PERSPECTIVES

Neuroactive alkaloids that modulate the neuronal nicotinic receptor and provide neuroprotection in an Alzheimer's disease model: the case of *Teline monspessulana*

Despite the advances in combinatorial or synthetic chemistry and bioinformatics, recent literature has demonstrated the relevance of nature and biomass as a source of new molecules to treat different pathologies, *i.e.*, bioactive compounds obtained from *Ecteinascidia turbinate* to treat some types of cancer or rapamycin from *Streptomyces hygroscopicus* to prevent organ rejection after transplant. This trend will continue simply due to the fact that Mother Nature has been synthesizing molecules for millions of years. In our laboratory, we have characterized several compounds obtained from natural sources and that possess important neuronal effects, *i.e.*, a picrotoxin-like molecule with selective action on $\alpha_1$homomeric glycinergic receptors (Fuentealba et al., 2007, 2011), and a steroid with synergic and potent sedative action on GABAergic receptors when associated with acepromazine. More recently, we have been studying the effects of a neuroactive compound obtained from microalgae that has a potent and fast blockade of sodium channels and could be the starting point for the development of a new and selective class of local anesthetics. All of this exciting research demonstrates the importance of nature as an inexhaustible source of biomolecules with structural complexity that synthetic chemistry cannot compete against.

For this reason, we believe that nature represents an opportunity for pathologies like Alzheimer's disease (AD), which has become the nemesis for biomedical development in that it robs our society of the hope to age successfully. The last report from the Alzheimer's Association indicates that the American population over 65 years old that have AD is almost 5 million people, making AD the fifth leading cause of death in this age group (Hebert et al., 2013). The most important problem for biomedicine is still the lack of effective drugs to treat and stop the progression of the disease. Several therapeutic approaches to manage AD have been tested, ranging from anti-Amyloid β antibodies to N-methyl-D-aspartate (NMDA) inhibitors (*i.e.*, memantine), however, none have achieved any significant success (Zemek et al., 2014). It is known that in early stages of AD there is a reduction in the density of neuronal nicotinic acetylcholine receptors (nAChR) in the central nervous system (CNS) and that preservation of cholinergic tone is essential to maintain proper synaptic communication and basic neurological functions like memory and learning; especially, in some important regions like the hippocampus. Therefore, the use of molecules that positively modulate nAChR or that inhibit acetylcholinesterase (AChE) should, in theory, act as neuroprotective agents against AD by maintaining cholinergic tone at a level similar to normal. This is the basis for the Cholinergic theory of AD and most of the FDA approved drugs to treat this disorder are targeted against AChE. The lack of success of anti-cholinergic therapies could be attributed to the initial timing of the treatment, the frequency and intensity of side effects (*e.g.*, dizziness, nausea, irritation, gastrointestinal symptoms, *etc.*), the low tolerance of patients, *etc.* One of the currently used drugs is galantamine, a molecule placed in a privileged site in the ups and downs of the Cholinergic theory, and which is still part of the pharmacological arsenal used to treat AD (Fuentealba and Gandia, 2006). Galantamine is an interesting molecule because it was initially isolated from a plant, *Galanthus nivalis*, and has an alkaloid nature (**Figure 1**). Used initially to revert the effects of muscle relaxing drugs and to counter smoking withdrawal symptoms, there is now plenty of evidence about the neuroprotective effects of galantamine in AD (Shimohama, 2009) associated to the dual action of this alkaloid: mild inhibition of AChE, and positive allosteric modulation of nAChR, especially α7 and α3β4 subtypes. Other classical and potent modulators of cholinergic neurotransmission that share the same characteristics as galantamine are cytisine, anatoxin and epibatidine (still used in experimental research), as well as nicotine and muscarine, two classical alkaloids obtained from tobacco plants (*Nicotiana tabacum*) and fungus (*Amanita muscaria*), respectively, that have been converted into fundamental pharmacological tools and starting points for important drug discovery and development.

Strong evidence supports the role of cholinergic neurotransmission in neuroprotectionin which activation of neuronal nAChR could lead to an effective target for AD treatment. For example, the neuronal loss in Nucleus basalis of Meynert (Behl et al., 2007), decrease in AChE activity (Yates, 2011) and reduction in number of functional nAChR could help to explain the decrease in memory and learning that has been blocked by nicotinic agonists (Morawe et al., 2012) reinforcing the need for identification and characterization of new alkaloids like quinolizidinic derivatives. Using an enriched quinolizidinic extract (TM extract) obtained from *Teline monspessulana* (L) K. Koch, a specie member of the Fabacea family, our laboratory recently demonstrated a neuroprotective effect of these alkaloids associated to the modulation of nAChR, principally the α7 subtype that is coupled to the activation of the anti-apoptotic AKT pathway (**Figure 2**) (Araya et al., 2014). Our data showed that the quinolizidinic alkaloids were capable of recovering fundamental parameters like synaptic activity and Ca^{2+} dynamics in neurons treated with Aβ peptide, whereas no effects were observed in a cellular model lacking α7 nAChR (HEK cells). Furthermore, the use of pharmacological tools like atropine, MLA and α-BTX blocked the neuroprotective effects of the TM alkaloid extract. In parallel, neuronal p-AKT and Bcl/Bax showed an important recovery with the TM alkaloid treatment suggesting a coupling between nAChR activation and an intracellular neuroprotective pathway. Other effects of these compounds cannot be discarded, for example, if they are able to inhibit AChE (similar to galantamine) and also the related enzyme butyrylcholinesterase (BuChE). Some other alkaloids have shown an additional interesting effect such as interference with the aggregation of Aβ and thus provide an additional mechanism of neuroprotective action (Kawamata

