β2 adrenergic receptors as novel players and targets in the modulation of adult hippocampal neurogenesis

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The formation of new neurons in the hippocampus of adult mammalian brain represents an exciting topic in neuroscience. In the last decade several groups demonstrated that adult Hippocampal Neurogenesis (AHN) is involved in learning and memory and that it is altered in several important neurodegenerative and neuropsychiatric disease characterized by cognitive deficits (1). Interestingly, chronic treatment with antidepressant drugs, characterized by monoaminergic mechanism, results in increased AHN in rodents, non human primates and human (2). As a consequence, increased knowledge of the molecular basis of AHN regulation may contribute to a better understanding of the pathophysiological basis of several neuropsychiatric disorders.

In recent years our group contributed to the identification of novel molecular regulators involved in AHN, among them the transcription factor NF-kB p50 (3,4). Recently we demonstrated that, *in vitro,* norepinephrine (NE) promotes neuronal differentiation of hippocampal NPC derived from wild type (WT) mice (5) but is totally devoid of effects when tested on NF-kB p50 knockout (KO) NPC, which lack expression of β2 adrenergic receptor (AR).

Based on such evidence, we decided to investigate the relevance of β2-AR, compared to other AR subtypes, in the modulation of AHN by NE and the potential involvement of NF-kB . NPC were differentiated in presence of selective β2-AR agonists that significantly increased the percentage of newly generated neurons (MAP-2^+/$nestin^-$ cells) and neuroblasts (MAP-2^+/$nestin^+$ cells). At all tested concentrations, β2-AR agonists had no effect on NPC survival suggesting a specific effect on NPC differentiation. The proneurogenic effect of β2-AR agonists was completely blocked by the selective β2-AR antagonist, ICI 118,551. Pretreatment of NPC with ICI 118,551 was able to block the proneurogenic effect of NE indicating that also NE promotes neuronal differentiation of NPC through activation of β2-AR. In order to investigate the involvement of NF-kB p50 subunit in β2-AR-mediated proneurogenic effects we then tested the effects of NE and β2-AR agonists in presence of a peptide, SN50, that interferes with p50 nuclear translocation. SN50, which alone has no effect, completely blocked NE- and β2-AR agonist-mediated proneurogenic effects.

Altogether these data confirmed that NE and β2-AR agonists are able to promote neuronal differentiation of adult hippocampal NPC *in vitro.* Additionally, they demonstrate that NF-kB p50 signaling lies downstream of β2-AR-mediated proneurogenic effects. At the moment a chronic treatment of adult C57BL/6 mice with selective β2-AR agonist is ongoing in order to evaluate if β2-AR activation is able to promote AHN also *in vivo.* If this will be confirmed we will add novel and important information on the role of β2-AR in the regulation of adult neurogenesis.

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2. Eisch and Petrik, Science, 2012.
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4. Bortolotto et al., Biomed Res Int, 2014.
5. Meneghini et al., Mol Pharmacol, 2014.