A novel pharmacological property for ß$_2$-adrenergic agonists

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Pharmacological modulation of adult neurogenesis is a novel field of investigation with important implications in neurological and psychiatric disorders. In recent years several groups demonstrated that chronic treatment with antidepressants results in increased neurogenesis in the dentate gyrus (DG) of rodents, non human primates and humans, suggesting that this property may contribute to the therapeutic activity of these drugs in depressive disorders (1). Recently our group also demonstrated that other clinically relevant drugs are proneurogenic, suggesting not only that their profile is more complex than expected, but that they may have new therapeutic indications or be used in special patient populations (2,3,4).

We recently demonstrated the presence of serotonin and noradrenaline transporters, as well as of most adrenergic and serotoninergic receptor subtypes, in adult mouse hippocampal neural progenitor cells (NPC). Since noradrenaline (NA) is a potent proneurogenic molecule in vitro (4), we focussed our attention on beta adrenergic (β-AR) receptors, and investigated the contribution of the different receptor subtypes to NA-mediated proneurogenic effects. NPC were incubated, under differentiating conditions, with the selective β_2-AR agonists salmeterol and formoterol, the selective β_3-AR agonist BRL 37344 and the non selective β-AR agonist isoprenaline. Drugs were tested in a range of concentrations correlating with their Ki values for β-ARs. After 24 hours of treatment, we observed that all drugs, except isoprenaline, increased the percentage of mature and immature neurons. Additionally, all drugs had no effect on NPC survival suggesting a specific effect on NPC differentiation. The positive effects of β_2-AR agonists and BRL 37344 on neuronal differentiation of hippocampal NPC were completely abolished in presence of β_2-AR selective antagonist, ICI-118,551 and β_3-AR selective antagonist SR 58611A, respectively. At all tested concentrations none of the drugs exerted effects on the percentage of astrocytes ($GFAP^+$ cells) and oligodendrocyte precursors ($NG2^+$ cells) generated by NPC in culture. Interestingly, preliminary data suggest that different intracellular pathways are involved in the proneurogeneic effects mediated by β_2- and β_3-AR subtypes. Altogether, these data demonstrate that activation of β_2- and β_3-AR positively modulates adult neurogenesis, at least in vitro.

The proneurogenic effects of β_2-AR agonists were also confirmed in vivo. Male adult mice (4-month old) were chronically treated (21 days) with salmeterol (10 μg/kg, s.c.), formoterol (10 μg/Kg and 2 mg/kg, i.p.) or vehicle. For the first five days of treatment, mice were also given a daily dose of bromodeoxyuridine (BrdU; 150 mg/kg, i.p.). Thirty days after the last BrdU administration, in β_2-AR agonist-treated mice we observed a significantly increased maturation of DCX^+ neuroblasts and, more importantly, significantly increased numbers of adult generated neurons ($BrdU^+/NeuN^+$ cells) in the DG, when compared to vehicle-treated mice.

On the basis of these data we propose a novel pharmacological activity for β_2-AR agonists, namely positive modulation of adult hippocampal neurogenesis. Since some, but not all, clinically relevant β_2-AR agonists are able to pass the blood brain barrier, this new property deserves further attention and investigation.

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