EDITORIAL

Nicotine and the Nicotinic Cholinergic System in Health and Disease

World-class researchers from highly reputable institutions from four different countries have contributed to this thematic issue. Review papers on the recent findings in basic and clinical sciences, with a translational perspective, covers the involvement of the nicotinic cholinergic system not only in physiological functions but also in disease states, including but not limited to tobacco addiction, as well as drug development. The review papers cover the latest findings on different aspects of nicotinic cholinergic system, ranging from the composition, stoichiometry, structure, localization and functional properties of nicotinic receptors to the role of nicotine in functions involving the hypothalamus or hippocampus and cognition. Understanding nicotinic receptor signaling also aids preventive medicine, and some reviews provide insights into this direction. Thought provoking discussions on the use of antidepressants for smoking cessation or on the possible involvement of the nicotinic receptors in pain control highlight the role of the nicotinic cholinergic system as targets for drug development. And finally one review sheds light on the debate over electronic cigarettes that are becoming alarmingly popular among the youth.

Following description of the nicotinic acetylcholine receptors, Zoli *et al*. [1] and Liu & Li [2] elaborate on the allosteric sites on the nAChRs and discuss how allosteric modulators of the nAChRs regulate function. The role of the accessory subunits and how the presence of different accessory subunits changes the pharmacological and biophysical properties of the receptor are evaluated [1].

Neuronal nAChRs in the brain are preferentially localized at presynaptic and/or preterminal sites, where they regulate the release of several excitatory or inhibitory neurotransmitters. However, nAChRs are also expressed in non-neuronal cells where they may be involved in different types of signaling mechanisms and may also be related to cancer [1]. Furthermore, nicotinic receptors are considered as targets for pain control; α7 nAChRs are widely expressed in non-neuronal cells of the immune system where they regulate the cholinergic anti-inflammatory pathway [3]. The nAChR subtype α7 apparently plays a critical role in the initiation, maintenance and modulation of inflammation in addition to direct neuronal signaling. Therefore, Bagdas *et al* [3] point to the importance of developing α7 nAChR ligands for translational research on pain and inflammation.

Zoli *et al*. [1] emphasize the importance of the nAChRs in critical periods of brain development: early pre- and post-natal circuit formation and age related degeneration. Zeid *et al.* [4] discuss the unique effects of nicotine exposure on hippocampal morphology, cholinergic functioning, and related cognitive processes across a lifespan. Hypothalamus is another brain region where nicotine regulates diverse functions, including the regulation of the stress responses. The nicotinic cholinergic system lies at the intersection of homeostatic and reward pathways and shows sex differences in some of its effects [5]. Balkan & Pogun [5] describe how different neuropeptides are involved in the nicotinic cholinergic regulation of the hypothalamic-pituitary-adrenal (HPA) axis at the hypothalamic level, and explain how nicotinic acetylcholine receptor modulation may offer significant potential for future drug development targeting pathologies related to hypothalamic functions.

Knock-out or knock-in mice, mice with deletions or mutations of various nAChR subunits provide us with clues about the function of these subunits [2]. Furthermore, the involvement of nAChRs in various pathological conditions such as cognitive disorders, anxiety, depression, Alzheimer's and Parkinson's disease, pain and epilepsy can be elucidated using beneficially modified animal models [1]. Along the same lines, drugs can be developed that target nAChR for the treatment of several disorders, including Shizophrenia and some cognitive disorders [2, 6, 7].

Zeid *et al*. [4] describe the hippocampal cholinergic activity and plasticity over different developmental stages (prenatal, adolescence and aging) and discuss the consequences of nicotine exposure on cognition, addiction and mental health. The authors point to the apparently controversial effects at different stages of life. While nicotine exposure during the prenatal period and adolescence may have detrimental effects on hippocampal function resulting in cognitive deficits, nicotine acting on the aging hippocampus may be neuroprotective and enhance cognition [4, 7].

Cognitive-enhancing effects of nicotine are especially important in smokers with comorbid psychiatric disorders with associated cognitive deficits. Cognitive enhancing effects also contribute to difficulties in smoking cessation [7]. Pharmacological agents that enhance cognition may help smokers quit smoking [6, 7]. Selective α7 nAChR agonists may be used to treat cognitive deficits in Schizophrenia, Alzheimer's and ADHD as well as in smoking cessation [7].

Liu & Li [2] elaborate on genetic associations: SNPs within genes encoding nAChR subunits are associated with phenotypes of nicotine addiction and smoking cessation. Brain regions associated with nicotine addiction are discussed and the relationship between psychiatric diseases and tobacco addiction is discussed with evidence from preclinical and clinical studies [6]. Shoaib & Buhidma [6] provide a comprehensive account of the use of antidepressant drugs in smoking cessation. The authors discuss the possible underlying link between depression and tobacco smoking and point to the importance of targeting more than one pathway in developing effective smoking cessation strategies.

While nAChRs are involved in neuronal survival, and nicotinic agonists have been shown to be neuroprotective in *in vivo* and *in vitro* models [1], prolonged exposure to nicotine in tobacco products can be neurotoxic [4]. Nicotine exposure is

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particularly important during different stages of development and specific brain regions, such as the hippocampus, are more vulnerable. This is a major concern since tobacco free nicotine delivery devices are becoming increasingly popular among adolescents, pregnant and lactating women [4]. DeVito & Kirshnan-Sarin [8] review recent developments in electronic cigarettes and discuss the possible consequences of exposure. Although e-cigarettes were initially introduced as nicotine replacement products to be used for quitting smoking, they are currently being used not only by smokers, but also by non-smoker young people. The authors discuss different features of e-cigarettes, ranging from nicotine yield to e-liquid ingredients and flavors. Flavors and additives used to increase the palatability and appeal of e-cigarettes receive special emphasis [8].

We all hope that the current special issue, prepared with a translational perspective, will trigger further research on the physiological and pathological involvement of the nicotinic cholinergic system in health and disease and aid in developing successful treatment strategies.

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