PHARMACOLOGICAL EVALUATION OF THE SYNTHETIC DERIVATIVE QUIN 02 IN THE VASCULAR REACTIVITY OF RATS

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Introduction

Systemic Arterial Hypertension (SAH) is the main cause of premature death in the world and has contributed significantly for the development of other cardiovascular diseases. Despite the vast therapeutic arsenal available for treatment, less than 1 of 5 people have the disease under control (WHO, 2019). In addition, the prevalence of patients with resistant hypertension, that remain uncontrolled despite adherence to antihypertensive therapy is about 5% (CAI et al., 2018). Therefore, interest remains in the discovery of new therapeutic alternatives for the treatment of SAH.

Hypertensive diseases such as SAH can be associated with disorders of the vascular system. In this context, synthetic substances that act on the regulation of vascular reactivity can contribute to the development of new drugs. Among the classes of substances with effects on the regulation of the vascular system described in the available literature, we can highlight quinazolines and their derivatives (MANJULA; BHARATH; DIUYA, 2011).

However, most of the studies described in the available literature have been carried out with derivatives of the 4-quinazolinone isomer, while the compounds derived from the 2-quinazolinone isomer have not yet had biological effects widely explored by researchers (RASHMI et al., 2011). In addition, other derivatives such as quinazolinthiones have not yet been evaluated for the effect on vascular reactivity. In view of those small structural changes in the molecular structures of bioactive substances their potency and effectiveness can increase, the pharmacological evaluation of molecules derived from the isomer 2-quinazolinone and 2- quinazolinthiones has great relevance in the treatment of hypertensive disease. The present study was initially designed to screen the activity of the Quin 02, a molecule derived from the 2-quinazolinone isomer on the vascular reactivity of the Wistar rat's aorta, mesenteric artery, and pulmonary trunk artery.

Method

Male Wistar normotensive rats (*Rattus norvegicus*) weighing between 200 and 300 grams were used. All experiments were conducted according to the guidelines established by the National Council for Animal Experimentation Control (CONCEA, Brazil). This study was approved by the Animal Use Ethics Committee of the Fluminense Federal University (CEUA-UFF), certified under protocol number: 795/2017. The animals were anesthetized with isoflurane (1% mg/kg) inhalation and, after motor control loss, they were euthanized by cervical dislocation. Subsequently, the tissue was dissected and cleaned from connective tissue to obtain rings, 4 mm in length, that were suspended in a 15 mL organ bath (Panlab four chamber organ bath, AD-Instruments, Sydney, Australia). Each arterial segment was

suspended between two steel hooks connected to an isometric transducer to measure tension through a data acquisition system (PowerLab 8 and LabChart Pro, AD-Instruments, Australia).

A 3-[4,5-dimehyl-2-thiazolyl]-2,5-diphenyl-2H-tetrazoliumbromide (MTT) assay was employed to assess the general cytotoxicity for QUIN 02 and VERO cells (African Green monkey (*Cercopithecus aethiops*) kidney cell line) were used in this experiment.

Results / Discussion

The Quin 02 molecule produced relaxation in the aorta artery (IC_{50} = 1.76 ± 0.29 μM), in the 2nd branch of the mesenteric artery (IC_{50} = 0.82 ± 0.18 μM) and in the pulmonary trunk artery (IC_{50} = 0.43 ± 0.07 μM), pre-contracted with phenylephrine (Phe). The vasorelaxant profile observed was similar for the conductance and resistance vessels, being dependent on the concentration and presence of the endothelium. However, Quin 02 was not able to inhibit the contraction obtained with high K^+ solution (80 mM) and thromboxane (1 μM) in aortic rings. In order to investigate the mechanism of action involved, the effect of the substance was evaluated in the presence of some antagonists and pharmacological inhibitors. We observed that the vasodilator effect of Quin 02 in the aorta was completely inhibited in the presence of ODQ (10 μM) and significantly reversed by L-NAME (100 μM) and in the presence of hemoglobin (10 μM). On the other hand, the vasodilating action of Quin 02 did not change in the presence of 4-aminopyridine, iberiotoxin, glibenclamide, atropine, indomethacin, loratadine, atenolol, suramine, HOE-140 and wortimanin (TEIXEIRA et al., 2020)

Based on the results of the MTT assay, it was observed that Quin 02 did not induce a significant difference in the percentage of cell viability (0.3–30 μM). The compound Quin 02 (90.79 ± 2.84%) did not have percentages significantly changed even at the highest concentration (30 μM). According to the ISO 10993: 5 (2009), only samples that reduce cell viability values lower than 70% should be considered cytotoxic (TEIXEIRA et al., 2020).

Conclusion

Preliminary cytotoxicity analyzes indicated that Quin 02 is not cytotoxic when evaluated using international standards. Nevertheless, further toxicity investigations are required to ensure these findings. Regarding the activity, Quin 02 showed *in vitro* a potent vasorelaxant effect in both conductance and resistance arteries. The observed relaxation profile and effectiveness were similar in the tissues studied. Furthermore, our results demonstrated that the vasorelaxant response is dependent on the endothelium and possibly occurs through the modulation of the NO/GCs/cGMP signaling cascade. Finally, our results pointed to the possibility that Quin 02 contributes to the pharmacological management of SAH, possibly as a model for the synthesis of new analogues.

Acknowledgments

We would like to thank Faculdade de Farmácia of Universidade Federal Fluminense, Núcleo de Ciências Biomédicas Aplicadas and Núcleo de Ciências Químicas of Instituto Federal do Rio de Janeiro on research facility support.

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