

## *Mechanism of action*

### Structural data and *in vitro* studies

- The bioactive peptide is an **amphipatic helix**: advantage to cross the biological barriers <sup>1-2</sup>
- Sequence **homology with DBI** (diazepam binding inhibitor, an endogenous ligand of the GABA<sub>A</sub> receptor) (P) <sup>3</sup>
- Similar distance between the centers of the 2 aromatic cycles from tyrosine residues and those of benzodiazepine rings <sup>1-2</sup>
- **Affinity for GABA<sub>A</sub> receptor (L+P)** <sup>3</sup>
- **Conclusion : lactium<sup>®</sup> contains a benzodiazepine-like peptide**

**P : bioactive peptide, L : lactium<sup>®</sup>**

<sup>1</sup>Lecouvey et al. (1997a). *Eur. J. Biochem.*, **248**, 872-878.

<sup>2</sup>Lecouvey et al. (1997b). *Let. Pept. Sci.*, **4**, 359-364.

<sup>3</sup>Miclo L. et al. (June 8, 2001). *FASEB J.* express article 10.1096/fj.00-0685fje. Publ. online.

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## In vivo studies

- **Anxiolytic activity** in elevated-plus maze and conditioned defensive burying models in Wistar rats even after oral administration (L+P)<sup>3-4-U</sup>
- **Anti-convulsant** activity after i.p. injection (L+P)<sup>3-U</sup>
- Drastic decrease of anxiolytic activity of lactium<sup>®</sup> by an antagonist of GABA<sub>A</sub> receptor (bicuculline) (L)<sup>U</sup>

**Conclusion : lactium<sup>®</sup> exhibits a benzodiazepine-like profile**

**P: bioactive peptide, L : lactium<sup>®</sup>**

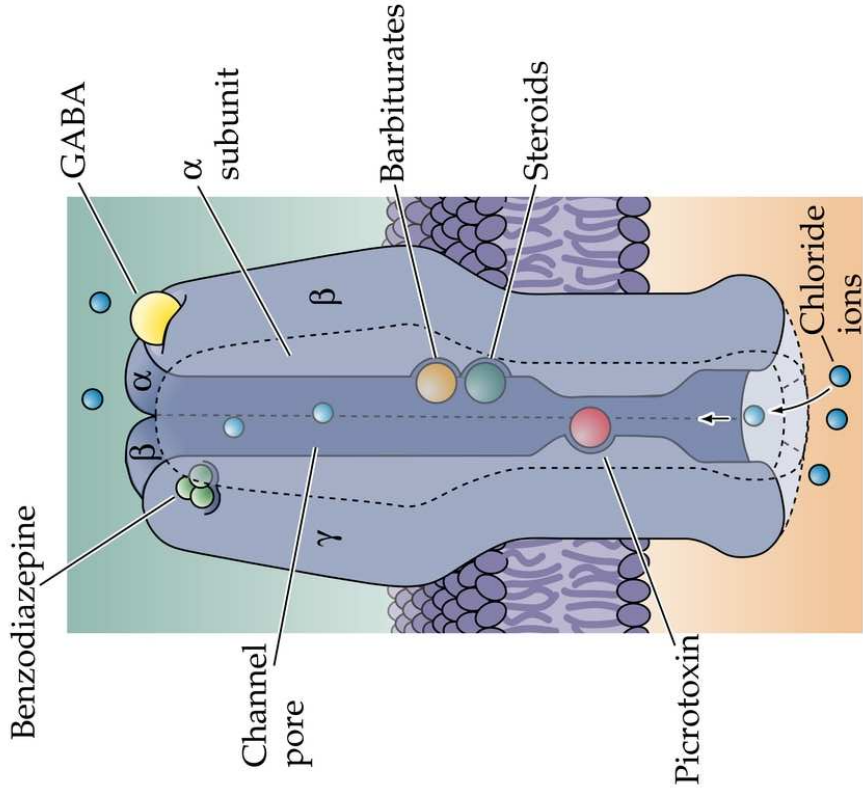
<sup>3</sup>Miclo L. et al. (June 8, 2001). *FASEB J.* express article 10.1096/fj.00-0685fje. Publ. online.

<sup>4</sup>Violle N. et al. (2006). Accepted for publication in *Pharm. Biochem. Behav.*

<sup>U</sup>Unpublished data

# The GABA<sub>A</sub> receptor

- Pentameric protein
- In the pre- and post-synaptic neuronal membrane
- Rosette containing a chloride ion channel
- Chloride flux modulated by GABA, benzodiazepines, alcohol, steroids...
- lots of different subunits  $\alpha_{1-6}$ ,  $\beta_{1-4}$ ,  $\gamma$ ,  $\delta$ ,  $\epsilon$ ,  $\rho$ ,  $\theta$ ,  $\tau_{1-3}$
- The composition in subunits determine the pharmacological profile of the receptor
- Limited and uncompleted knowledge:  $\alpha_1$  (sedation, anticonvulsant),  $\alpha_2$  and perhaps  $\alpha_3$  (anxiolytic)...



**Hypothesis: the bioactive peptide is selective of some subunits**