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EDITORIAL

NEURAL-IMMUNE-EFFECTOR (NIE) CROSS-TALK SN VASCULAR TROPHOBIOLOGY: PROPOSAL FOR NEW AND NOTYET EXPLOITED PUR1NERGSC 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 P_2 purinoceptors of smooth muscle cells, endothelial cells, platelets and mast cells, without addressing P_1 (adenosine) purinoceptors.

Recently, the Burnstock's purinoceptorology (1, his Refs 3,4,7,10-12,33,35,45,46,48,51,66,70,71, 76,78,100, and two personal communications) is "arborizing" into a variety of members of P: and P_2 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.

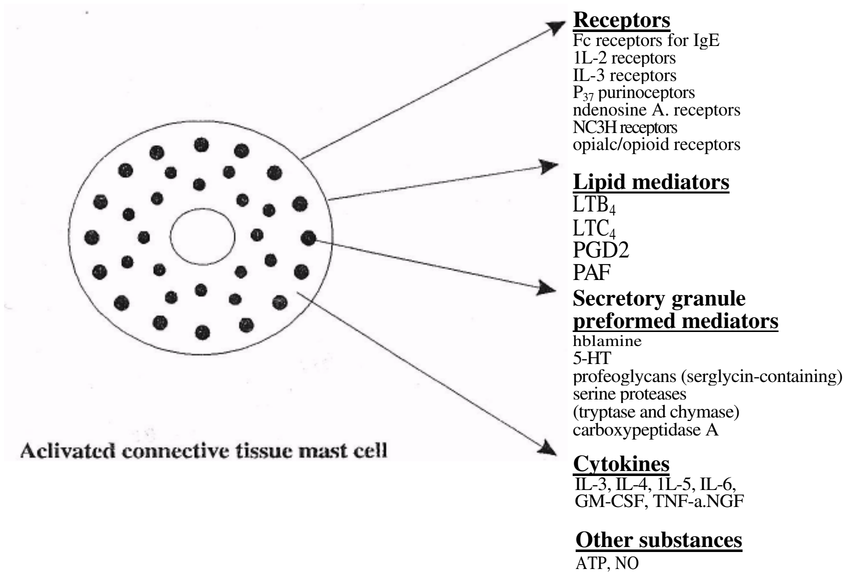


Figure 1. *Biological active substances released from the activated connective tissue mast cell. The mast cell is a receptor-bearing cell, which releasesplasmalemma-derivedlipid mediators, preformed secretory granule-stored mediators, and newly synthesized cytokines, including nerve growth factor (NGF). IL - interleukin, LT- leukotriene, PG-prostaglandin, PAF-platelet activating factor, 5-HT- 5-hydroxytriptamine, 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

