● PERSPECTIVE

Nootropics with potential to (re)build neuroarchitecture

Development of effective treatments for neurodegenerative disorders is a clinical conundrum that has puzzled many researchers. Currently available drugs target symptomatic relief rather than suppressing, ceasing or repairing the devastating neural damages. For Alzheimer's disease, two classes of procognitive compounds are approved as a treatment. One class is acetylcholinesterase (AChE) inhibitors, including tacrine, donepezil, galantamine and rivastigmine, which increase the acetylcholine neurotransmitter level by inhibiting the hydrolysis of acetylcholine. The other class of drugs is N-methyl-D-aspartate (NMDA) receptor antagonists, including memantine, which are intended to suppress β-amyloid induced excitotoxicity. These compounds have produced only modest improvements in cognitive and behavioral symptoms in some Alzheimer's disease patients. Thus, tremendous efforts are being made to discover and develop more effective treatments for Alzheimer's disease.

In the midst of the intense investigation for new treatments, there have been increasing efforts to understand the cellular effects of the existing nootropic compounds on neurogenesis and neuritogenesis, a central process for the formation of neural networks during brain plasticity and (re)growth, to determine their potential for molding neuroarchitecture. Interestingly, studies have shown that selective procognitive compounds indeed possess such properties. We have recently reported that an AChE inhibitor donepezil can significantly promote neurite outgrowth in an embryonic primary cortical culture system (Page et al., 2015). In fact, donepezil can also induce cholinergic sprouting in a rodent model of basocortical degeneration (Ginestet et al., 2007). Interestingly, in addition to its main target, donepezil is known to bind $sigma_1$ receptors with high affinity at a low nanomolar range *in vitro* and behave as an effective $sigma_1$ receptor agonist. In fact, $sigma_1$ receptor ligands Pre-084 and 4-IBP promote neuritogenesis. Other compounds, including NMDA receptor antagonist memantine and anti-histamine dimebon, which also have been reported to bind $sigma_1$ receptors at its effective dose of micromolar range (Peeters et al., 2004), also improve neurite outgrowth (Page et al., 2015). In contrast, non-$sigma_1$-binding compounds, including antioxidants, synaptic vesicle 2A (SV2A) ligands and β-secretase 1 (BACE1) inhibitors, do not exhibit neuritogenic properties when examined under the same experimental conditions. These findings support the notion that $sigma_1$ receptors may mediate, in part, the neuritogenic properties of the tested compounds and that $sigma_1$ receptors hold a central role in regulating neural plasticity and growth. However, the fact that $sigma_1$ receptor compounds are not as potent as the multi-target drug donepezil in our study suggests that more than one molecular target may be ideal in promoting neuritogenesis.

With regard to neuroprotective effects of procognitive compounds, again, donepezil has been reported to enhance the survival of new cells through cAMP response element binding (CREB) signaling. It effectively modulates adult hippocampal neurogenesis and suppresses neurotoxic damage induced by β-amyloid peptide or glutamate exposure (reviewed in Jacobson and Sabbagh, 2008). AChE inhibitors may indeed stimulate neurogenesis as cholinergic receptors are expressed on neuronal progenitors and are coupled to cell proliferation. However, we must take into account that donepezil and other compounds have multiple molecular targets. In fact, similar to the aforementioned neuritogenic property of donepezil, neuroprotective effects of donepezil are thought to be mediated by $sigma_1$ receptor interaction in a mouse model (Meunier et al., 2006) and in rodent cortical culture (Marrazzo et al., 2005). For instance, donepezil and $sigma_1$ receptor agonist Pre-084 provide a complete neuroprotection while AChE inhibitor tacrine provides only a partial neuroprotection in mice treated with β-amyloid peptide 25–35. Furthermore, the memory-enhancing effect of donepezil is blocked by pre-administration of the $sigma_1$ receptor antagonist BD1047 or *in vivo* antisense probe treatment (Meunier et al., 2006). These studies suggest that the procognitive and neuroprotective activities of donepezil are at least partially mediated by $sigma_1$ receptors.

