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Title: Role of nicotinic receptors in the regulation of cytokines production by human lung macrophages

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Body: Background: In addition to its functions as a neurotransmitter, ACh may also serve as an autocrine/paracrine modulator of pulmonary inflammation. Our aims were to investigate the role of cholinergic receptors in the M1 (proinflammatory) /M2 (immunomodulatory) polarization of lung macrophages (LM). Methods: LM were isolated from human resected lungs challenged for 24hrs with LPS to obtain M1 LM or with IL-13 to obtain M2 LM. Expression of α4/α7 nicotinic ACh receptors (nAChRs), M1-5 muscarinic receptors and cytokines was assessed with RT-qPCR. M1- (TNF-α, CCL3, CXCL8 and IL-6) and M2-cytokines (CCL18, CCL22) were quantified in supernatants. Results: Expression of α7nAChR and M2 and M3 receptors was found in LM. The selective α7nAChR agonist and desensitizing agent GTS-21 (100 µM) inhibited (~65%) the production of M1 cytokines after LPS stimulation and of M2 cytokines after IL-13 stimulation. On the other hand, unstimulated LM in the presence of the α7nAChR antagonist α-bungarotoxin (10µM) showed an increased expression of M1 cytokines at both the transcriptional (5- to 157-fold) and protein level (2.5- to 46-fold), whereas M2 cytokines were not affected. Two agonists with mixed nicotinic/muscarinic activity that do not induce stable α7nAChR desensitization (acetylcholine and carbachol) and the muscarinic antagonists tiotropium and 4-DAMP were devoid of effect. Conclusions: The blockade of α7nAChR in basal conditions favours LM polarization toward the M1 phenotype, whereas ligand-bound, but potentially non-conducting states of α7nAChR in proinflammatory conditions inhibit the production of M1 cytokines. α7nAChR may thus constitute a pharmacological target in lung inflammatory diseases.