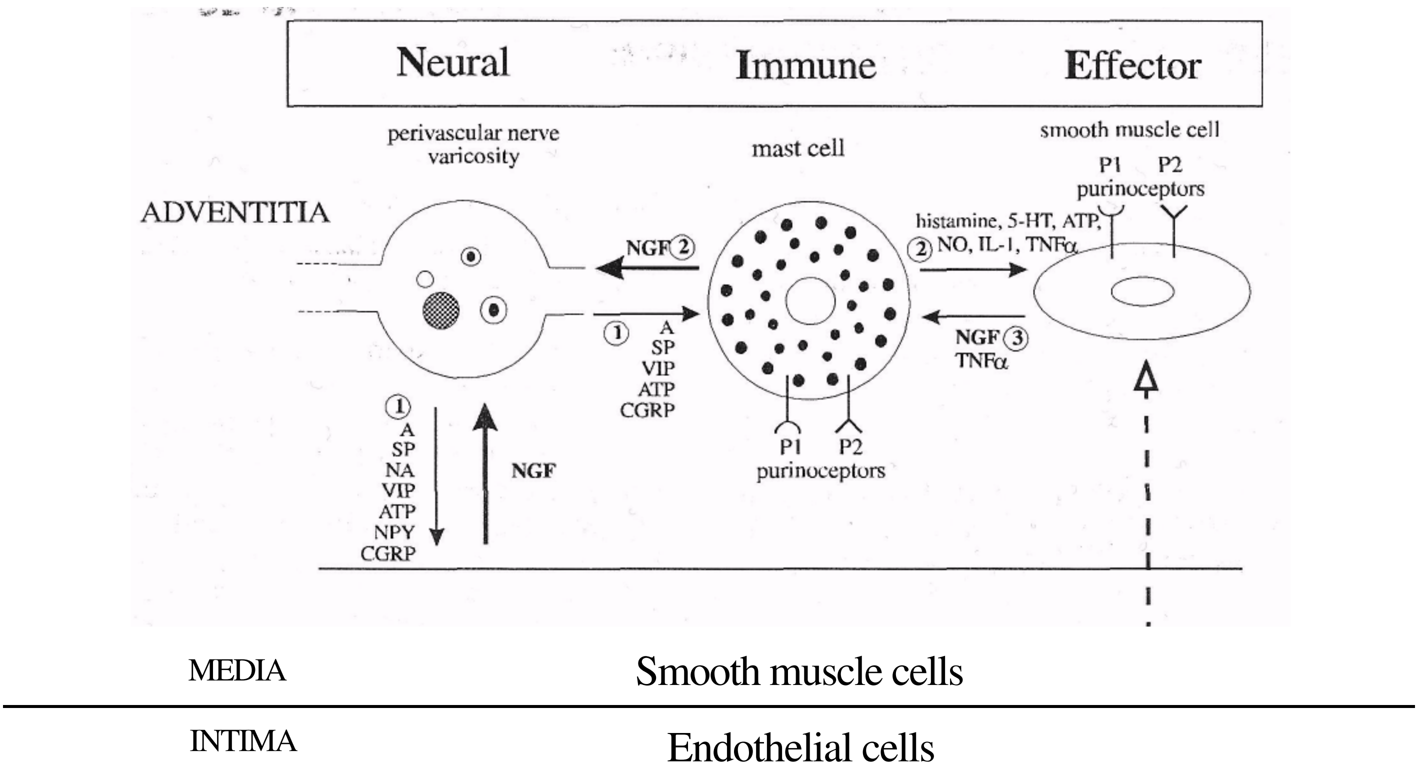
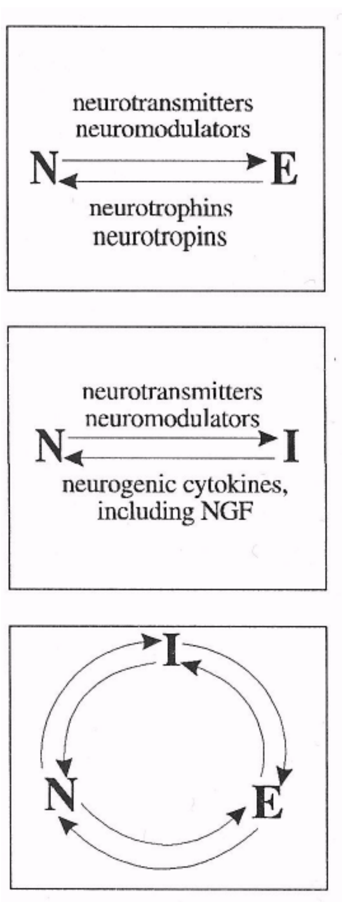


***Figure** 2. A schematic representation of the hypothetical involvement of neural-immune-effector (NIE) components in vascular trophobiological cross-talk, with special reference to some purinoceptor-mediated processes. Stimuli acting on perivascular sympathetic, purinergic, parasympathetic and/or sensory nerves produce the corresponding release of noradrenaline (NA), neuropeptide Y(NPY), ATP, adenosine (A), 5-HT, SP, vasoactive intestinalpolypeptide (VIP),calcitoningene-relatedpeptide (CGRP) and/or other neurotransmitters andneurornodulators(l). 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 TNFcc (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 ").*



S.Ram6n y Cajal (hypdtesis 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-Montalcin (1977)
J.Bienenstock et al
H. Thoenen et al
V.Dimitriadou et al

Figure 3. *A brie/chronology of the ideogenesis oftrophobiological 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 7,12-14,20,21,24,31-35, 37and 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. 5,6,17,109-114 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-endocrine 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 5,6,115-118) and in the development of, for example, new selective P_t (10) and P_2 (1) purinoceptor and histamine H_3 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^V mice (25)?

