agonists, such as rilmenidine, may be effective in modulating the stress-induced increases in sympathetic activity even at low doses.

The present study determined the acute pharmacological effects of a single low dose of rilmenidine on the hemodynamic response to stress as a ground for future trials with therapeutic purposes. Therefore, the clinical impact of the present results should be investigated in future clinical trials using hard endpoints. Nevertheless, it is conceivable that centrally acting imidazoline drugs, such as rilmenidine, exert a protective effect during physiological stress since previous studies have shown that this class of drugs is useful in other stressful conditions. For example, the clinical use of centrally acting sympathomodulatory drugs in the protection of the ischemic heart during surgery is well established [30,31]. Several clinical trials have shown that clonidine induces hemodynamic stability and reduces plasma catecholamines levels and myocardial oxygen demand in patients undergoing coronary artery bypass grafting, resulting in a decreased incidence of perioperative myocardial ischemia [32]. This cardioprotective action of clonidine is clearly the result of the blockade of sympathetic overactivity induced by the surgical stress. Thus, besides their antihypertensive properties, clonidine-like drugs present protective actions towards cardiac events induced by sympathetic overactivity and can potentially be useful in the protection of patients with ischemic heart disease [10]. In

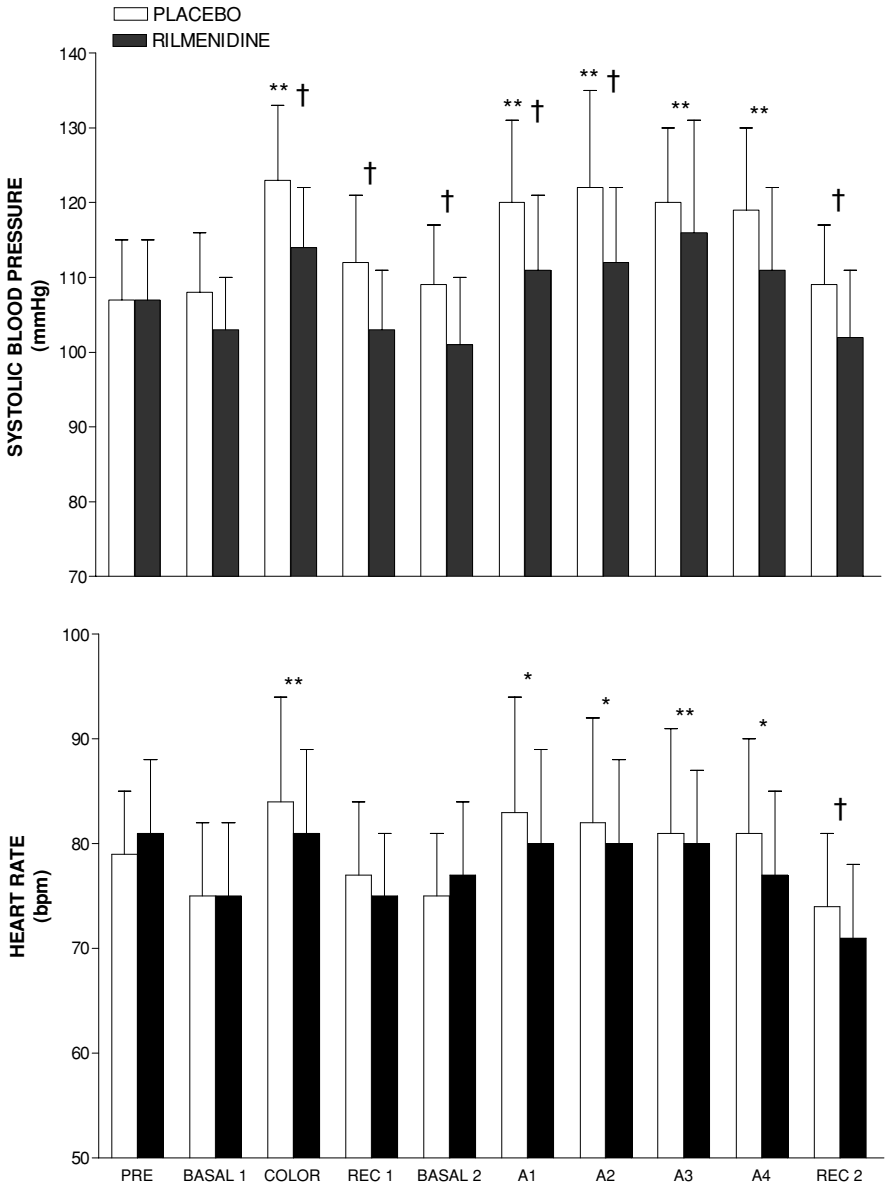

Fig. 1. *Values of systolic blood pressure and heart rate of healthy subjects before (PRE), 2 h after oral ingestion (BASAL 1) of placebo (white bars) or rilmenidine 0.5 mg p.o. (black bars) and during mental stress tests: COLOR = during Stroop color test; REC 1 = recovery period after Stroop color test; BASAL 2 = before arithmetic test; A1-4 = each two minutes during arithmetic test; REC 2 = recovery period after arithmetic test.* $^{*}P < 0.05$*, placebo vs. baseline (BASAL 2),* $^{**}P < 0.001$*, placebo and rilmenidine vs. respective baseline (PRE or BASAL 2),* $^{\dagger}P < 0.01$*, rilmenidine vs. placebo.*

addition to its cardioprotective effects during surgical procedures characterized by high SNS stimulation, clonidine has also proved to present anti-ischemic effects in the setting of nonsurgical patients with coronary artery disease [33]. In fact, low doses of clonidine reduce the ischemic ECG alterations observed during the acute phase of myocardial infarction [34,35] and improve exercise tolerance in patients with chronic stable effort angina pectoris [36,37]. Thus, besides their classical antihypertensive properties, clonidine-like drugs present protective actions towards cardiac events induced by sympathetic overactivity and could be potentially useful in the protection of patients with ischemic heart disease.

