Seredenin *et al.: Intrinsic Activity*, 2015; **3**(Suppl. 2):A2.11
http://www.intrinsicactivity.org/2015/3/S2/A2.11
published online: 9 September 2015

21st Scientific Symposium of the Austrian Pharmacological Society: Joint Meeting with the British Pharmacological Society and the Pharmacological Societies of Croatia, Serbia and Slovenia

Graz, 16–18 September 2015

MEETING ABSTRACT

A2.11

The Pro-Gly-containing dipeptidic cognitive enhancer noopept increases the DNA-binding activity of HIF-1

Sergey SEREDENIN[1], Julia VAKHITOVA[2], Rita OSTROVSKAYA[1,*] and Tatyana GUDASHEVA[1]

[1]Zakusov Institute of Pharmacology, Russia, Moscow; [2]Institute of Biochemistry and Genetics, Ufa Scientific Centre, Russian Academy of Sciences, Ufa, Russia

Background: Noopept (the ethyl ester of *N*-phenylacetyl-L-prolyl-glycine, GVS-111) was synthetized and studied pharmacologically at the Institute of Pharmacology. The experimental study of this orally active substituted dipeptide revealed a wide spectrum of cognitive improving and neuroprotective effects. Noopept was shown to increase the survival and to restore the memory damaged by hypobaric hypoxia, to diminish the volume of necrotic area on different models of stroke, to attenuate the degree of cognitive disturbances as well as NGF and BDNF deficits in a model of Alzheimer's disease (AD). *In vitro* experiments revealed noopept's ability to attenuate the manifestations of oxidative stress, to restore the calcium homeostasis, to stimulate the neurogenesis and to diminish tau-protein aggregation in the amyloid model of AD, to attenuate α-synuclein aggregation in a model of parkinsonism, to increase the survival of human cultivated cortical neurons from the fetus with prenatally diagnosed Down syndrome. Noopept increases the expression of NGF and BDNF in hippocampus and hypothalamus, inhibits the stress-induced kinases pSAPK/JNK and pERK. Meanwhile, looking for the interaction of noopept with more than 100 conventional receptors, we failed to reveal the primary target for this dipeptide. The aim of the present investigation was to evaluate the influence of noopept on DNA-binding activity of various transcriptional factors: CREB, NFAT, NF-κB, p53, STAT1, GAS, VDR, HSF1 and HIF-1.

Methods: Experiments were performed on HEK 293 cells, transiently transfected by luciferase reporter constructions containing sequences for CREB, NFAT, NF-κB, p53, STAT1, GAS, VDR, HSF1 and HIF-1.

Results: Noopept (10 μM) increased the DNA-binding activity of HIF-1 only, while lacking an ability to affect that of CREB, NFAT, NF-κB, p53, STAT1, GAS, VDR and HSF1. Being applicated in the condition of $CoCl_2$-induced HIF-1 stabilization, noopept provoked an additional increase of DNA binding of HIF-1. The degree of this HIF-positive effect was shown to be concentration-dependent. The common nootropic drug piracetam (1 mM) failed to significantly affect any of the transcriptional factors in this study. The results of molecular docking showed that the L-isomer of noopept, unlike its pharmacologically ineffective D-isomer, is able to bind with the active site of prolyl-hydroxylase 2, the enzyme responsible for HIF-1 degradation. The energy of enzyme–ligand binding for noopept and its metabolite phenylacetylproline was close to that for standard inhibitors of prolyl-hydroxylase.

Discussion: Taking into account the important role of genes activated by HIF-1 in the arrangement of adaptive reaction to hypoxia, data on noopept's ability to provoke a selective increase of DNA-binding activity of HIF-1 explain the wide spectrum of noopept's neurochemical and pharmacological effects revealed before. The results of this study suggest the HIF-positive effect as a primary mechanism of noopept's activity.

*Corresponding author e-mail: *rita.ostrovskaya@gmail.com*

© 2015 Intrinsic Activity, ISSN 2309-8503; Austrian Pharmacological Society (APHAR)