BMC Pharmacology

Poster presentation

Open Access

3-(3-[1,2,4]triazolo)-oxatriazolium-5-olate causes vasodilatation by NO-independent activation of soluble guanylate cyclase

Anton Bonartsev*, Alexander Postnikov, Marina Artemieva and Natalia Medvedeva

Address: Faculty of Biology, Lomonosov Moscow State University, Moscow, Russia.

Email: Anton Bonartsev* - ant_bonar@mail.ru

* Corresponding author

from 2nd International Conference of cGMP Generators, Effectors and Therapeutic Implications
Potsdam, Germany, 10–12 June, 2005

Published: 16 June 2005

BMC Pharmacology 2005, **5**(Suppl 1):P6 doi:10.1186/1471-2210-5-S1-P6

Background

Soluble guanylate cyclase (sGC) is a crucial enzyme at NO/cGMP-mediated vasodilation. There are NO-independent mechanisms of sGC activation besides well-known enzyme activation by NO. Since 1966 oxatriazolium-5-olate derivatives are known as hypotensive agents at narcotized animals [1]. But the mechanism of their activity is not clarified. The goal of this research is to examine the ability of 3-(3-[1,2,4]triazolo)-oxatriazolium-5-olate (AS-6) to generate NO, to activate sGC, and to cause vasodilatation.

Material and Methods

The ability of AS-6 to generate NO was estimated by its reaction with oxyhemoglobin in the presence and absence of glutathione. Also NO (nitrite) formation in the presence of AS-6 was measured by the Griess reaction. Activity of sGC was measured by using purified enzyme from porcine lung in the presence of 100 microM AS-6. cGMP formation was measured by immunoenzymatic method. To examine vasodilator activity of AS-6, perfusion pressure responses of isolated tail artery (of male Wistar rats) precontracted with 0.5 mikroM norepinephrine was measured. AS-6 was perfused at concentrations $1 \cdot 10^{-9}$–$1 \cdot 10^{-5}$ M.

Results

We demonstrated that AS-6 doesn't generate detectable levels of NO both in the presence and absence of glutathione. AS-6 at concentration 100 microM caused 29 ± 3-fold activation of purified sGC in thiol-independent manner. This activation was 2.0 ± 0.2-fold potentiated by 50 microM allosteric sGC activator YC-1 and completely blocked by heme-dependent sGC inhibitor ODQ. In isolated tail artery AS-6 caused concentration-dependent ($1 \cdot 10^{-9}$–$1 \cdot 10^{-5}$ M) decrease of perfusion pressure with 26 ± 6 % maximal decrease at $1 \cdot 10^{-5}$ M.

Conclusion

AS-6 causes dose-dependent vasodilatation of isolated systemic artery. It seems to be that AS-6 activates sGC in heme-dependent NO-independent manner.

References

1. Kier LB, Al-Shamma A, Campbell D, Patil PN, Tye A: **A new class of hypotensive agents.** *Nature* 1966, **210:**742.