Recent experimental evidence suggests that in addition to their antihypertensive effect of central origin, second-generation sympathomodulatory agents such as rilmenidine also present cardioprotective effects [10]. To our knowledge, no study has investigated previously the role of I_1-imidazoline receptor agonists at low doses on the hemodynamic responses to stress. It has been shown previously that chronic treatment of

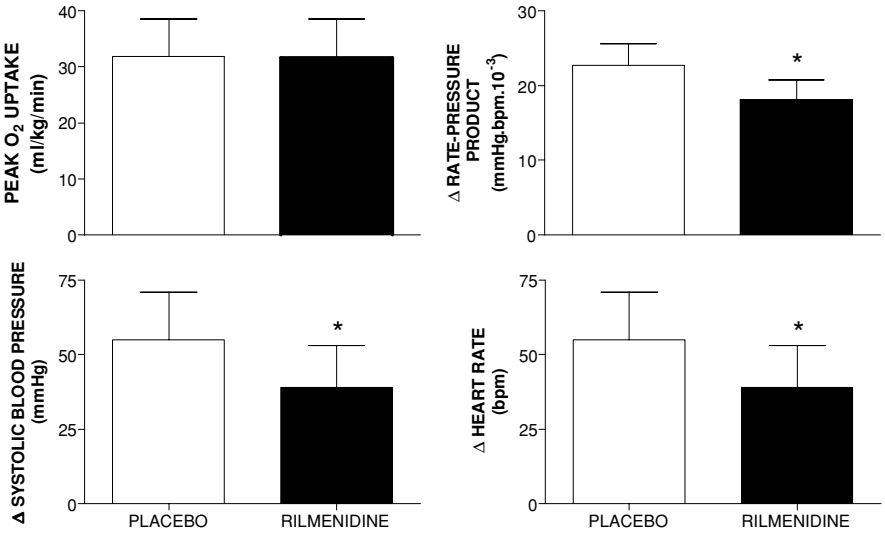

Fig. 2. *Peak values of oxygen uptake and peak changes of cardiovascular parameters of healthy subjects during exercise performed 2 h after placebo (white bars) or rilmenidine 0.5 mg p.o. (black bars). *P < 0.05, rilmenidine vs. placebo.*

hypertensive patients with therapeutic doses of rilmenidine (1–2 mg/day) not only caused rest hypotension, but also, inhibited blood pressure increase during mental stress and physical exercise [27]. It is noteworthy that the potential cardioprotective effects of rilmenidine shown in the above mentioned study can also be obtained with lower doses of the drug than the ones used to treat hypertension, as observed in the present study.

Sympathetic overactivity usually happens during mental and physical stress augmenting the risk of death in patients with coronary artery disease [5,26]. Different drugs, including beta-blockers, are useful to counteract this risk. Although beta-blockers can have similar effects on blood pressure during physical and mental stress, when compared to rilmenidine, there are some issues that must be taken into account in this scenario. Beta-blockers are known to reduce maximal exercise tolerance in humans [38]. In the present study, rilmenidine at a low dose did not affect exercise tolerance of healthy individuals. Thus, rilmenidine counteracted sympathetic increases during maximal exercise test, inhibiting the increase in rate-pressure product without reducing peak VO_2. This aspect is clinically relevant since peak VO_2 is a major indicator of survival in healthy individuals [39], as well as in those with risk factors [40] or established cardiovascular disease [39]. Also, as low-dose rilmenidine reduced maximal rate-pressure product at peak exercise, which is an indirect marker of myocardial oxygen consumption, rilmenidine has a potential to protect subjects with stress-induced myocardial ischemia.

