BMC Pharmacology

Meeting abstract

Chronic treatment with a selective neurokinin-1 receptor antagonist in a mouse model of trait anxiety and depression: focus on behaviour and neuropeptidergic mechanisms

Simone B Sartori[1], Stefano Gaburro[1], Rainer Landgraf[2] and Nicolas Singewald*[1]

Address: [1]Department of Pharmacology and Toxicology and Center for Molecular Biosciences Innsbruck, University of Innsbruck, 6020 Innsbruck, Austria and [2]Department of Behavioural Neuroendocrinology, Max Planck Institute of Psychiatry, 80804 Munich, Germany

Email: Nicolas Singewald* - nicolas.singewald@uibk.ac.at

* Corresponding author

from 14th Scientific Symposium of the Austrian Pharmacological Society (APHAR)
Innsbruck, Austria. 21–22 November 2008

Published: 5 November 2008

BMC Pharmacology 2008, **8**(Suppl 1):A19 doi:10.1186/1471-2210-8-S1-A19

This abstract is available from: http://www.biomedcentral.com/1471-2210/8/S1/A19

Current pharmacotherapy of anxiety disorders and depression mainly targets $GABA_A$ receptors and monoamines such as the serotonin and noradrenaline systems, respectively. They are effective, but an improvement of their therapeutic efficacy in regard of therapeutic onset, side effects and the number of treatment responders is desired. Here, we tested the sensitivity of a mouse line characterised by extremely high levels of trait anxiety and co-occurring depression (HAB) to the selective neurokinin-1 receptor (NK_1R) antagonist [2-cyclopropoxy-5-(5-(trifluoromethyl)tetrazol-1-yl)benzyl]-(2-phenylpiperidin-3-yl)amine using a battery of established tests revealing anxiety- and depression-related behaviours. Chronic administration of the NK_1R antagonist via the drinking water increased the time spent in the brightly lit compartment of the light/dark test and attenuated fear responses in a classical cued fear conditioning paradigm in male and female HAB animals. In addition, the enhanced immobility times of HABs displayed in the forced swim and tail suspension tests were reduced. These findings indicate a clear anxiolytic and antidepressant effect of chronic NK_1R antagonist treatment in HAB animals which have not responded to any classical, clinically effective pharmacotherapy tested so far including paroxetine or diazepam. Moreover, they raise the possibility of a hyperactive substance P/NK_1R neurotransmission in the HAB line. To test this hypothesis, we performed in situ hybridisation studies in the forebrain of HAB mice, their low anxiety/depression (LAB) counterparts and unselected CD1 (NAB) mice. Indeed, the abundance of Tac1 mRNA, the precursor of substance P was elevated in the habenula and ventromedial hypothalamus of HAB compared to NAB and/or LAB mice suggesting that up-regulated transcriptional processes in the substance P system may contribute to the enhanced anxiety- and depression-related behaviours of HABs. Chronic NK_1R antagonist treatment did not alter the high Tac1 mRNA expression of HAB mice. In addition, the HAB vs. the other two lines displayed reduced BDNF mRNA expression in the dentate gyrus and increased met-enkephaline mRNA expression in the hippocampal CA3 region which both were not altered following chronic NK_1R antagonist treatment. Taken together, the present results indicate that the HAB mouse line may represent a unique, clinically relevant model to study drug targets and underlying neurochemistry with potential clinical benefit in treatment-resistant pathological anxiety and co-occurring depression.

Acknowledgements

Supported by the FWF W1206-B05 (NS).