The contribution of 5-HT1A receptors in improving plasticity and function of the brain

CHAPTER 7

SUMMARY

The present thesis aimed to demonstrate the involvement of 5-HT_{1A} receptors in different experimental conditions including cerebral ischemia and aging. It was hypothesized that selective activation of 5-HT_{1A} post-synaptic receptors by NLX-101, a 'biased' 5-HT_{1A} receptor agonist, would increase neuroplasticity and promote functional recovery.

Chapter 1 represented the general introduction and aim for the research described in the thesis.

In **chapter 2**, the currently available data on the effects of 5-HT_{1A} agonists in experimental models of cerebral ischemia was summarized. The studies described in this review provide a clear demonstration that detrimental parameters associated with cerebral ischemia can be attenuated via activation of 5-HT_{1A} receptors. Such studies support the rationale for pursuing an investigation of this class of compounds and suggest that they could lead to promising pharmacotherapeutics for cerebral ischemic diseases.

In **chapter 3** an experimental study using NLX-101 and the selective serotonin reuptake inhibitor (SSRI) Escitalopram (Esc) in mice with bilateral common carotid oclusion (BCCAO) was presented. NLX-101 attenuated cognitive impairments and despair-like behaviors in BCCAO mice. Moreover, NLX-101 blocked the increase in plasma corticosterone levels and restored hippocampal protein levels of plasticity markers including brain-derived neurotrophic factor (BDNF), synaptophysin (SYN), and postsynaptic density protein-95 (PSD-95). This compound also impacted positively dendritic remodeling in the hippocampus and PFC of ischemic mice. The results suggest that biased 5-HT_{1A} post-synaptic receptor agonists might constitute promising therapeutics for the treatment of functional deficits after brain ischemia.

Experimental and clinical evidence suggests that pattern separation linearly declines with increasing age. In **chapter 4** the effects of acute and repeated treatment with NLX-101 on spatial object pattern separation (OPS) performance in aged rats were described. Aged rats were incapable to discriminate any new position of the objects in the arena, reflecting the detrimental effects of aging on OPS performance. However, when aged animals were treated acutely or repeatedly with NLX-101 they showed a significant cognitive improvement in the OPS task. This effect was accompanied by an increase in the BDNF and PSD-95 protein levels in the hippocampus of those animals.

NLX-101 also stimulated neurogenesis (DCX-positive neurons) in the DG of the hippocampus of aged rats. These findings support a rationale for targeting cortical 5-HT_{1A} post-synaptic receptors as a strategy for treating cognitive impairments related to aging.

Chapter 5 presents the impact of CB1 receptor blockade on the behavioral and neuroplasticity effects of the SSRI Esc and the serotonin–norepinephrine reuptake inhibitors (SNSRI) velanfaxine (VFX) in mice submitted to the chronic unpredictable stress (CUS) paradigm. Chronic blockade of the CB1 receptor by the CB1 receptor antagonist AM251 attenuated the antidepressant-like effects of Esc, but not its anxiolytic-like effects. AM251, however, failed to change the antidepressant- and anxiolytic-like effects of VFX. On the other hand, AM251 attenuated the pro-proliferative effects of Esc in the dentate gyrus of the hippocampus. Moreover, Esc increased the expression of the CB1 receptor and PSD-95 in the hippocampus, an effect attenuated by AM251. These results suggest that antidepressants, in particular SSRIs, might exert their behavioral effects with a minor participation of CB1 receptors.

Taken together, the findings of the present thesis demonstrate that 5-HT_{1A} post-synaptic receptors could represent a promising pharmacological target to treat the detrimental consequences of cerebral ischemia and the cognitive decline due to aging.