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Vasorelaxant Effect of Copsinine and N4-Iodine Methylate Copsinin Alkaloids

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Abstracts

In the present research, it has been studied the vasorelaxant effect of the copsinine alkaloid and it's derivative N4-iodomethylate copsinin isolated from the aerial parts of the plant Vinca erect in isometric conditions and analyzed the chemical structure-activity relationship of biological activity on the smooth muscles of the rat aortic blood vessel. In experiments, it was obtained that the vasorelaxant effect of copsinine and N4-iodomethylate copsinine depend on their concentration and chemical structure as well as with blockade of Ca_L^{2+} channels in the plasma membrane of smooth muscle cells of blood vessels.

Keywords: Alkaloid; Copsinin; N4-iodomethylate copsinin; Blood vessel; Smooth muscle; Ca_L^{2+} channel; α1-Adreno adrenergic receptor; Relaxant

Introduction

At present, alkaloids have been described and isolated from more than ~400 plants. The classification, synthesis/biotransformation and wide spectrum of pharmacological activities of alkaloids have been studied in detail by many researchers, and it is established that alkaloids of Vinca erect plant species are the potential sources of alkaloids [1]. Vinca erect plant species are grown mainly in the mountainous region and are biennial or perennial herbaceous plants. In folk medicine, Vinca erect plant species are used as a decrease in body temperature, anesthetizing, as well as in the treatment of gastritis, tonsillitis, anti-inflammatory drugs, blood pressure, liver diseases, malaria and tonic [2].

The aim of this study is to analyze the effect of the vasorelaxant effect of the alkaloids copsinine and its derivative N4-iodomethylate copsinin. The obtained experimental data showed that the alkaloids copsinine (50–300 μM) and N4-iodomethylate copsinine (5–30μM) have a significant vasorelaxant effect on the isometric activity of rat aortic vessel contraction (*in vitro*) caused by KCl (50 μM). It was found that copsinine reduces the force of contraction at a concentration of 50 μM by 6.1±3.1% compared with the control and by 62.2±4.9% at a maximum concentration of 300 μM (n = 4–6). It was also found that N4-iodomethylate copsinine at a concentration of 5 μM reduces the reduction force by 34.5 ± 4.7% compared with the control and by 83.2±3.2% at a maximum concentration of 30 μM. At the same time, it was found that (EC50) the value of copsinine and N4-iodomethylate of copsinine (ES_{50}) is 178.8 μM and 8.7 μM, respectively (Figure 1A & 1B) [3].

In the experiments, the participation of the potential of L-type dependent Ca^{2+} channels was assessed to ensure the relaxing effect of the copsinine and copsinine N4-iodomethylate alkaloids and their effect on the reduction of aortic drugs caused by the cumulative addition of $CaCl_2$ to calcium-free medium with 50 mM KCl. In these experiments, increasing the concentration of $CaCl_2$ (0–2.5 mM) in the incubation medium led to a gradual increase in the force of aortic contraction due to the influx of Ca^{2+} ions through the L-type Ca^{2+} channels. The presence of alkaloids in the studied incubation medium significantly reduce the development of contractile forces in response to an increase in $CaCl_2$. These results show that the relaxing effects of the studied alkaloids can be associated with a decrease in the input of L-type Ca^{2+} channels and a decrease in $[Ca^{2+}]i$, as well as a decrease in the activity of this restoration [4,5].

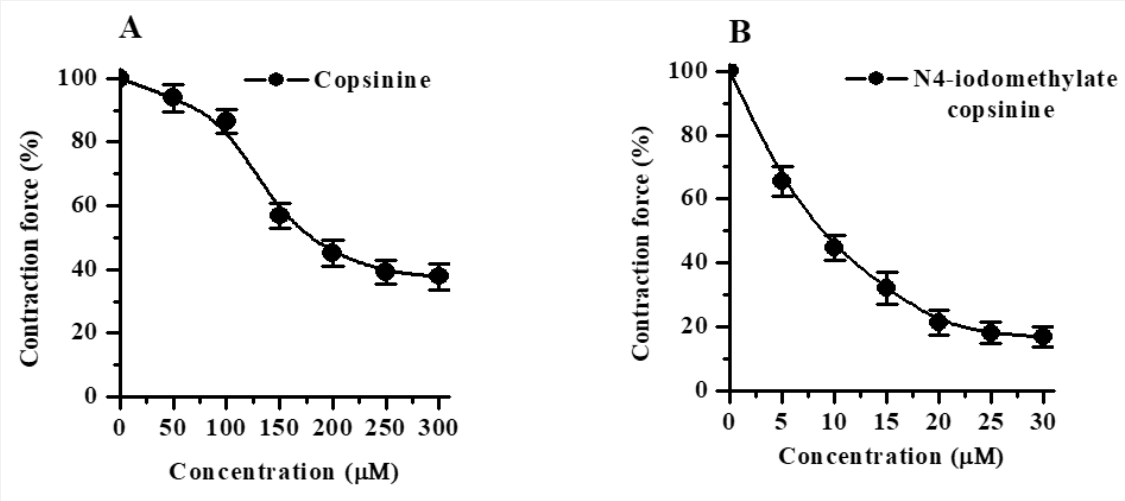

Figure 1: vasorelaxant effect of alkaloids copsinine A) and N4-iodomethylate copsinine and B) depending on the concentration on the aortic drug caused by KCl (50 mM), (* – p<0,05; **p<0,01; n=4–6).

Based on the obtained results, it can be said that the relaxing effect of the copsinine and the copy sinine N4-iodomethylate alkaloids, there is a blockade of the L-Ca^{2+} channels. However, under conditions in the presence of verapamil, partial preservation of the relaxing effect of alkaloids along with blockade of the L-Ca^{2+} channels, with a decrease in Ca^{2+} ions in smooth muscle cells, other mechanisms could be involved. In the regulation of Ca^{2+} homeostasis in smooth muscle cells, in addition to the potential of dependent Ca^{2+} channels, receptor regulated Ca^{2+} channels also play an important role [6]. In order to evaluate the effect of studied the alkaloids in subsequent experiments on the receptor-regulated Ca^{2+} channels, muscle contraction of the aorta induced by the α1-adrenergic agonist, phenylephrine is mainly provided by Ca^{2+} ions via Ca^{2+} -controlled channels [4-9].

Conclusion

Alkaloids - copsinine and its derivative N4-iodomethylate copsinine have a relaxing effect and effectively reduce rat aortic contraction caused by hyperpotassium solution and phenylephrine. Based on an analysis of the literature and experimental results, the alkaloids copsinine and N4-iodomethylate copsinine isolated from Vinca erecta plant species *in vitro* exert a vasorelaxant effect on the activity of isometric contraction of the rat aortic vessel preparation and this effect can be mainly associated with the blockade of Ca^{2+} - channels of L type. The scientific/experimental results obtained in this study can be used as a theoretical basis for the development of antihypertensive pharmacological drugs based on diterpenoid alkaloids.

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