Role of 5-HT$_{2A}$ receptor and α_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 α_2-adrenoceptor antagonistic activity *in vivo*. Whereas its 5-HT$_{2A}$ blocking property preferentially influenced the release of serotonin and dopamine and to a lesser extent noradrenaline, blockage of α_2-adrenoceptors preferentially influenced dopamine and noradrenaline release, albeit the effect was somewhat delayed.

Thus, 5-HT$_{2A}$-receptor antagonism and α_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.

Results

Figure 1

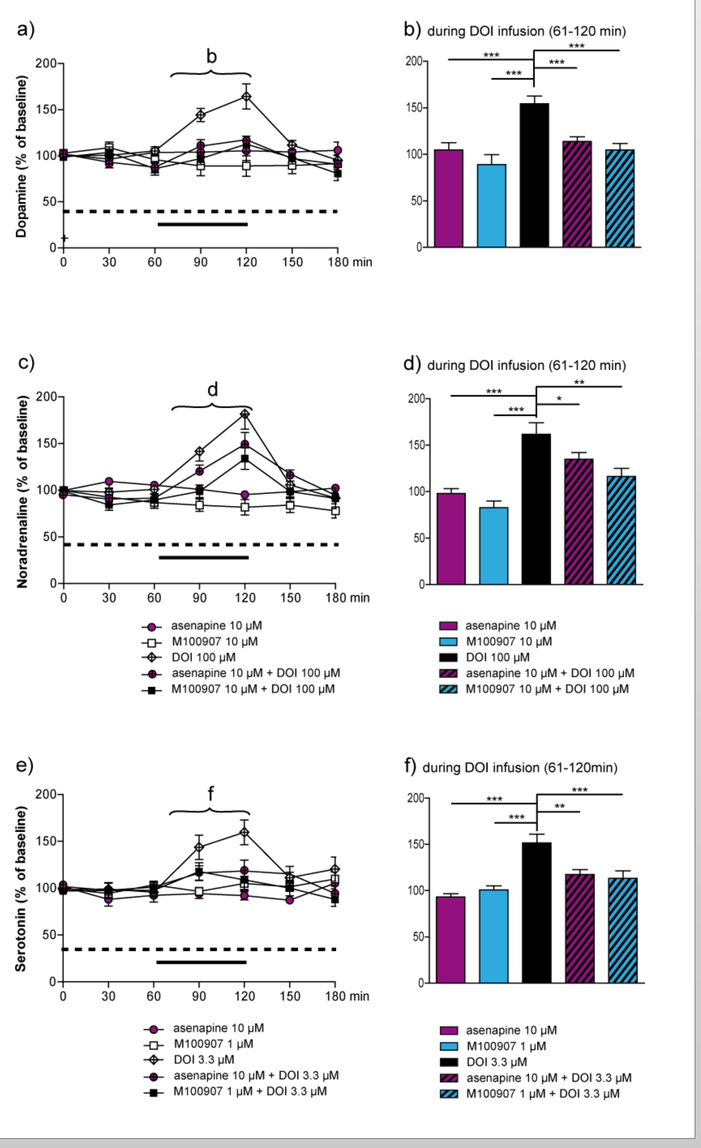
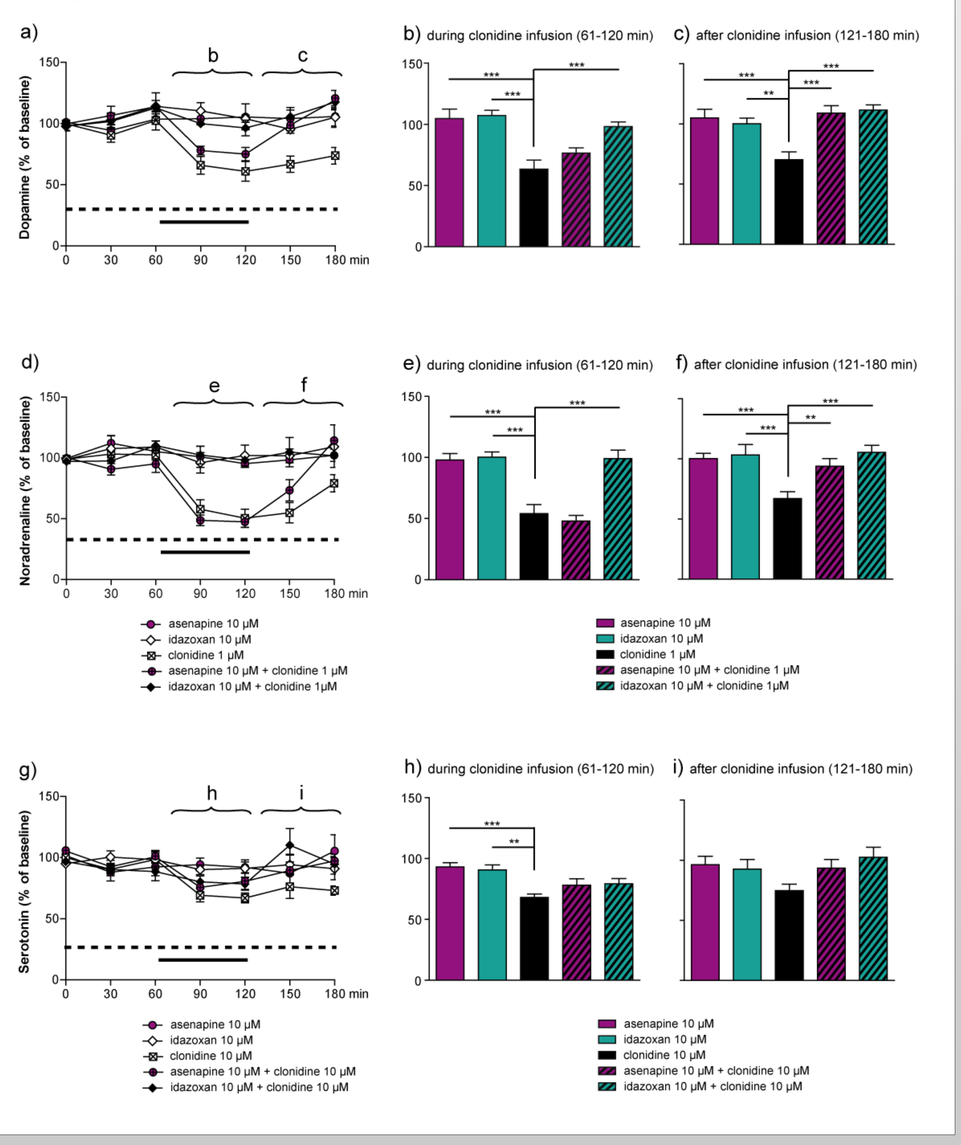