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REFERENCES

1. Hass6sian HM. Old, new and not yet exploited purinergic vasomechanisms of the pulmonary circulation. Biomed Rev 1994; 3: 11-25

2. Crivellato E, Darmiani D, Mallardi F, Travan L. Suggestive evidence for a microanatomical relationship between mast cells and nerve fibers cantaining subtance P, calcitonin gene-related peptide, vasoactive intestinal polypeptide, and somatostatin in the rat mesentery. Acta Anat 1991; 141: 127-131

3. Blennerhassett MG, Tomioka M, Bienenstock J. Formation of contacts between mast cells and sympathetic neurons in vitro. Cell Tissue Res 1991; 265: 121-128

4. Reynier-Rebuffel A-M, Callebert J, Dimitriadou V, Mathiaau P, Launay J-M, Seylaz J, Aubinean P. Carbochol induces granular cell exocytosis and serotonin release in rabbit cerebral arteries. Am J Physiol 1992; 262: R105-R111

5. Chaldakov GN, Andrew T, Burnstock G, Cowen T. An ultrastructural study of ageing in perivascular nerves and mast cells of the rat.[abstract]. J Neurol 1992; 239 (Suppl 2): 127S

6. Chaldakov GN, Andrew T, Burnstock G, Cowen T. The vascular adventitia: neural-immune-effector (NIE) link - a triarchic model of trophic interactions [abstract]. 11-th Natl Cong Anat Histol Embryol, September 1993, Sofia, Bulagria, 13A

7. Dimitriadou V, Rouleau A, Tuong MDT, Newlands GJF, Miller HRP, Luffau G, Schwartz J-C, Garbarg M. Functional relationship between mast cells and C-sensitive nerve fibers evidenced by histamine H3-receptor modulation in rat lung and spleen. ClinSci 1994;87:151-163

8. Burnstock G. Mechanisms of interaction of peptide and nonpeptide vascular neurotransmitter system. J Cardivasc Pharmacol 1987; 10(Suppl 12): S74-S81

9. Burnstock G. Vascular control by purines with emphasis on the coronary system. Europ Heart J 1989; 10(Suppl F): 15-2

10. Linden J. Cloned adenosine A3 receptors: pharmacogical properties, species differences and receptor functions. Trends Pharmacol Sci 1994; 15: 298-306

11. Janiszewski J, Bienenstock J, Blennerhassett MG. Picomolar doses of substance P trigger electrical responses in mast cells without degranulation. Am J Physiol 1994; 267: C138-C145

12. Heumann R, LindholmD, Bandtlow Ch, Meyer M, Radeke MJ, Misko TP, Shooter E, Thoenen H. Differentical regulation of mRNA encoding nerve growth factor and its receptor in rat sciatic nerve during development, degeneration, and regeneration: role of macrophages. Proc Natl Acad Sci USA 1987; 84: 8735-8739

13. Leon A, Buriani A, Toso RD, Fabbis M, Romanello S, Aloe L. Mast cells synthesize, store, and release nerve growth factor. Proc Natl Acad Sci USA 1994; 91: 3739-3743

14. AloeL, AllevaE, RicceriL. Mast cells, NGFand neurobehavioural regulations in developing and adult mice. In: Husband AJ, editor, Psychoimmunology. CNS-Immune Interactions. CRC Press Boca Raton, Ann Arbor, London, Tokyo 1993; 51-63

15. TungelN. Mast cells, vasoactive intestinal peptide (VIP), and the hemorrhagic shock: a pos-

sible relationship? Biomed Rev 1993; 2 :37-46

16. Proctor GB, Chan K-M, Garrett JR, Smith RE. Proteinase activities in bovine atrium and the possible role of mast cell tryptase in the processing of atPdi natriuretic factor (ANF). Comp Biochem Physiol 1991; 99B: 839-844

17. Salvemini D, Masini E, Anggard E, Mannaioni PF, Vane J. Synthesis of nitric oxide-like factor fromL-arginineby rat serosal mast cells: stimulation of guanylate cyclase and inhibition of platelet aggregation. Biochem Biophys Res Commun 1990; 169: 596-601

18. Masani E, Mannaioni PF, Pistelli A, Salvemini D, Vane J. Impairment of the L-arginine-nirric oxide pathway in mast cells from spontaneously hypertensive rats. Biochem Biophys Res Commun 1991; 177: 1178-1182

