trations, and compared their response to a fixed ACh test pulse. A significant reduction in the RG3487 (3 and10 nM) induced current potentiation was observed in cells expressing the α7β2 nAChRs compared to cells expressing the α7nAChR alone. These data illustrate that the presence of the β2 in the α7 receptor complex modifies the overall properties of the nAChRs and could result in a differential sensitivity to compounds as the α7 and β2 are co-expressed in some areas of the brain.

doi:10.1016/j.bcp.2011.07.012

1.11

A-582941, a pro-cognitive α7 nAChR agonist, differentially modulates mitochondrial membrane potential

Marian Namovic*, Min Hu, Vivek Abraham, Danli Towne, Chih-Hung Lee, Murali Gopalakrishnan, Tim Esbenshade, Diana Donnelly-Roberts

Abbott, Neuroscience Research and Advance Technology, Dept R4DH, Abbott Park, IL, USA

Alzheimer's disease involves multiple pathogenic processes such as abnormal amyloid deposition, tau phosphorylation, oxidative stress as well as mitochondria dysfunction leading to progressive impairment and loss of cognitive function. An assay was established in SK-N-SH cells using JC-1 dye to measure mitochondrial membrane potential (MMP), as an indicator of mitochondrial health, and the effects of compounds on MMP. A-582941, an α7 nAChR partial agonist, was able to enhance MMP with a potency of 11.4 μM and 45% efficacy after overnight serum starvation, which reflects the early stages of apoptosis based on cell viability. Dimebolin and donepezil, other pro-cognitive compounds, but not memantine, also preserved MMP with potency and efficacy values of EC_{50} = 4.6 μM (100%) and 2.2 μM (93%), respectively. Similar results were obtained using either kainic acid or ionomycin as insults. From previous studies, these four compounds exhibit either preclinical or clinical efficacy in models of memory consolidation and short-term recognition. In addition, these compounds are neuroprotective against Aβ insult or promoting neurite outgrowth in primary cortical cultures. Dimebolin and donepezil also increase the MMP over a relatively wide concentration range without compromising nuclear morphology or plasma membrane integrity, both of which are indications of irreversible cellular injury. This approach may allow for further differentiation of pro-cognitive compounds. Studies further demonstrated that concentrations of A-582941, which gave less than a 25% response in preserving MMP was significantly potentiated (to 75%) when cells were simultaneously treated with combinations of A-582941 and dimebolin. Studies are underway to compare the effects of other α7 nAChR agonists with different profiles. Preservation of MMP is an essential event in rescuing neurons from energy-depletion in neurodegenerative states and inhibiting release of pro-apoptotic components.

doi:10.1016/j.bcp.2011.07.013

1.12

Discovery of nicotinic acetylcholine receptor ligands in the chemical universe database GDB-13

L.C. Blum[1,*], R. van Deursen[1], J. Bürgi[1], J.-L. Reymond[1], M. Maver[2], S. Bertrand[2], D. Bertrand[2]

[1] *Department of Chemistry and Biochemistry, University of Bern, Switzerland*
[2] *HiQScreen Sàrl, Geneva, Switzerland*

It is a dream for every medicinal chemist to examine how any possible molecule could interact with a given target. Using parallel processing, we recently reported the exhaustive computational enumeration of all possible organic molecules up to 13 non-hydrogen atoms (C, N, O, S, Cl) in form of the chemical universe database GDB-13 (www.gdb.unibe.ch) [1]. We also showed that a previous version of the database, GDB-11, could be used to design analogs of known nicotinic ligands for synthesis and testing [2]. Here we used the database GDB-13 to search for analogs of the natural product nicotine. A fast similarity classification [3] was used to select 5000 close analogs of nicotine in GDB-13. While several (ca. 150) of these analogs were known AChRs ligands, 50 compounds with no reported activity on AChRs were selected and purchased from commercial vendors. The compounds were probed at α7 neuronal nicotinic receptors expressed in *Xenopus* oocytes using the fully automated electrophysiology HiClamp (Multichannel System). Three of the most active molecules were characterized in detail by determination of the EC_{50}'s and/or IC_{50}'s. Moreover, the mode of action of inhibitors was analyzed in competition experiments. Such ligand-based similarity searching in GDB-13 should be generally useful to rapidly expand the pharmacology of acetylcholine receptors and should help to identify potent and subtype selective agonists and antagonists.

Acknowledgments: This work was supported by the University of Bern, the Swiss National Science Foundation, and the NCCR TransCure and by Neurocypres to DB.

References

[1] Blum LC, Reymond J-L. J Am Chem Soc 2009;131:8732–3.
[2] Garcia-Delgado N, et al. ACS Med Chem Lett 2010;1:422–6.
[3] van Deursen R, et al. J Chem Inf Model 2010;50:1924–34.

doi:10.1016/j.bcp.2011.07.014

1.13

Ligand-based QSAR modeling of neuronal nicotinic receptor data and its impact on drug design

Philip S. Hammond*, Yun-De Xiao, David C. Kombo, Daniel Yohannes

Targacept, Inc., Winston-Salem, NC, USA

Neuronal nicotinic receptors (NNRs) belong to the Cys-loop family of ligand-gated ion channels and form from five subunits as homologous or heterologous, oligomeric receptors. NNRs are of interest as targets for the treatment of a variety of central and peripheral nervous system disorders, including Alzheimer's, Parkinson's, and schizophrenia, as well as for cessation of smoking and pain management. Consequently, designing subtype selective ligands, i.e., orthosteric agonists and antagonists, allosteric modulators, and channel modulators of NNRs, is an active area of pharmaceutical research. Work on membrane-bound NNR proteins has provided key information on both the structure and function of NNRs, but a lack of high resolution protein structures limits structural design efforts. However, much progress has been achieved