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Characterizing the mode of action of beta-2 adrenergic receptor agonists: A therapeutic agent for Parkinson's disease

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The long acting Beta2 Adrenergic Receptor (β2AR) Agonist salmeterol has been shown to be neuro-protective against the loss of dopaminergic neurons in animal models of Parkinson's disease (PD). Salmeterol was found to work by inhibiting the inflammatory response of microglial cells, a key cell in the pathogenesis of PD. Recently, super-long acting β2AR agonists, vilanterol andindacaterol, have been described, and the objective of this study was to examine the effects of these super long-acting agonists on the inflammatory response of the microglial cell line BV-2, and compare their mode of action to that of salmeterol. We found that the dose-dependent inhibitory action of both indacaterol and vilanterol are similar to that of salmeterol with respects to the production of TNF-alpha by BV-2 cells stimulated with the inflammogen LPS. Conversely, we find that at higher concentrations indacaterol, vilanterol and salmeterol enhance IL-6 production and release by stimulated BV-2 cells, while lower concentrations exert an inhibitory effect on the IL-6 production and release.Furthermore, like salmeterol, indacaterol and vilanterol also exert their inhibitory effecton TNF-α production through the inhibition of NF-kB in a TAK-1 and Beta-arrestin-2-dependent manner. Interestingly, both these b2AR agonists inhibit the classical and alternate pathways of NF-kB, but the kinetics of inhibition vary between pathways. These findings provide further insight into how β2AR agonists work to reverse the CNS inflammation that occurs in Parkinson disease, and may provide a new and more effective therapeutic for PD.

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