Pharmacodynamic differences of afobazole and its active metabolite

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Afobazole (5-etoxy-2[2-(morpholino)ethylthio]benzimidazole dihydrochloride) was developed as an anxiolytic at the Zakusov Institute of Pharmacology (Moscow). Among 17 metabolites of afobazole, the active compound (2-[2-(3-oxomorpholine-4-yl)-ethylthio]-5-ethoxy benzimidazole hydrochloride) M-11 was found.

Afobazole - multitargeting drug, interacts with MT₁ (K_i=1,6E-5 M), Quinone Reductase 2 (NQO2) (K_i=9,7E-7 M), sigma 1 receptors (K_i=5,9E-6 M) and MAO-A (K_i=3,6E-6 M).

M-11, in contrast to afobazole, interacts only with Quinone Reductase 2 (NQO2) (K_i=3,9E-7 M).

Thus, a comparative analysis of the pharmacological effects of afobazole and M-11 can be a useful tool for determining the contribution of the NQO2 to the pharmacological activity.

It was established previously that the stress-induced benzodiazepine binding decrease could be considered as a marker of anxiety level and of anxiolytic effect.

The purpose of this work was a comparative study of afobazole and M-11 effects on the level of benzodiazepine receptors as a marker of anxiolytic action.

Methods: Open field (OF), Exposure to a predator (EP), Radioligand binding assay. The experiments were carried out on inbred C57Bl/6 and BALB/c with opposite OF behavior.

Results: The level of specific [N-methyl-³H]-flunitrazepam binding with P1+P2 membrane fraction of C57Bl/6 and Balb/c mice brain tissue was studied after OF and EP. After OF decrease of benzodiazepine reception was registered in Balb/c mice only. EP test provoked the decrease of labeled ligand binding both in Balb/c and C57Bl/6 mice.

Afobazole restored anxiety-induced decrease of [N-methyl-³H]-flunitrazepam binding in all used stress irrespective of mice strain.

Active metabolite M-11 demonstrated the anxiolytic effect in the OF test and prevents the anxiety -induced radioligand binding decrease only in Balb/c mice. Pretreatment with M-11 did not restore of the anxiety-induced behavior and benzodiazepine binding in Balb/c and C57Bl/6 mice after EP.

Conclusion:

1. Being ligand of MT₁, NQO2, sigma 1 receptors and MAO A regulatory site afobazole has more pronounced anxiolytic activity than M-11 which interacts with NQO2 only.
2. NQO2 inhibition contributes to anxiolytic effect of afobazole.