Nootropics prevent the effect of scopolamine in an phMRI provocation model

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Introduction:

The effective treatment of cognitive decline is still a major challenge. Therefore drug research plays important role in this area. Several animal models are known to test the cognitive effect of drugs; however these models lack translational power. The recently evolved small animal fMRI proved to be a more suitable translational method. Unfortunately, the direct examination of drug effects is not always possible by fMRI. These problems can be overcome if drugs are tested in a proper provocation model. In order to establish an phMRI based animal model, first we studied the effect of scopolamine on BOLD responses in rat brain as a provocation drug, and the reversibility of its effect by the gold standard donepezil and other nootropic agents.

Material and methods:

Male Wistar rats weighing 240-260 g anaesthetized with isoflurane were used in the experiments. Radiofrequency (RF) pulses were transmitted using a volume coil. A receive-only phased array rat brain coil was placed on the dorsal surface of the rat's head. After 1000 second control period scopolamine were administered as a challenge agent. The test drug was administered one hour before scopolamine. ROI analysis was performed comparing the effect of scopolamine on BOLD responses in drug pretreated or in vehicle treated animals in various brain regions [1].

Results:

Scopolamine strongly decreased the BOLD responses in the prefrontal cortex (PFC) but had no visible effect on hippocampus and other brain areas (Fig. 1). Several nootropics were tested against scopolamine. The cholinergic acting donepezil fully prevented the negative BOLD response of scopolamine in the PFC. Vinpocetin and piracetam reversed partially this decline (of BOLD response) on another signaling pathway but the effect of vinpocetin was more convincing. A new vinpocetin derivative compound (compound X) which is still in preclinical research at G. Richter Plc. had a significant effect in the area of PFC.

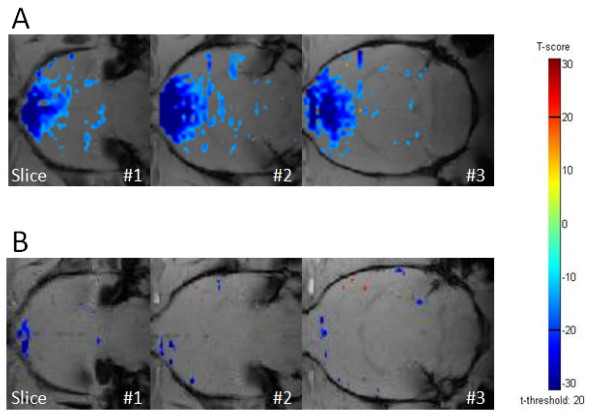

Fig. 1.
Scopolamine strongly decreased the BOLD responses in the prefrontal cortex (PFC) but had no visible effect on hippocampus and other brain areas(A).
The cholinesterase inhibitor donepezil fully prevented the negative BOLD response of scopolamine in the PFC(B).

Discussion:

Functionally, the prefrontal cortex (PFC) of rats is implicated in working-memory, attention, response initiation and management of autonomic control and emotion[2]. The strong negative effect of scopolamine on PFC well explains its memory disturbing effect. It could be fully prevented with the pretreatment of cholinergic donepezil, whereas vinpocetin and piracetam caused a partial reversal in the BOLD response. The efficacy of the new nootropic RG compound was similar to that of vinpocetin, but it was effective in a very low (1.25mg/kg ip.) dose range. Based on these results the model is suitable to test nootropics and also can help to elucidate the mechanism of action of various centrally acting drugs via the analysis of their effects on various brain regions. Further validation of the model with various nootropic and memory disturbing agents is in progress.

References:

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