Figure 1
Intracortical administration of DOI, a 5-HT$_{2A/2C}$ receptor agonist, increased cortical monoamine release, effects that were antagonized both by asenapine and the selective 5-HT$_{2A}$ antagonist M100907.

Figure 2
Application of clonidine, an α_2-adrenoceptor agonist, significantly reduced monoamine release in the mPFC. The selective α_2-adrenoceptor antagonist idazoxan blocked, whereas asenapine partially blocked clonidine-induced cortical dopamine and noradrenaline decrease. The effects of asenapine and idazoxan on clonidine-induced serotonin decrease were less pronounced.

Data are presented as % of baseline (mean ± SEM). *p<0.05, **p<0.01 and ***p<0.001 comparisons vs. DOI or clonidine infusion alone.

Figure 2



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 α_2-adrenoceptors than for D_2 receptors[1]. 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[2,3,4,5]. 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 α_2-adrenoceptor[3].

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[3], we have now examined the potency of asenapine to cause a pharmacologically significant blockage of prefrontal 5-HT$_{2A}$ receptors and α_2-adrenoceptors and, thereby, its ability to affect cortical monoamine release by these receptors *in vivo*.

References
1. Shahid et al. 2009, J Psychopharmacol 23: 65-73
2. Frånberg et al. 2008, Psychopharmacol 204: 251-264
3. Frånberg et al. 2009, Psychopharmacol 196: 417-429
4. Potkin et al. 2007 J Clin Psychiatry 68:1492-1500.
5. Kane et al. 2010, J Clin Psychopharmacol 30:106-115

Materials and Methods

Animals

Adult male Wistar rats were used (300-350g). 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 Institutet, Sweden.

Microdialysis

Anesthetized rats were implanted with dialysis probes with an angle of 12 degrees in the mPFC [AP +2.5: ML -1.4; DV -6.0 relative to bregma and dural surface (in mm)]. Dialysis occurred through a semipermeable membrane (AN69 Hospal) with an active surface length of 5.5 mm. Dialysis experiments were conducted approximately 48 h after surgery in freely moving rats. 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.

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

E-mail: Olivia.Franberg@ki.se