SALMETEROL, A SELECTIVE AND LONG-LASTING β2-ADRENERGIC AGONIST, PROMOTES HIPPOCAMPAL NEUROPLASTICITY

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Adult hippocampal neurogenesis (AHN) is a unique form of neural plasticity that results in the generation of new neurons in the dentate gyrus (DG) of most mammalian species, throughout the entire life span. AHN is an extremely dynamic process that is regulated by a variety of environmental and endogenous factors. Moreover, AHN was found deregulated in various neurological and psychiatric disorders, including major depressive disorders (MDD). Preclinical studies indicate that chronic administration of different classes of antidepressant drugs results in enhanced neurogenesis in the adult rodent DG. These observations suggested that AHN may play an important role in the clinical effects of antidepressants and, possibly, the reduced neurogenesis may be involved in hippocampal atrophy associated with depression, supporting the neurogenic theory of MDD. The capability of noradrenaline reuptake inhibitor antidepressants to promote adult neurogenesis may underline the involvement of noradrenaline in the regulation of this process.

Recently, we demonstrated the crucial role of β2-adrenergic receptors (AR) in the proneurogenic effects of noradrenaline in vitro. Based on our preliminary in vitro results, we treated male adult C57BL/6J mice (4-month old) with salmeterol (10 μg/kg s.c.), a long-acting selective β2-AR agonist, or with vehicle for 21 days. Animals were sacrificed 14 days after the last drug administration, and brain tissues were collected. By immunohistochemistry, we quantified the number of doublecortin-immunopositive (DCX+) neuroblasts within the DG, determining also their position within this area. Moreover, using 3D reconstructions, we evaluated the effect of salmeterol versus vehicle on the dendritic morphology of DCX+ cells, using both the classical Sholl analysis and a more complete morphometric characterisation, coupled with a robust statistical analysis.

Our results show that, compared to vehicle, salmeterol elicited a significant increase in the number of DCX+ neuroblasts, together with a redistribution of these cells within the DG. Indeed in salmeterol-treated mice, we found more DCX+ cells with soma located in the granule cell layer, than in the subgranular zone, compared to vehicle-treated mice. In addition, DCX+ cells displayed an increased dendritic arborisation and complexity after salmeterol treatment. Worth of note, we highlighted distinct and region-specific effects of salmeterol on dorsal versus ventral DG.

All together, these data may suggest that salmeterol positively modulates AHN, inducing not only an increase in the amount of DCX+ immature neurons, but an enhancement in their maturation process, in a region-specific manner.

However, to achieve a more complete understanding of the effects of salmeterol on AHN, we plan to evaluate other aspects of AHN, including the maturation and survival of newborn mature neurons in the hippocampal region.