In vivo photocontrol of mechanosensory circuits in spinal cord

Maleeva G[1], Nin-Hill A[2], Rustler K[3], Wirth U[3], Gomila A[1], Ranucci M[4], Rovira C[2], Bregestovski P[5], Zeilhofer HU[4], König B[3], Alfonso-Prieto M[6], Gorostiza P[1,7]

[1]Institute for Bioengineering of Catalonia,The Barcelona Institute of Science and Technology, Barcelona; [2]Departament de Química Inorgànica i Orgànica, University of Barcelona, Barcelona; [3]Institute of Organic Chemistry, University of Regensburg, Regensburg; [4]Institute of Pharmacology and Toxicology, University of Zurich, Zurich; [5]Institut de Neuroscience des Systemes, Aix-Marseille University, Marseille; [6]Institute of Neuroscience and Medicine INM-9, Forschungszentrum, Jülich; [7]Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona.

Inhibitory neurotransmission in the central nervous system is mainly mediated by $GABA_A$Rs. Disequilibrium in their function leads to many sever neurological disorders, such as epilepsy, anxiety, depression. Thus, development of allosteric modulators that would regulate the activity of these receptors with minimized side effects is of great importance. Photopharmacology is a unique tool for these purposes allowing precise spatial and temporal light-driven control of pharmacophores´ activity, and consequently of their target proteins.

Pursuing the goal to develop a $GABA_A$Rs positive photomodulator, we successfully functionalized the benzodiazepine nitrazepam into a light-controllable molecule via extension by a photochromic fulgimide. The molecule that was obtained, Fulgazepam, was demonstrated to be the first photochromic switch-on potentiator of $GABA_A$Rs and its ability to photomodulate neuronal activity and behavior was successfully demonstrated in vivo in zebrafish. Next, through azologization of a partial agonist of $GABA_A$Rs we have obtained a photoswitchable activator of $GABA_A$Rs. Similarly to the Fulgazepam, it was shown to activate gabaergic currents only after illumination with UV light. Its advantage, comparing to the Fulgazepam, is its higher synthetic accessibility and an activation wavelength shift towards blue part of the spectra – 400-405 nm, which allows better penetration of light into the tissue. We demonstrate that our new photoswitchable $GABA_A$Rs modulator can photocontrol mechanical sensitivity of mice *in vivo*, without disrupting locomotion.

In summary, we have developed a toolbox of photoswitchable modulators of GABARs that can be used for variety of tasks when studying gabaergic neurotransmission. Our latest light-switchable gabaergic molecule is a promising model compound for further therapeutic developments in photopharmacology.