The mechanisms by which $sigma_1$ receptors support cellular plasticity and neuroprotection from embryonic stages to adulthood may be many folds. Widely distributed in brain and enriched at focal contacts between mitochondria and endoplasmic reticulum, $sigma_1$ receptors form heterodimers with many other membrane receptors. As such, they play a significant neuromodulatory role in common mechanisms for plasticity and neurodegeneration, such as intracellular calcium homeostasis, reactive oxygen specie (ROS) mitigation, mitochondrial function and cholinergic and glutamatergic neurotransmission. Furthermore, several recent studies have indicated the receptor's role in mitigating reactive astrogliosis in a rodent stroke model and amyotrophic lateral sclerosis (ALS) as well as modulating microglial activity in animal models of Parkinson's disease and ALS. In fact, the relevance of $sigma_1$ receptors in neuroprotection and repair is evident in several neurodegeneration models. Daily treatment with a $sigma_1$ receptor agonist PRE-084 for 5 weeks produces a gradual and significant improvement of spontaneous forelimb use in a 6-OHDA model of Parkinson's disease. This behavioral recovery is paralleled by an increased density of tyrosine hydroxylase (TH)-positive dopaminergic fibers in striatum and substantia nigra and upregulation of neurotrophic factors BDNF and GDNF. However, PRE-084 has no effect in $sigma_1$ receptor knockout animals under the same treatment regime (Francardo et al., 2014). Likewise, PRE-084 or SA4503 attenuates the gradual loss of motor neurons in SOD1G93A mice, a rodent model of ALS (for review, see Ruscher and Wieloch, 2015). In the realm of Alzheimer's disease, plethora of findings indicate significant role of $sigma_1$ receptors in attenuating or reversing the learning impairments or neurotoxicity induced by for example, β-amyloid peptides, ischemia, the cholinergic muscarinic antagonist scopolamine or NMDA receptor antagonist MK-801 in rodents. In some cases, the protective effects of $sigma_1$ agonists have been shown to be reversible by antisense oligodeoxynucleotides against $sigma_1$ receptors or $sigma_1$ antagonists (for review, see Cobos et al., 2008). In support of underlying neuroprotective potential of $sigma_1$ receptor activation, amyloid toxin-induced neuronal death can be significantly inhibited by concomitant treatment of PRE-084 or (-)MR-22 with β-amyloid peptides in culture or *in vivo* (for review, see Ruscher and Wieloch, 2015). Together, these studies show that $sigma_1$ receptor activity may antagonize brain pathology of neurodegenerative diseases in preclinical models.

Worthy of mention, there has been a fascinating advancement in the development of a multi-target drug involving $sigma_1$

receptor. The aminotetrahydrofuran derivative ANAVEX2-73 is a mixed ligand for sigma$_1$ and muscarinic receptors. The compound possesses an anti-amnesic effect when administered shortly before the injection of the muscarinic receptor antagonist scopolamine, NMDA receptor agonist dizocilpine or A$\beta_{25–35}$ oligomers in mice (Villard et al., 2011). In addition, ANAVEX2-73 prevents the mitochondrial respiratory dysfunction and resulting oxidative stress and apoptotic processes in hippocampus of A$\beta_{25–35}$ treated animals (Villard et al., 2011; Lahmy et al., 2015). Intriguingly, administration of ANAVEX 2-73 7 days after A$\beta_{25–35}$ also significantly attenuates learning deficit and lipid peroxidation (T. Maurice and A. Vamvakides, Alzheimer's Association International Conference® (AAIC) 2012 poster presentation). Moreover, pathological hallmarks of Alzheimer's disease, Tau hyperphosphorylation and glycogen synthase kinase 3 beta (GSK-3β) activation as well as A$\beta_{1–42}$ seeding induced by A$\beta_{25–35}$ injection, can be mostly blocked by ANAVEX 2-73 treatment in mice (Lahmy et al., 2013). In fact, Anavex Life Sciences Corp. has released a preliminary result of the on-going ANAVEX 2-73 phase 2a clinical trial in both male and female mild-to-moderate Alzheimer's patients (mostly on donepezil) at AAIC held in Washington, DC this year (S. Macfarlane et al., AAIC 2015 poster presentation). Their preliminary data based on the EEG/ERP p300 signal, a real-time physiological measure of cognitive processes with demonstrated sensitivity to Alzheimer's disease pathology, indicates a 38% improvement in the neurophysiological effect in 10 out of 12 patients during part A of the study, which consists of a 36-day on-off-on not-yet-optimized dosing regimen to assess bioavailability. This effect is reported to be consistent with the observed trend in Mini Mental State Examination (MMSE) and Cogstate scale improvements. Taken together, these preclinical studies and the preliminary clinical trial results of ANAVEX 2-73 suggest that sigma$_1$ receptors may be a good candidate as a treatment for neurodegenerative diseases indeed. Given the previous clinical failures of selective sigma$_1$ receptor ligands to protect against neurodegeneration, it would be of a great interest to see whether a multi-target ANAVEX2-73 could also provide a disease-modifying improvements in the brains of relevant populations of Alzheimer's disease patients in a long-term. Furthermore, the trial outcome of the combined therapeutic, ANAVEX PLUS, which has shown a synergistic effect of ANAVEX2-73 and donepezil when co-administered with A$\beta_{25–35}$ in mice (Maurice, 2015), would be of a great interest for the field.

