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Anti-inflammatory potential of α7 nicotinic receptor silent agonists in human blood immune cells

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ABSTRACT:
Nicotinic acetylcholine receptors (nAChRs) are pentameric ligand-gated ion channels expressed on both neuronal and non-neuronal cells. Recent evidence has shown that agonist binding to α7 subunits can suppress inflammatory responses. Specifically, it is thought that metabotropic signaling of these receptors following activation and channel closing are responsible for the anti-inflammatory properties of nAChRs. The recent development of α7 nAChR specific molecules, referred to as silent agonists, elicit prolonged channel closing with minimal channel activation and are thought to provoke unique nAChR-dependent metabotropic signaling cascades. This study assessed the anti-inflammatory potential of several silent agonists in modulating LPS-induced immune responses in human blood immune cells. Fresh whole blood from healthy volunteers was pre-treated at different time points with silent agonists followed by a 24hr lipopolysaccharide (LPS) stimulation. Cytometric bead arrays (CBAs) were used to quantify the levels of cytokines IL-1β, IL-6, IL-10, IL-12, and TNF-α in sample supernatants. Then, BioPlex phosphoprotein kits were used to measure phosphorylation levels of various signaling pathway proteins (NF-kB, Akt, ERK1/2, STAT1, and STAT3). For this experiment, peripheral blood mononuclear cell (PBMC) cultures and monocytes isolated from PBMCs were treated with a silent agonist during the LPS stimulation (15-120min). Finally, cell phenotyping studies were carried out in PBMC cultures treated with silent agonists and stimulated with LPS (48hrs). The markers CD14, CD16, CCR2, CD36, CD11c, and HLA-DR were studied. We report that the silent agonist pCF3 diEPP significantly downregulated the secretion of pro-inflammatory cytokines and phosphorylation of signaling proteins. We did not observe any significant findings with our cell phenotype studies. Overall, our data show that silent agonists modulate LPS-induced release of pro-inflammatory cytokines and signaling events in human peripheral blood immune cells. Silent agonists selective for α7 nAChRs may thus offer a new therapeutic strategy for the treatment of inflammatory diseases.