19. Masani E, Salvemini D, Pistelli A, Mannaioni PF, Vane JR. Rat mast cells synthesize a nitric oxide-like factor which modulates the release of histamine. Agents Actions 1991; 33: 61-63

20. Purves D, Snider WD, Voyvodic JT. Trophic regulation of nerve cell morphology and innervation in the autonomic nervous system. Nature 1988; 336: 123-128

21. Head RJ. Hypernoradrenergic innervation: its relationship to functional and hyperplastic changes in the vasculature of the spontaneously hypertensive rat. Blood Vessels 1989; 26: 1-20

22. Chaldakov GN, Andrews T, B urnstock G, Cowen T. An ultrastructural study of ageing in cerebral blood vessels: accumulation of neurofilaments and muscle basal lamina in old age [abstract]. Neurosci Lett 1992; 42(Suppl): S28

23. Chaldakov GN. *Textbook of Cell Biology.* 1995, In press (in Bulgarian)

24. Levi-Montalcini R. The nerve grouth factor 35 years later. Science 1987; 237: 1154-1162

25. Johnson D, Yasui D, Seeldrayers P. An analysis of mast cells in the rodent nervous system: numbers vary between different strains and can be reconstituted in mast cell-deficient mice. J Neuropath Exp Neurol 1991; 50: 227-234

26. Tuveri MA, Passiu G, Mathieu A, Aloe L. Nerve growth factor and mast cell distribution in the skin of patients with systematic sclerosis. Clin Exp Rheumatol 1993; 11: 319-322

27. AloeL,ProbertL,Kollias G,Bracci-LaudieroL, Spillantini MG, Levi-Montalcini R. The synovium of transgenic arthritic mice expressing human tumor necrosis factor contains a high level af nerve growth factor. Growth Factors 1993; 9: 149-155

28. Ghenev P, Krasnaliev I, Chaldakov G. Human atherosclerosis: comparative study of mononuclear infiltration in aorta, coronary and cerebral arteries [abstract]. Proceedings of NATO Advanced Institute Meeting, Crete, Greece, June 1994; In press

29. Warner SJC, Libby P. Human vascular smooth muscle cells: target for and source of tumor necrosis factor. J Immunol 1989; 142: 100-109

30. Kilbourn RG, Gross SS, Jubran A et al. N^G methyl-L-arginine inhibits TNF-induced hypotension: implications for the involvement of nitric oxide. Proc Natl Acad Sci USA 1990; 87: 3629-3632

31. Lindholm D, Heumann R, Mayer M, Thoenen H. Interleukin-1 regulates synthesis of nerve growth factor in non-neuronal cells of rat sciatic nerve. Nature 1987; 330: 658-659

32. Rameshwar P, Gascon P, Ganea D. Immunoregulatory effects of neuropeptides. Stimulation of interleukin-2 production by substance P. J Neuroimmunol 1992; 37: 65-74

33. Yoshida K, Gage FH. Cooperative regulation of nerve growth factor synthesis and secretion in fibroblasts and astrocytes by fibroblast growth

factor and other cytokines. Brain Res 1992; 569: 14-25

34. MuraseK, Murakami Y, TakayanagiK, Furukawa Y, Hayashi K. Human fibroblast cells sinthesize and secrete nerve growth factor in culture. Biochem Biophys Res Commun 1992; 184: 373-379

35. Burnstock G. Neurohumoral control of blood vessels: some future directions. J Cardiovas Pharmacol 1985; 7 (Suppl 3): S137-S146

36. Huang R. Characterization and expression studies of mast cell granule components. Comprehensive Summaries of Uppsala Dissertations from the Faculty of Medicine 440, Acta Universitatis Upsaliensis, Uppsala, Sweden, 1993;9

37. Angelov DN, Neiss WF. Neuronal recovery after peripheral traumatic lesions of the facial motor nerve. Biomed Rev 1994; 3: 39-53

38. Murthy KS, Zhang K-M, Tin J-G, Grider JR, Makhlouf GM. VIP-mediated G protein-coupled Ca^{2+} influx activates a constitutive NOS in disprersed gastric muscle cells. Am J Physiol 1993; 265: G660-G671