POTENTIATION OF DONEPEZIL EFFICIENCY PROFILE BY CONNEXIN INHIBITORS IN AGE-RELATED COGNITIVE IMPAIRMENT

[1]Vandesquille M, [3]Chauveau F, [4]Decros-Tesolin B, [3]Pierard C, [4]Sebban S,
[2]Mouthon F, [1]Beracochea D, [2]Charvériat M.

[1] University of Bordeaux, CNRS-UMR5287, INCIA, Talence, France; [2] Theranexus, CEA-DSV/IMETI, Fontenay-aux-Roses, France;
[3] IRBA, Brétigny-sur-Orge, France; [4] Charles Foix Hospital, Functional Imaging Exploratory Unit, Ivry-sur-Seine, France.

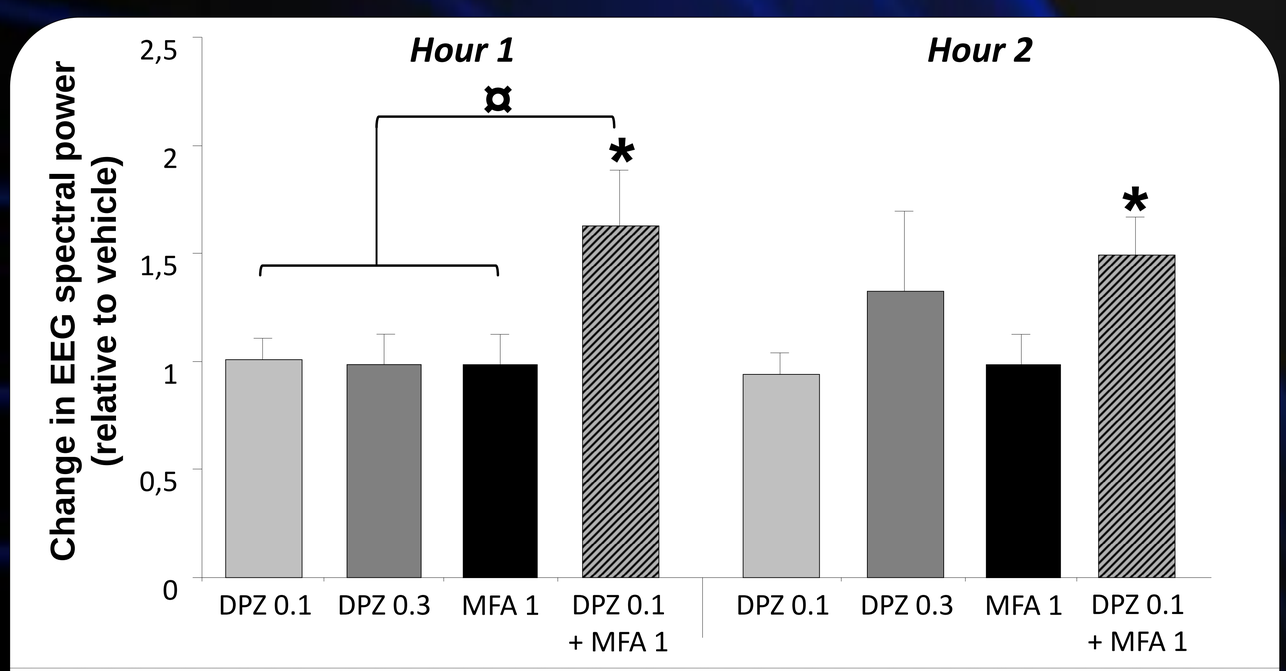
Content:

➢ ***Context:*** **donepezil (DPZ), the main inhibitor of acetylcholinesterase used in Alzheimer's disease leads to several side effects, along with decreased patients' reactivity over time. Hence, we aim to develop molecules which potentiate efficiency and lowered active doses.**

➢ ***Rationale:*** **connexins are transmembrane proteins forming gap junctions involved in several physiological processes in the brain, notably neuronal synchronization. Moreover, modulating their functionality as been described as modifying, either positively or negatively, pharmacological effects of psychoactive drugs (modafenil for instance; Urbano et al., 2007).**

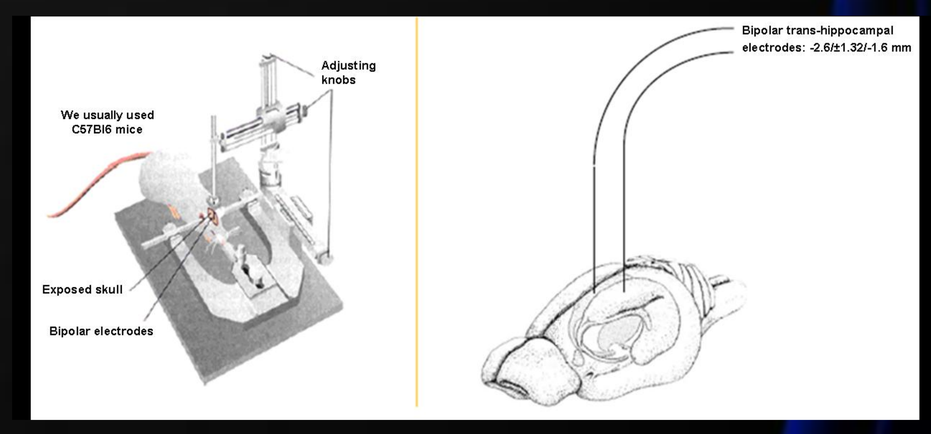
➢ ***Methods:*** **the pharmacological modulation of DPZ by the gap junction inhibitor meclofenamic acid (MFA), was investigated in aged mice (18-20 months). Since DPZ modifies hippocampal theta activity (Sambeth et al., 2007), we firstly quantified the effect of MFA on such activity. In addition, as working memory (WM) is enhanced by DPZ (Vandesquille et al., 2012), we tested whether MFA modified this promnesiant effect.**

Experiment 1: EEG
Hippocampal theta relative activity



The changes in EEG spectral power were calculated as the ratio of mean spectral power in drugs-injected mice (in mg/kg) over the mean spectral power obtained in vehicle-injected mice. *n=7* per group.

