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Short communication

Circulatory effect of TCS-80, a new imidazoline compound, in rats

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ABSTRACT

Background: Synthesis and hypotensive properties of centrally acting imidazoline agents: 1-[(imidazolidin-2-yl)imino]-1*H*-indazole (Marsanidine) and 7-chloro-1-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]-1*H*-indazole (TCS-80) were tested in rats. We have recently synthesized two novel Marsanidine analogues which decrease blood pressure and heart rate in rats: 1-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]-1*H*-indole (TCS-54), and 7-chloro-1-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]-1*H*-indole (TCS-213). Among all these analogues, compound TCS-80 exhibits the highest affinity to I_1-imidazoline receptors and the lowest α_2/I_1 selectivity ratio. The observed cardiovascular effects of the compounds might be mediated through α_2-adrenergic and I_1-imidazoline receptors and subsequent decrease of the symphathetic nerve activity. The present studies were performed to determine whether α_2-adrenergic and/or I_1-imidazoline receptors are involved in the decrease of blood pressure and heart rate induced by Marsanidine, TCS-54, TCS-80, and TCS-213 in rats.

Methods: Anesthetized rats were infused *iv* with the tested compounds and selective α_2-adrenoceptor antagonist, RX821002, or nonselective α_2-adrenergic/I_1-imidazoline receptor antagonist, Efaroxan. The mean arterial blood pressure and heart rate were monitored directly and continuously throughout the experiment.

Results: Efaroxan inhibited the hypotensive effect of TCS-80 stronger than RX821002. The degree of inhibition of the hypotensive effect of the remaining compounds was similar for both antagonists. The presence of Efaroxan and RX821002 diminished the heart rate decrease induced by all compounds administration, though the influence on the maximal chronotropic effect was attenuated significantly in the TCS-80 and TCS-213 treated animals only.

Conclusion: Our results indicate that hypotensive and negative chronotropic activities of all tested compounds are mediated by both the α_2-adrenergic and I_1-imidazoline receptors. Moreover, the circulatory effect of TCS-80 might be mediated to relatively higher degree by the I_1-imidazoline receptors than by the α_2-adrenergic ones.

Introduction

Hypertension is one of the most prevalent risk factors of cardiovascular diseases. It is estimated that more than 25% of adult population of the industrialized countries suffer from hypertension [1]. Numerous reports have emphasized the role of the nervous system in regulating the blood pressure and indicated that the sympathetic nervous system is involved in cardiovascular control which may be modified in the early phase of hypertension [2]. In hypertension the medulla oblongata centres may malfunction increasing activity of the sympathetic nervous system, which consequently leads to increased peripheral vascular resistance and cardiac output [3,4]. These observations suggest there is a need to search for new drugs capable of modifying the blood pressure regulation centres located in medulla oblongata.

Drugs acting on the central nervous system include the discovered imidazoline derivatives due to clonidine which was initially used as a nasal decongestant drug [4]. It has been established that clonidine participates in central inhibition of the sympathetic nervous system through α_2-adrenergic receptors agonist located in the presynaptic membrane of synapses with noradrenalin acting as neurotransmitter in the nucleus tractus

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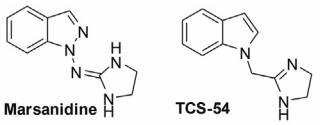
solitaries (NTS) located in the rostral ventrolateral medulla (RVLM). Stimulation of these receptors reduces noradrenalin secretion through a negative feedback loop, thus decreasing tension in the sympathetic nervous system activity which finally results in blood pressure drop [5].

The interpretation proposing that clonidine exerts impact on blood pressure by acting as an α_2-adrenergic receptor agonist is more difficult because of structural proximity of the I_1-imidazoline receptors in the RVLM, as was discovered by Bousquet and colleagues. These receptors are sensitive to clonidine and other clonidine-like imidazoline derivatives [6]. The I_1-imidazoline receptors located in RVLM just like the α_2-adrenoceptors, participate in central regulation of blood pressure and are responsible for inhibition of the sympathetic nervous system activity [4].

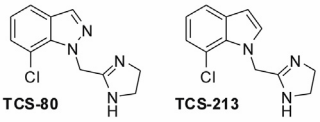
Centrally acting clonidine-like antihypertensive compounds exert their pharmacological effect by interacting with the α_2- and I_1-imidazoline receptors [6]. However, it is necessary to search for more selective I_1-agonits in clinical use because of the compounds side effects, especially sedation which is due to α_2-adrenergic receptors stimulation [7,8]. There is mutual dependence between I_1-imidazoline and α_2-adrenergic receptors in RVLM, the fact confirmed in experiments with mice lacking α_2-adrenergic receptors that markedly attenuated the hypotensive response of imidazoline derivative – LPN509 [9]. The observation supports the hypothesis that imidazoline compounds reduce blood pressure due to their affinity to both imidazoline I_1 and α_2-adrenergic receptors. However, the α_2/I_1 selectivity ratio is not known to date [6].