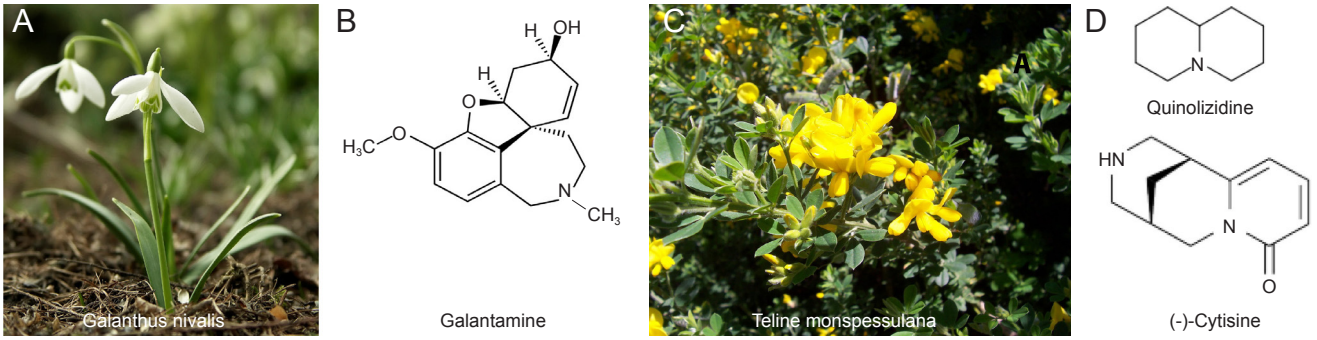

Figure 1 (A) ***Galanthus nivalis*****, the plant from where galantamine was first isolated, showing its characteristic flower. (B) Chemical structure of Galantamine. (C)** ***Teline monspessulana*** **the source of TM extract. Note its characteristic yellow flowers and fruit which accumulate quinozilinidinic alkaloids. (D) The chemical structures of quinozilidine and (-)-cytisine, one of the most common quinozilinidinic derivatives.**

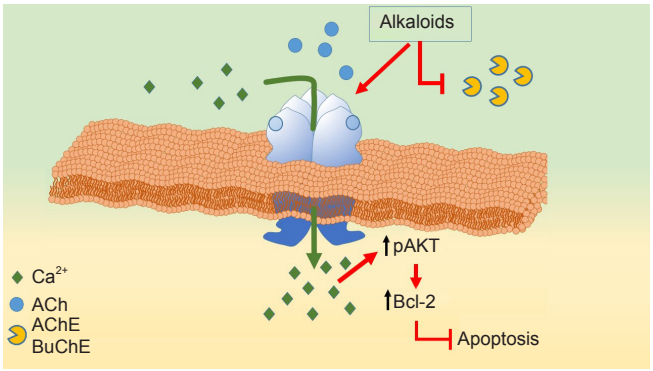

Figure 2 Schematic representation of the action of alkaloids with potential cholinergic effects in Alzheimer's disease.
These alkaloids can modulate acetyl- and/or butyrylcholinesterase (AChE/BuChE) and can also allosterically modulate nAChR, like α7 (central structure in the figure), and promote the activation of the AKT pathway and neuroprotection.

and Shimohama, 2011). These data further emphasize the need to search for new molecules that can achieve therapeutic aims and that possess some important properties like: 1) "multi-target" effect in which several abnormal cellular processes could be modulated simultaneously (*e.g.*, inhibit AChE and/or BuChE, allosteric modulation of nAChR, inhibition of Aβ aggregation) in complex pathologies like AD; and 2) high potency so they can be used at lower doses with better tolerance and low side effects. These requirements for new molecules must be associated with the development of new biomarkers that could provide early treatment and quality of life for these patients. Our results suggest that TM could be a new potential source for anti-AD drugs and may have multi-target actions, reinforcing the hypothesis that cholinergic transmission is important for neuroprotection and synaptic network activity. Therefore, the challenge for us and other groups is to take advantage of these findings and to work on the characterization of new alkaloids from this type of pharmacophore, considering its high structural complexity, with the focus on the development of highly selective compounds for nAChR, especially the α7 subtype, and to design adequate pharmaceutical formulations to guarantee the delivery of these drugs to the CNS.

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