To conclude, Alzheimer's disease is a complex multifactorial pathology, fed by self-amplifying neurodegenerative processes. Monotherapy targeting only a single step of this vicious cycle of degeneration may explain the disappointments in previous clinical trials. Although sigma$_1$ receptor presents itself to be a promising candidate, it would be necessary to explore the possibilities of a combinatorial or multi-target therapy, aimed to ameliorate different disease-related mechanisms. As such, it will be crucial also to understand the results of the ongoing and future clinical trials targeting the pathological hallmarks of Alzheimer's disease, β-amyloid and tau, to investigate whether they could work together to improve the clinical outcomes of the patients with Alzheimer's disease.

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References

Cobos EJ, Entrena JM, Nieto FR, Cendan CM, Del Pozo E (2008) Pharmacology and therapeutic potential of sigma(1) receptor ligands. Curr Neuropharmacol 6:344-366.

Francardo V, Bez F, Wieloch T, Nissbrandt H, Ruscher K, Cenci MA (2014) Pharmacological stimulation of sigma-1 receptors has neurorestorative effects in experimental parkinsonism. Brain 137:1998-2014.

Ginestet L, Ferrario JE, Raisman-Vozari R, Hirsch EC, Debeir T (2007) Donepezil induces a cholinergic sprouting in basocortical degeneration. J Neurochem 102:434-440.

Jacobson SA, Sabbagh MN (2008) Donepezil: potential neuroprotective and disease-modifying effects. Expert Opin Drug Metab Toxicol 4:1363-1369.

Lahmy V, Long R, Morin D, Villard V, Maurice T (2015) Mitochondrial protection by the mixed muscarinic/sigma1 ligand ANAVEX2-73, a tetrahydrofuran derivative, in Abeta25-35 peptide-injected mice, a nontransgenic Alzheimer's disease model. Front Cell Neurosci 8:463.

Lahmy V, Meunier J, Malmstrom S, Naert G, Givalois L, Kim SH, Villard V, Vamvakides A, Maurice T (2013) Blockade of Tau hyperphosphorylation and Abeta(1)(-)(4)(2) generation by the aminotetrahydrofuran derivative ANAVEX2-73, a mixed muscarinic and sigma(1) receptor agonist, in a nontransgenic mouse model of Alzheimer's disease. Neuropsychopharmacology 38:1706-1723.

Marrazzo A, Caraci F, Salinaro ET, Su TP, Copani A, Ronsisvalle G (2005) Neuroprotective effects of sigma-1 receptor agonists against beta-amyloid-induced toxicity. Neuroreport 16:1223-1226.

Maurice T (2015) Protection by sigma-1 receptor agonists is synergic with donepezil, but not with memantine, in a mouse model of amyloid-induced memory impairments. Behav Brain Res 296:270-278.

Meunier J, Ieni J, Maurice T (2006) The anti-amnesic and neuroprotective effects of donepezil against amyloid beta25-35 peptide-induced toxicity in mice involve an interaction with the sigma1 receptor. Br J Pharmacol 149:998-1012.

Page M, Pacico N, Ourtioualous S, Deprez T, Koshibu K (2015) Procognitive compounds promote neurite outgrowth. Pharmacology 96:131-136.

Peeters M, Romieu P, Maurice T, Su TP, Maloteaux JM, Hermans E (2004) Involvement of the sigma 1 receptor in the modulation of dopaminergic transmission by amantadine. Eur J Neurosci 19:2212-2220.

Ruscher K, Wieloch T (2015) The involvement of the sigma-1 receptor in neurodegeneration and neurorestoration. J Pharmacol Sci 127:30-35.

Villard V, Espallergues J, Keller E, Vamvakides A, Maurice T (2011) Anti-amnesic and neuroprotective potentials of the mixed muscarinic receptor/sigma 1 (sigma1) ligand ANAVEX2-73, a novel aminotetrahydrofuran derivative. J Psychopharmacol 25:1101-1117.