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Novel molecular probes to investigate the alpha7 nicotinic acetylcholine receptor silent activation: New insights and perspectives

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The α7 nicotinic acetylcholine receptor (nAChR) is a homopentameric ion channel, widely expressed in neuronal and non-neuronal cells, including immune cells, adipocytes, lung endothelial, and epithelial cells. This nicotinic receptor subtype is characterized by both ionotropic and metabotropic activation modes. The channel-dependent activation has been deeply investigated and its modulation appeared to be implicated in central and peripheral diseases such as cognitive disorders, schizophrenia, autism, anxiety, and depression. The channel-independent activation was hypothesized to be closely associated with the signal transduction through sites located in the well-conserved α7 intracellular domain. 1 This hypothesis was supported by a class of compounds identified as "silent agonists", which are able to desensitize the receptor with little if any channel activation and promote metabotropic signalling associated with the generation of cellular inflammatory responses. 2 With the aim of deepening the alternative modulations of the α7 nAChR and giving a contribution to elucidating the mechanistic complexity surrounding this nicotinic subtype activation and function, we studied the archetypal silent agonist NS6740.3 Through the synthesis of fragments and analogs, and their electrophysiological investigation employing the human α7 nAChRs expressed in Xenopus laevis oocytes by two-electrode voltage clamping, we provided important knowledge about the pharmacophore features for silent agonism. 4 Using α7 receptor mutants, we also clarified that the unique properties of NS6740 are mainly due to the interaction with the orthosteric α7 binding site.5 Moreover, the results of our recent investigation of a series of sulfonium derivatives will be presented and discussed in an effort of rationalizing structure-activity relationships and progressing drug optimization of α7 receptor activators useful to deepen the metabotropic signalling and endowed with promising anti-inflammatory therapeutic potential.

Recent Publications

1. Pismataro M.C.; Horenstein N.A.; Stokes C.; Quadri M.; De Amici M.; Papke R.L.; Dallanoce C*. Eur. J. Med. Chem. 2020, 205, 112669.

2. C. Matera, M. Kauk, D. Cirillo, M. Maspero, C. Papotto, D. Volpato, U. Holzgrabe, M. De Amici, C. Hoffmann, C. Dallanoce*. Molecules 2023, 28(5), 2407.

Biography

Clelia Dallanoce has received her master's degree in Pharmaceutical Chemistry and Technology in 1990 and her master's degree in Pharmacy in 1995 from the University of Milan. After working in Pierrel SPA and in Marion Merrel Dow, in 1996 she joined the University of Milan becoming assistant professor of Medicinal Chemistry. Since 2018, she is an associate professor at the Department of Pharmaceutical Sciences where she coordinates the scientific activities of the IAMC Group (Innovative Approaches in Medicinal Chemistry Group). During her academic career, her research lines have focused on the design and synthesis of muscarinic orthosteric and dualsteric molecules, and nicotinic compounds for studying ligand-receptor interactions and activation. Recently she has also directed her research to stable and unstable isotope-labeled ligands for drug discovery and development. She has more than seventy papers cited over 1450 times, and her publication H-index is 21. She is a co-inventor of 5 patents.

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