In our recent papers, we have described the synthesis and hypotensive properties of the following centrally acting imidazoline compounds: 1-[(imidazolidin-2-yl)imino]-1*H*-indazole (**Marsanidine**) and 7-chloro-1-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]-1*H*-indazole (**TCS-80**), both tested in rats [10–12]. We have also synthesized two novel Marsanidine analogues displaying hypotensive activity: 1-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]-1*H*-indole (**TCS-54**) and 7-chloro-1-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]-1*H*-indole (**TCS-213**) (Fig. 1).

In our earlier study we also indicated that two of the tested compounds, Marsanidine and TCS-54, demonstrated relatively a high affinity to the α_2-adrenoceptors (K_i values 14.05 and 33.50 nM, respectively), and very low affinity to the I_1-imidazoline receptors (represented as IC_{50} nM, 54500 and 81400, respectively) [10]. Moreover, the TCS-80 and TCS-213 compounds exhibited a comparably higher affinity to the α_2-adrenoceptors (K_i 6.41 and 1.43 nM) and lower to the I_1-imidazoline receptors (IC_{50} 856 and 13300 nM) [12]. Furthermore, compound TCS-80 was found to be characterized by the lowest α_2/I_1 selectivity ratio of 133 when compared to TCS-213, TCS-54, and Marsanidine, where the ratio was as high as 9300, 2429, and 3879, respectively [10,12].



Marsanidine: 1-[(imidazolidin-2-yl)imino]-1*H*-indazole
TCS-54: 1-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]-1*H*-indole



TCS-80: 7-chloro-1-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]-1*H*-indazole
TCS-213: 7-chloro-1-[(4,5-dihydro-1*H*-imidazol-2-yl)methyl]-1*H*-indole

Fig. 1. The tested imidazoline compounds.

Therefore, the present experiments were performed to determine whether α_2-adrenergic and/or I_1-imidazoline receptors were involved in the mechanism which mediates the hypotensive effect of the tested imidazoline compounds in rats. In our experiments we used RX821002, a selective antagonist of the α_2-adreneceptors [13], and Efaroxan which binds primarily to the I_1 imidazoline receptors of clonidine-like drugs [14,15].

Materials and methods

Experimental animals

Male Wistar rats weighing 200–250 g were purchased from the Animal House of the Medical University of Gdańsk, Poland. The rats were kept at constant room temperature (20 °C) and humidity (70%), under the 12-h dark/light cycles. All experiments were approved by the Local Ethical Committee on Animal Experiments. The animals were fed commercial rodent chow (Labofeed-B, Warszawa, Poland) and provided tap water *ad libitum*. On the experiment day, the rats were anesthetized by intraperitoneal injection of inactin at the dose of 100 μg/kg b.w. The animals were placed on a heated table and their body temperature was maintained between 36 and 37 °C. Tracheostomy was performed, and catheters into the carotid artery for pressure monitoring, into the jugular vein for infusions, and into the bladder for free diuresis were inserted. After all surgical procedures, a 40 min recovery period was allowed to establish a steady state. Over the whole experiment, the rats were infused with isotonic saline supplemented with heparin (20 U/ml of the solution) at the rate of 1.2 ml/h.

After 40 min of saline infusion, the tested compound was administered in 100 μl bolus through the venous catheter. The time of compound administration was assumed to mark "time 0". *iv* injections of RX821002, selective antagonist of α_2-adrenoceptors, or of Efaroxan, I_1-imidazoline and α_2-adrenergic receptor antagonist, were given 5 min before the tested compounds. Blood pressure and heart rate were monitored continuously throughout the experiment.

Groups of animals

The effect of RX821002 on the hypotensive and chronotropic activity of the tested compounds

The imidazoline compounds: Marsanidine, TCS-54, TCS-80, and TCS-213 were administered *iv* at the dose of 100 μg/kg. RX821002, a selective α_2-adrenoceptors antagonist, was given *iv* at the dose of 10 μg/kg, 5 min before injecting each of the tested compounds. The experimental protocol was identical to that described above.

The effect of Efaroxan on the hypotensive and chronotropic activity of the tested compounds

The imidazoline compounds: Marsanidine, TCS-54, TCS-80, and TCS-213 were administered *iv* at the dose of 100 μg/kg. Efaroxan, antagonist of the I_1-imidazoline and α_2-adrenoceptors, was given *iv* at the dose of 100 μg/kg, 5 min before injecting each of the tested compounds. The experimental protocol was identical to that described above.

Control group

At "time 0", the animals were infused *iv* with 100 μl of saline instead of the tested compounds. Otherwise, the experimental protocol was identical to that described above.

Measurements and calculations

The arterial blood pressure and heart rate were monitored directly and sampled continuously at 100 Hz, as previously