NEURAL-IMMUNE-EFFECTOR (NIE) CROSS-TALK SN VASCULAR TROPHOBIOLOGY: PROPOSAL FOR NEW AND NOT YET EXPLOITED PURINERGIC REGULATORY MECHANISMS

H In a state-of-the-art approach, Dr. Hass6ssian (1) presents purinoceptor-mediated vasoconstriction/vasodilation mechanisms of the pulmonary circulation. He focuses on P2 purinoceptors of smooth muscle cells, endothelial cells, platelets and mast cells, without addressing P1 (adenosine) purinoceptors.

Recently, the Burnstock's purinoceptorology (1, his Refs 3, 7, 10-12, 33, 35, 45, 46, 48, 51, 66, 70, 71, 76, 78, 100, and two personal communications) is "arborizing" into a variety of members of P- and P2 purinoceptor families classified by the International Union of Pharmacology (1, his Ref 12).

Here we would like to add some possible, new and not yet exploited, purinergic regulatory mechanisms to the Hass6ssian's work (see 1, his Fig. 3). Accordingly, we shall briefly focus on the involvement of connective tissue (adventitial) mast cells (Fig. 1) and their interactions with perivascular nerves and medial smooth muscle cells.

**Figure 1.** Biological active substances released from the activated connective tissue mast cell. The mast cell is a receptor-bearing cell, which releases plasma membrane-derived lipid mediators, preformed secretory granule-stored mediators, and newly synthesized cytokines, including nerve growth factor (NGF). IL - interleukin, LT- leukotriene, PG-prostaglandin, PAF-platelet activating factor, 5-HT- 5-hydroxytryptamine, GM-CSF - granulocyte-macrophage colony-stimulating factor, TNF - Tumor necrosis factor, ATP - adenosine-S'-triphosphate, NO - nitric oxide. This figure is an enriched version of Fig. 1 of Huang (36).
Recent studies show that (i) mast cells and other immune cells occur in close proximity to nerves (2-7), (ii) neurotransmitters, including ATP (1,8,9) and adenosine (10), induce mast cell degranulation, (iii) picomolar doses of substance P (SP) result in "priming" of mast cells (11), (iv) activated macrophages induce NGF synthesis in Schwann cells (12), (v) mast cells synthesize, store, and release NGF.

**Figure 2.** A schematic representation of the hypothetical involvement of neural-immune-effector (NIE) components in vascular trophobiological cross-talk, with special reference to some purinoceptor-mediated processes. Stimuli acting on perivascular sympathetic, purinergic, parasympathetic and/or sensory nerves produce the corresponding release of noradrenaline (NA), neuropeptide Y(NPY), ATP, adenosine (A), 5-HT, SP, vasoactive intestinalpolypeptide (VIP),calcitonin-gene-relatedpeptide (CGRP) and/or other neurotransmitters andneurornodulators(1). They act on two types of target cells: adventitial mast cells and medial smooth muscle cells, resulting in mast cell activation (2) and regulation of vascular tone, respectively. According, a dual neurotrophic effect of NGF released from these target cells is depicted (thick arrows). Also shown are the effector cell-derived NGF acting on the mast cell as a degranulator (3) and TNFα (Ref29) acting as a possible inducer of mast cell NO production (Ref30). Noteparacrinefeedback loops created at the vascular adventitia. Other immune cells, such as macrophages and lymphocytes, and fibroblasts, are not placed in the adventitia. Their possible involvement in NIE trophobiological cross-talk should also be kept in mind (Refs 5,6,12,23,31-34, and note Ref 35, where Burnstock wrote "that a recent observation in our laboratory that may open new areas of research concerns a novel interaction between mast cell and endothelial cell andfibroblasts ").
Neural-immune-effector cross-talk

S. Ramón y Cajal (hypothesis de la quimiotaxis, 1892)
R. Levi-Montalcini and G. Levi (1943)
V. Hamburger and R. Levi-Montalcini (1949)
S. Cohen (1960)
G. Burnstock et al
D. Parves et al
H. Thoenen et al
GW Kreutzberg et al

L. Aloe and R. Levi-Montalcini (1977)
J. Bienenstock et al
H. Thoenen et al
V. Dimitriadou et al

Figure 3. A brief chronology of the ideogenesis of trophobiological concepts; neural-effector (NE), neural-immune (NI), and neural-immune-effector (NIE). Also shown are the names of the pioneering authors in trophobiology. From (23); see also 7, 12-20, 21, 24, 31-35, 37 and Refs therein.

(13) and possess NGF receptors (14) and opiate/opioid receptors (15 and Refs therein), (vi) NGF stimulates histamine release from mast cells (14), (vii) NGF affects non-neuronal cells thus being involved in inflammatory and immune responses, and growth/differentiation of mast cells and other immune cells (14, their Table 1), i.e. acts both as neurotrophin and immunotrophin, (viii) mast cell tryptase is involved in the processing of atrial natriuretic peptide (16), and, last not least, (ix) mast cells synthesize a NO-like substance (17-19); see also 1, his Refs 5, 6, 110-114 for ATP effects on mast cells and other immune cells.

Inserting such immune logic (say "I") data to the classical vascular neurotrophic concept (nerve-effector, say "NE", bidirectional interactions; 20-22), we (6) have recently proposed a NIE cross-talk hypothesis in vascular trophobiology (Fig. 2). It also appears to be a new and not yet exploited area in general trophobiology (Fig. 3). Note that NIE may also mean neural-immune-endoctrine in a sense of neuroendocrine-immune interactions that are more studied (13, 14, 24, and Refs therein) than the NIE cross-talk herein discussed.

We hope that further studies on NIE trophobiological hypothesis may have some potential implications in the pathogenesis of human diseases (10, 12-15, 23-28, and 1, his Refs 5, 6, 110-118) and in the development of, for example, new selective P₁ (10) and P₂ (1) purinoceptor and histamine H₃ receptor (7) agonists or antagonists for their therapies.

In direct reference to the pulmonary circulation purinergic regulation (1), we would like to address the following "NIE" questions: (i) may mast cell production of NO (17, 19, 38, see also Fig. 2) induce vasodilation as an ATP-induced NO release from endothelial cells does it (1), and (ii) how the purinergic vasomechanisms of the pulmonary circulation operate in mast cell-deficient W/W mice (25)?

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