Conclusions

A single low dose of rilmenidine reduced the hemodynamic responses to mental and physical stress testing in healthy volunteers, without affecting their maximal aerobic exercise tolerance. Future studies should evaluate the clinical impact of these results when applied in patients with cardiovascular disease.

References

1. Brook RD, Julius S. Autonomic imbalance, hypertension, and cardiovascular risk. Am J Hypertens 2000;13(6 Pt 2):112S–122S.
2. Schlaich MP, Kaye DM, Lambert E, Sommerville M, Socratous F, Esler MD. Relation between cardiac sympathetic activity and hypertensive left ventricular hypertrophy. Circulation 2003;108:560–565.
3. Julius S, Valentini M. Consequences of the increased autonomic nervous drive in hypertension, heart failure and diabetes. Blood Press 1998;3(Suppl):5–13.
4. Verrier RL, Antzelevitch C. Autonomic aspects of arrhythogenesis: the enduring and the new. Curr Opin Cardiol 2004;19:2–11.
5. Curtis BM, O'Keefe JH Jr. Autonomic tone as a cardiovascular risk factor: the dangers of chronic fight or flight. Mayo Clin Proc 2002;77:45–54.
6. Hjalmarson A. Prevention of sudden cardiac death with beta blockers. Clin Cardiol 1999;22(Suppl 5):V11–15.
7. De Ferrari GM, Salvati P, Grossoni M, et al. Pharmacologic modulation of the autonomic nervous system in the prevention of sudden cardiac death. A study with propranolol, methacholine and oxotremorine in conscious dogs with a healed myocardial infarction. J Am Coll Cardiol 1993;22:83–290.
8. Grabe-Guimaraes A, Alves LM, Tibirica E, Nobrega AC. Pyridostigmine blunts the increases in myocardial oxygen demand elicited by the stimulation of the central nervous system in anesthetized rats. Clin Auton Res 1999;9:83–89.
9. Castro RRT, Porphirio G, Serra SM, Nobrega ACL. Cholinergic stimulation with pyridostigmine protects against exercise induced myocardial ischaemia. Heart 2004;90:1119–1123.
10. Bousquet P, Feldman J. Drugs acting on imidazoline receptors: a review of their pharmacology, their use in blood pressure

