DOPAMINERGIC MODULATION OF REGULATORY T LYMPHOCYTES: NEW PHARMACOTHERAPEUTIC TARGETS FOR MULTIPLE SCLEROSIS?

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$CD4^+CD25^+$ regulatory T lymphocytes (Treg) are specialized T cells which play crucial roles in the control of immune homeostasis and are critically involved in immunological diseases, tumor immunity, and transplantation tolerance. We have recently shown that human Treg constitutively express tyrosine hydroxylase, the rate-limiting enzyme in the synthesis of catecholamines, dopaminergic receptors (DRs), α- and β-adrenoceptors (ARs), and contain high amounts of catecholamines stored in reserpine-sensitive compartments. Upon release, endogenous catecholamines (likely DA) subserve an autocrine/paracrine modulatory loop involving the activation of D1-like DRs, leading to impaired suppressive activity of Treg towards mitogen-induced effector T lymphocyte (Teff) proliferation. Candidate agents which may induce the release of catecholamines from lymphocytes include reserpine, type I IFNs, tetrabenazine. Increasing evidence indicates that DA and dopaminergic agents profoundly influence the immune response acting at several levels. DRs are expressed on several lymphocyte subsets, however receptor activity closely depends upon the functional status of the cells (e.g., resting or activated). Upon stimulation, expression and function of DRs may undergo significant changes. Under these conditions, endogenous catecholamines produced by lymphocytes may either directly affect cell survival and apoptosis from within the cell, or they can be released to act upon lymphocytes themselves and/or upon neighbouring cells. DRs (as well as α- and β-ARs) on Teff may also represent the targets for catecholamines released by nearby Treg cells, which might also induce direct activation of nearby Teff, resulting for example in cytokine secretion and integrin-mediated T-cell adhesion to the extracellular matrix (and in turn activated Teff themselves may represent local sources of DA acting upon Treg and finally resulting in downregulation of their inhibitory function). Autoimmune disease seems to be associated with altered brain dopaminergic neurotransmission in animal models, as well as with impaired dopaminergic mechanisms in peripheral lymphocytes, in particular in multiple sclerosis (MS) patients. Interestingly, IFN-β, which is the mainstay for MS pharmacotherapy, in human lymphocytes profoundly affects endogenous catecholamines and restores dopaminergic signalling. In a longitudinal study in MS patients on IFN-β we are presently investigating dopaminergic function in circulating Treg. A wide array of dopaminergic agents with a usually favourable therapeutic index is currently used for various clinical indications. In-depth characterization of dopaminergic mechanisms modulating human lymphocyte function could thus provide the rationale for the therapeutic use of dopaminergic agents as novel drugs in MS (as well as in a wide number of other immune-related disease conditions).