Role of 5-HT$_{2A}$ receptor and $\alpha_2$-adrenoceptor blockade in the asenapine-induced elevation of prefrontal cortical monoamine outflow

Olivia Frånberg, Monica M. Marcus and Torgny H. Svensson

Department of Physiology and Pharmacology, Section of Neuropsychopharmacology, Karolinska Institutet, S-171 77 Stockholm, Sweden

Summary and Conclusions

The major finding of this study is that cortical application of asenapine exhibits a pharmacologically significant 5-HT$_{2A}$ receptor and $\alpha_2$-adrenoceptor antagonistic activity in vivo. Whereas its 5-HT$_{2A}$ blocking property preferentially influences the release of serotonin and dopamine and to a lesser extent noradrenaline, blockage of $\alpha_2$-adrenoceptors preferentially influenced dopamine and noradrenaline release, albeit the effect was somewhat delayed.

Thus, 5-HT$_{2A}$-receptor antagonism and $\alpha_2$-adrenoceptor blockage induced by asenapine in the mPFC may contribute to enhance prefrontal monoamine release in vivo and, secondarily, its effect on positive and negative symptoms in schizophrenia as well as pro-cognitive and antidepressant effects.

Background

The psychotropic drug asenapine was recently approved for treatment of schizophrenia and manic or mixed episodes associated with bipolar I disorder. Asenapine exhibits a multireceptor binding profile with higher affinity for several 5-HT receptors and $\alpha_2$-adrenoceptors than for D$_2$ receptors. We have previously analyzed its atypical profile using a series of well-established preclinical methods. Interestingly, asenapine was found to increase monoamine release in the medial prefrontal cortex (mPFC), which most probably contributes to its beneficial clinical profile. Mechanisms involved in the increased cortical monoamine release were suggested to be related to e.g. antagonism at the serotonergic 5-HT$_{2A}$ receptor and the $\alpha_2$-adrenoceptor.

Aim

Since our previous experimental results provide evidence that the increased cortical monoamine release by asenapine may involve a local action at nerve terminals in the mPFC, we have now examined the potency of asenapine to cause a pharmacologically significant blockage of prefrontal 5-HT$_{2A}$ receptors and $\alpha_2$-adrenoceptors and, thereby, its ability to affect cortical monoamine release by these receptors in vivo.

Materials and Methods

Animals

Adult male Wistar rats were used (300–350 g). They were kept under standard laboratory conditions with food and water available ad libitum. Experiments were approved by and conducted in accordance with the local Animal Ethics Committee, Stockholm-North and the Karolinska Institute, Sweden.

Microdialysis

Anesthetized rats were implanted with dialysis probes with an angle of 12 degrees in the mPFC (AP +2.5; ML -4.4; DV -8.0 relative to bregma and dural surface). Dialysis occurred through a semipermeable membrane (AN69 Hospal) with an active surface length of 1.4 mm. The dialysis probe was perfused with a physiological perfusion solution at a rate of 2.5 μl/min set by a microinfusion pump. On-line quantification of monoamines in the dialysate was accomplished by high performance liquid chromatography (HPLC) coupled to electrochemical detection, with a detection limit of ~0.2 fmol/min. The location of the probe was later verified in slices stained with neutral red. Statistical evaluation was performed by one-way ANOVA followed by planned comparison test.

The article including these data has recently been accepted in Synapse.

Defending my thesis spring 2012

"Mode of Action of Asenapine vs. Other Antipsychotic Drugs. An Experimental Analysis."

Acknowledgement and Disclosure

The present study was supported by the Swedish Research Council (grant no 4747), the Karolinska Institutet and supported in part by a research grant from the Investigator Initiated Studies Program of an Affiliate of Merck Sharp & Dohme Corp.

E-mail: Olivia.Franberg@ki.se

The opinions in this poster are those of the authors and do not necessarily represent those of Merck Sharp & Dohme Corp, nor its Affiliates.