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

VALORIZATION

Cerebral ischemia is one of the principal causes of death and disability worldwide according to the World Health Organization and represents an increased economic burden due to treatment and post-ischemia care. In Europe, more than one million of new cases occur each year, and currently six million of survivors are estimated to be alive. In 27 European Union (EU) countries, the annual costs for brain ischemia treatment and care are estimated to be 27 billion euros, with 18.5 billion accounting for direct medical costs and 8.5 billion for indirect costs with loss of productivity for example. In the USA, a total of $65.5 billion was spent on brain ischemia care in 2008. The American Heart Association and The American Stroke Association projected for the years 2012 to 2030, that the total direct medical cost for brain ischemia will triple and reach up to $184.1 billion. Costs related to brain ischemia care in Brazil are also considerable, with an aggregate national health care expenditures for the acute treatment of brain ischemia of $449.3 million in 2006-2007. In face of the high costs and the economic impact behind this disease, the problem lies in the fact that advances in pharmacotherapy for cerebral ischemia have been limited. Therefore, the research and development of new drugs is imperative.

Global cerebral ischemia occurs commonly in patients who have a variety of clinical conditions including cardiac arrest, shock, asphyxia and in patients undergoing complex cardiac surgery. The commonest postulated mechanism for ischemic brain injury after cardiac arrest is global cerebral ischemia from systemic hypoperfusion affecting the whole brain. Irrespective of the etiology of cerebral ischemia, cellular and molecular processes trigger a cascade of events that culminate in a final common pathway, resulting in ischemic neuronal injury. Identification of these injury mediators and pathways in a variety of experimental animal models of global cerebral ischemia, such as bilateral common carotid artery occlusion as used in this thesis, has led to the investigation of target-specific neuroprotective strategies that are critical to clinical brain injury outcome.

Usually a patient who survives from cerebral ischemia, as also observed in rodents, may develop a vast number of neurological and neuropsychiatric disorders, including cognitive and/or affective dysfunctions. These impairments impact directly the costs regarding the health care of the patients. Thus, the effective treatment of the

detrimental consequences of brain ischemia is relevant not only from a medical perspective but also from a socioeconomic standpoint.

Many different pharmacological strategies have been considered for the treatment of cerebral ischemia. In this context, some preclinical studies supported the idea that activation of the 5-HT_{1A} receptor with conventional agonists of this receptor, could have benefical effect on the consequences of cerebral ischemia in different animal models. Although these receptor agonists have shown interesting results in these preclinical studies, disappointed results were observed in clinical trials. The reason for this could be related to poor selectivity resulting in partial agonist, i.e. weak, activity on 5-HT_{1A} receptors. Moreover, these receptor agonists activate indiscriminately both 5-HT_{1A} presynaptic autoreceptors and postsynaptic heteroreceptors, and this lack in receptor discrimination of 5-$HT1_A$ agonists may result in divergent or even opposite effects.

Interstingly, a new generation of so-calles biased receptor agonists has become available that discriminate between receptor subpopulations in specific brain regions. NLX-101, a biased postsynaptic 5-HT_{1A} receptor agonist, has been extensively tested in preclinical studies and presents interesting antidepressant and pro-cognitive effects that could contribute to the treatment of the functional impairments after cerebral ischemia. In this thesis, for the first time to my knowledge, the effects of the biased 5-HT_{1A} receptor agonist NLX-101 was evaluated in a mouse bilateral common carotid artery occlusion (BCCAO) model of brain ischemia. It was demonstrated that the functional deficits of these mice can be restored by selective 5-HT_{1A} post-synaptic activation.

In summary, it was shown that:

- NLX-101 attenuated cognitive impairments induced by BCCAO in mice.
- NLX-101 improved passive coping strategies of BCCAO mice in the forced swimming test.
- NLX-101 decreased basal plasma corticosterone levels in BCCAO mice.
- NLX-101 affected BDNF protein levels in the prefrontal cortex (PFC) and hippocampus of BCCAO mice.
- NLX-101 impacted dendritic remodeling in the PFC and hippocampus of BCCAO mice.

- NLX-101 decreased neurodegeneration and increased synaptic plasticity markers in BCCAO animals.

Thus, direct targeting of a 5-HT_{1A} receptor subpopulation with biased agonists such as NLX-101 might constitute a new strategy for therapeutic intervention in brain ischemia patients.

Another topic addressed in this thesis is related to the cognitive decline caused by aging. Themes related to aging have been increasingly studied due to the increase in the elderly population in the world. The number of older persons (over 65 years old) that is an age above X years, is expected to double again by 2050, when it is projected to reach nearly 2.1 billion. An aging global population will have a serious impact on the world's economies to the point of hampering growth and changing public policy. Nations will be forced to improve their healthcare systems so they are more effective and efficient in order to provide better treatment for the elderly at a lower cost.

It is vital to understand how age impacts cognition and which preventative or treatment strategies might preserve cognition into advanced age. Pharmacological intervention aimed at enhancing or maintaining cognitive functions has been the focus of intensive research in the recent years. In this context, 5-HT_{1A} receptors have been shown to be involved in important aspects of cognitive function including attention, learning and memory, and neuroplasticity processes. Of note, acute administration of the biased 5-HT_{1A} receptor agonist NLX-101 has been shown to improve performance of healthy adult rats in the object pattern separation (OPS) task. In this thesis, it was demonstrated that aged rats presented a cognitive deficit in the OPS task, reflecting the detrimental effect of aging on pattern separation performance. Moreover, when these aged animals were treated acutely or repeatedly with NLX-101 they showed a cognitive improvement in the OPS task, and this effect was accompanied by an increase in neuroplasticity. These findings support the rationale for targeting post-synaptic cortical 5-HT_{1A} receptors as a treatment for cognitive deficits related to aging.

Clearly, the results from these studies provided new insights regarding the contribution of the 5-HT_{1A} receptor in improving plasticity and functional recovery in different neurological conditions. Specifically, the use of a new class of drugs known as biased 5-HT_{1A} receptor agonists, e.g. the drug NLX-101, targeting the serotoninergic

system could represent a promising strategy to treat cerebral ischemia diseases and cognitive decline due to aging. However, this issue needs to be investigated in future studies. More scientific evidence is needed to address whether biased 5-HT_{1A} agonism underlied the NLX-101 positive effects in cerebral ischemia and pattern separation in aged rats. Depending on the concentration, NLX can act as a conventional agonist at both pre-and postsynaptic receptors and, the range between biased and non-biased 5-HT_{1A} receptor agonism can be narrow. Thus, the present results could open up a new world of possibilities to be explored in the treatment of functional deficits impacting daily living and could represent a viable way to improve the quality of life of patients eventually.