control and their potential interest in cardioprotection. Drugs 1999;58:799–812.
11. Tibiriçá E, Feldman J, Mermet C, Gonon F, Bousquet P. An imidazoline-specific mechanism for the hypotensive effect of clonidine: a study with yohimbine and idazoxan. J Pharmacol Exp Ther 1991;256:606–613.
12. Tibiriçá E, Feldman J, Mermet C, Monassier L, Gonon F, Bousquet P. Selectivity of rilmenidine for the nucleus reticularis lateralis, a ventrolateral medullary structure containing imidazoline-preferring receptors. Eur J Pharmacol 1991;209:213–221.
13. Bousquet P, Feldman J, Schwartz J. Central cardiovascular effects of alpha-adrenergic drugs: Difference between catecholamines and imidazolines. J Pharmacol Exp Ther 1984;230:232–236.
14. Reis DJ, Regunathan S, Wang H, Feinstein DL, Meeley MP. Imidazoline receptors in the nervous system. Fund Clin Pharmacol 1992;6:23S–29S.
15. Chan CK, Sannajust F, Head GA. Role of imidazoline receptors in the cardiovascular actions of moxonidine, rilmenidine and clonidine in conscious rabbits. J Pharmacol Exp Therap 1996;276:411–420.
16. De Sarro GB, Ascioti C, Froio F, Libri V, Nistico G. Evidence that locus coeruleus is the site where clonidine and drugs acting at alpha1- and alpha2-adrenoceptors affect sleep and arousal mechanisms. Br J Pharmacol 1987;90:675–685.
17. Reid JL. Update on rilmenidine: Clinical benefits. Am J Hypert 2001;14(11 Pt 2):322S–324S.
18. van Zwieten PA, Peters SL. Central I1-imidazoline receptors as targets of centrally acting antihypertensive drugs. Clinical pharmacology of moxonidine and rilmenidine. Ann N Y Acad Sci 1999;881:420–429.
19. van Zwieten PA. The renaissance of centrally acting antihypertensive drugs. J Hypertens 1999;17(Suppl 3):S15–S21.
20. Reid JL, Panfilov V, MacPhee G, Elliott HL. Clinical pharmacology of drugs acting on imidazoline and adrenergic receptors. Studies with clonidine, moxonidine, rilmenidine, and atenolol. Ann N Y Acad Sci 1995;763:673–678.
21. Roegel JC, Yannoulis N, De Jong W, Monassier L, Feldman J, Bousquet P. Inhibition of centrally induced ventricular arrhythmias by rilmenidine and idazoxan in rabbits. Naunyn Schmiedebergs Arch Pharmacol 1996;354:598–605.
22. Poisson D, Christen MO, Sannajust F. Protective effects of I(1)-antihypertensive agent moxonidine against neurogenic cardiac arrhythmias in halothane-anesthetized rabbits. J Pharmacol Exp Therap 2000;293:929–938.
23. Mammoto T, Kamibayashi T, Hayashi Y, Yamatodani A, Takada K, Yoshiya I. Antiarrhythmic action of rilmenidine on adrenaline-induced arrhythmia via central imidazoline receptors in halothane-anaesthetized dogs. Br J Pharmacol 1996;117:1744–1748.
24. Hayashi Y, Kamibayashi T, Maze M, et al. Role of imidazoline-preferring receptors in the genesis of epinephrine-induced arrhythmias in halothane-anesthetized dogs. Anesthesiology 1993;78:524–530.
25. Catelli M, Feldman J, Bousquet P, Tibirica E. Protective effects of centrally acting sympathomodulatory drugs on myocardial ischemia induced by sympathetic overactivity in rabbits. Braz J Med Biol Res 2003;36:85–95.
26. Rozanski A, Blumenthal JA, Kaplan J. Impact of psychological factors on the pathogenesis of cardiovascular disease and implications for therapy. Circulation 1999;99:2192–2217.
27. Panfilov V, Morris AD, Donnelly R, Scemama M, Reid JL. The effects of rilmenidine and atenolol on mental stress, dynamic exercise and autonomic function in mild to moderate hypertension. Br J Clin Pharmacol 1995;40:563–569.
28. Dollery CT, Davies DS, Duchier J, Pannier B, Safar ME. Dose and concentration-effect relations for rilmenidine. Am J Cardiol 1988;61:60D–66D.
29. Steptoe A, Vogele C. Methodology of mental stress testing in cardiovascular research. Circulation 1991;83(Suppl. II):II14–II24.
30. Hayashi Y, Maze M. Alpha$_2$ adrenoceptor agonists and anaesthesia. Br J Anaesth 1993;71:108–118.
31. Fulgencio JP, Rimaniol JM, Catoire P, Bonnet F. Clonidine and postoperative myocardial ischemia. Can J Anaesth 1994;41:550–551.
32. Dorman BH, Zucker JR, Verrier ED, Gartman DM, Slachman FN. Clonidine improves perioperative myocardial ischemia, reduces anesthetic requirement, and alters hemodynamic parameters in patients undergoing coronary artery bypass surgery. J Cardiothorac Vasc Anesth 1993;7:386–395.
33. Thomas MG, Quiroz AC, Rice JC, Sander GE, Giles TD. Antianginal effects of clonidine. J Cardiovasc Pharmacol 1986;8:S69–S75.
34. Zochowski RJ, Lada W. Intravenous clonidine treatment in acute myocardial infarction (with comparison to a nitroglycerin-treated and control group). J Cardiovasc Pharmacol 1986;8:S41–S55.
35. Zochowski RJ, Lada W. Intravenous clonidine in acute myocardial infarction in men. Int J Cardiol 1984;6:189–205.
36. Ceremuzynski L, Zaleska T, Lada W, Zalewski A. Clonidine effect in chronic angina pectoris. Double-blind, crossover trial on 60 patients. Eur J Cardiol 1979;10:415–427.
37. Giles TD, Thomas MG, Sander GE, Quiroz AC. Central alpha-adrenergic agonists in chronic heart failure and ischemic heart disease. J Cardiovasc Pharmacol 1985;7:S51–S55.
38. Maki T, Naveri H, Leinonen H, Sovijarvi A. Effect of beta-blocking agents with and without intrinsic sympathomimetic activity on work efficiency in healthy men. Clin Physiol 1996;16:543–550.
39. Myers J, Prakash M, Froelicher V, Do D, Partington S, Atwood JE. Exercise capacity and mortality among men referred for exercise testing. N Engl J Med 2002;346:793–801.
40. Laukkanen JA, Kurl S, Salonen R, Rauramaa R, Salonen JT. The predictive value of cardiorespiratory fitness for cardiovascular events in men with various risk profiles: A prospective population-based cohort study. Eur Heart J 2004;25:1428–1437.