Dunnett's comparison: to vehicle: *:p<0.05; between groups: ¤: p<0.05.

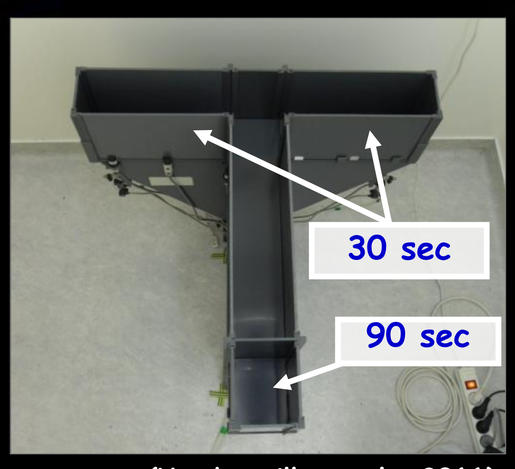


➢ **DPZ 0.1 and MFA 1 have no effect by themselves.**

➢ **MFA 1 + DPZ 0.1 induce modification of theta power earlier than DPZ 0.1 or 0.3.**

➢ **MFA 1 potentiate DPZ 0.1 theta power, to become more efficient than DPZ 0.1 or 0.3.**

Experiment 2: WM task
Spontaneous sequential alternation

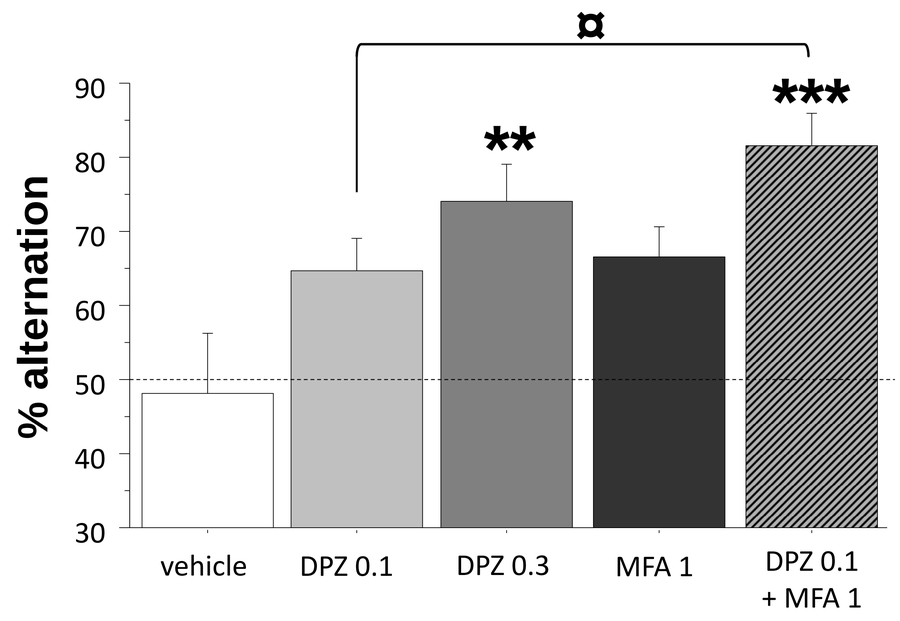


(Vandesquille et al., 2011)

➢ **MFA 1 and DPZ 0.1 have no behavioral effect by themselves.**

➢ **DPZ 0.3 enhance WM performance of aged mice.**

➢ **MFA 1 enhance DPZ 0.1 efficiency on WM.**



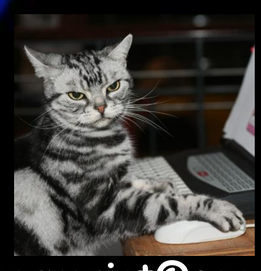
% of alternation on 7 successive trials in a T-maze with a 90 sec intertrial interval. Treatments (mg/kg) were injected i.p. 30 min prior to test. *n=9* per group. Dunnett's comparison: to vehicle: **: p<0.01; ***: p<0.001; between groups: ¤: p<0.05.

Discussion:

➢ ***Summary:*** **The inhibitor of connexins activity does not have any effect by itself on the hippocampal theta and WM performance. MFA given in addition to an inactive dose of DPZ enhances theta power and WM.**

➢ ***Hypothesis:*** **Blocking connexins activity could sharpen neuronal excitability, and therefore might modify the psychopharmacological profile of DPZ to enhance its efficiency.**

➢ ***Perspective:*** **Promising perspective to increase efficiency of several psychotropic drugs, associated with lowered active doses.**



email: mathieu.charveriat@cea.fr

No conflict of interest