INTRODUCTION

Some marketed atypical antipsychotics and new antipsychotic drugs in development display direct or indirect 5HT1A agonism. This mechanism may be important to elevate DA release in medial prefrontal cortex (mPFC), an effect thought to be beneficial for the treatment of cognitive and negative symptoms in schizophrenia (1, 2).

The 5HT1A receptor is expressed postsynaptically (mPFC, hippocampus, lateral septum...) and presynaptically (Raphe nuclei). In the mPFC –key area in the symptomatology and treatment of schizophrenia- this receptor is expressed by 50-60% of pyramidal neurons and 20-30% of GABAergic interneurons (3,4).

Endogenous 5HT mainly inhibits mPFC pyramidal neurons acting through 5HT1A receptor yet the systemic administration of 5-HT1A receptor agonists paradoxically increases pyramidal cell activity (5), which suggests the involvement of 5-HT1A receptors in other cell types (e.g. GABAergic interneurons) or in afferent areas to the PFC, such as hippocampus, raphe, entorhinal cortex, etc.

General aim: To study the neuronal networks involved in the effect of 5HT1A agonists and atypical antipsychotic drugs. Specific objective: To evaluate the role of prefrontocortical GABAergic interneurons, hippocampal pyramidal neurons and (R)+(-)8-OH-DPAT enantiomer on the disinhibitory effect of low doses of 8-OH-DPAT on PFC pyramidal neurons.

RESULTS

CONCLUSIONS

8-OH-DPAT appears to act on two different populations of cortical 5HT1A receptors to modulate mPFC pyramidal activity, located on GABAergic interneurons and pyramidal neurons. The hippocampus does not seem to be involved in the effects of 8-OH-DPAT on mPFC, although the involvement of other mPFC afferent areas cannot be discarded.

There are not apparent differences between the (R)-(+)-8-OH-DPAT enantiomer and (±)-8-OH-DPAT.

Drugs with a preferential effect on GABAergic 5-HT1A receptors could have a favourable therapeutic profile for the treatment of negative symptomatology in schizophrenia patients.

REFERENCES

(3) Santana N. et al (2001), Involvement of 5-HT1A receptors in prefrontal cortex in the treatment of schizophrenia- this receptor is expressed by 50-60% of pyramidal neurons and 20-30% of GABAergic interneurons (3,4).

METHODS

Animals: Male Wistar rats (250-300 g) (Lab-Cedex, Lyon, France).

Doses 4-CON: (1) 8-OH-DPAT (±)- 3.5µg/kg i.v. (spikes/s); (2) 8-OH-DPAT (+)- 3.5µg/kg i.v. (spikes/s). Double injections of (+) and (±)-8-OH-DPAT in prefrontal cortex (5-HT1A agonist, Sigma, injected i.v.), Gabazine 20mM in 0.2M saline in the recording electrode (5-HT1A antagonist, Sigma-RBI, 20mM in 0.2M saline in the experimental group). Recordings of mPFC pyramidal neurons projecting to the VTA. Identification by antidromic activation from the VTA.

CONCLUSIONS

8-OH-DPAT appears to act on two different populations of cortical 5HT1A receptors to modulate mPFC pyramidal activity, located on GABAergic interneurons and pyramidal neurons. The hippocampus does not seem to be involved in the effects of 8-OH-DPAT on mPFC, although the involvement of other mPFC afferent areas cannot be discarded.

There are not apparent differences between the (R)-(+)-8-OH-DPAT enantiomer and (±)-8-OH-DPAT.

Drugs with a preferential effect on GABAergic 5-HT1A receptors could have a favourable therapeutic profile for the treatment of negative symptomatology in schizophrenic patients.