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EDITORIAL

LEYDIG CELL-IMMUNE CELL INTERACTION: AN EXAMPLE OF NEUROENDOCRINE-IMMUNE COMMUNICATION IN TESTIS

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"Never before has the pace of change been so great or so widespread; nothing will ever be the same again. What an opportunity!"

Kathleen L. Wishner
Things will never be the same again.
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• In her paper "Tilings will never be the same again" Dr Kathleen L. Wishner (Lilly Corporate Center, Indianapolis, IN) quoted Alvin Toffler's book *Future Shock* written in 1970. Toffler defined "future shock" as a time phenomenon, a product of the greatly accelerated change in society. The scientific research itself is a demonstration of this accelerated change. In particular, data systematized by Davidoff *et al* (1) in this volume of *Biomedical Reviews* indicate the change in the understanding of the nature and origin of Ley dig cells of the human testis.

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Paracrine, autocrine and intracrine mechanisms are obviously important in all organs since they enable the efficient coordination of functions of the different cell types that constitute these organs. The testis needs such mechanisms not only because of the presence of many different cell types, e.g. Leydig cells, Sertoli cells, peritubular myofibroblasts, germ cells, and immune cells, but also because of the changing requirements to coordinate the functions of these cells in a cyclic and time-dependent manner (1,2). Furthermore, all these events have to be coordinated with different body functions. This is accomplished by an interaction between paracrine and endocrine signalling, the Leydig cell being a component of the hypothalamic-pituitary-gonadal axis.

Using antibodies directed against a large panel of neuronal and neuroendocrine marker substances, Davidoff *etal* (1) provide conceptual evidence strongly suggestive of a dual, endocrine and neuroendocrine nature and of a neural crest origin of human Leydig cells. Thus these authors propose Leydig cells as a new member of the diffuse neuroendocrine system.

Recently, the bidirectional interaction between the neuroendocrine and immune systems is a subject of intensive research (3-8). The reasons for this are: (/) cytokines as well as neurotrophins and neuropeptides are mediators of both neural and immune responses, (/'/') neuroendocrine and immune cells have common receptors for hormones, cytokines, neurotrophins, and neurotransmitters, and (/'//') immune cells produce over 20 different neuroendocrine peptides (5,8) and neurotrophins. Also, cytokines exert pronounced endocrine effects on the hypothalamic-pituitary-adrenocortical axis (6,8) and the hypothalamic-pituitary-gonadal axis (4, 6, 9).

Collectively, these findings (3-8), Davidoff and colleagues' data (1 and Refs therein) and the recent results about Leydig cell-immune cell interactions (9-16) suggest that a local neuroendocrine-immune link may exist within the testis. The Leydig cell-macrophage interaction in rodent testis was described (10-12), suggesting a role of testicular macrophages in both regulation of Leydig cell functions and promotion of Leydig cell development. Yet another part of this testicular neuroendocrine-immune cross-talk is the possible involvement of Leydig cells in estrogen-induced mast cell proliferation in the rat testis, where Leydig cells are proposed to regulate interstitial mast cells proliferation *via* negative paracrine way (13-15). Indeed, Leydig cell express and/or secrete regulatory modules (1, 4, 6, 9), with both activating and inhibitory effects on testicular immune cells. For example, the Leydig cell-derived substance P, vasoactive intestinal polypeptide and (3-endorphin (1) may affect mast cell activity (16, 17) and T cell proliferation (6, 8). Recently we observed mast cell increase in the heart after suppressing the Leydig cells by estrogen treatment of newborn rats indicating that Leydig cells also influence extratesticular immunocytes *via* negative endocrine way (15). Not surprisingly, mast cells and Leydig cells were described to proliferate simultaneously in the testis after selective Leydig cell destruction by ethane dimethane sulfonate (11, see also 1 and Refs 45, 65 therein). Hence, it worths to examine whether mast cell-derived neurotrophins, e.g. nerve growth factor (18) and leukemia inhibitory factor (19), exert some influence on Leydig cells.

Altogether these data would suggest that the Leydig cell-immune cell link is an example of neuroendocrine-immune communication in testis (Fig. 1). We realize that the rapidly developing tale of this interaction warns us that generalization may be premature, and it is better to conclude that there is an *opportunity* here for (/) additional data (31), (/';') new interpretations of hitherto unexplained, "neurotrophic" facts (32-34, see also 1 and Refs 218, 219 therein), and *(Hi)* broadening the international scientific community involved in this research field

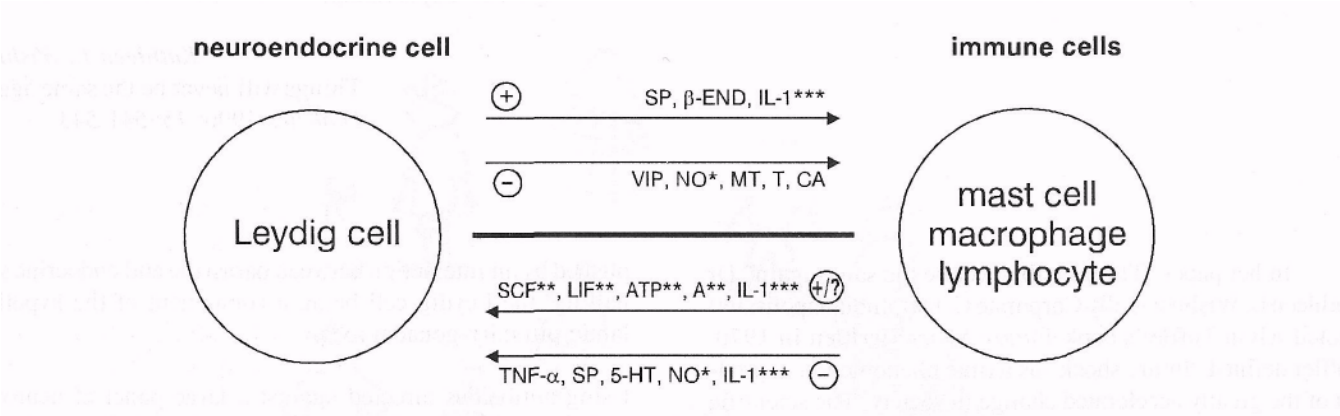

Figure 1. Suggested bidirectional paracrine links bet\veen neuroendocrine and immune cells in the testis. A possible cross-talk behveen Leydig and immune cells via neuroendocrine peptides produced by these cells (1, 5, 8), herein depicted /?-endorphin (fi-END) (16, 17) only, should also be considered.

** effects of nitric oxide (NO) on immune cells (20) may also be depicted in Fig. 11 of Davidoff et al (21), illustrating schematically the possible functional significance of Leydig cell-produced NO.*

*** as found for nerve growth factor receptors (1), we suggest that the receptors for these neurotrophic cytokines (19, 22, 23) as well as some purinoceptors (24, 25) may also be considered in further studies of Leydig cells.*

**** note that interleukin-1 (IL-1) stimulates Leydig cell proliferation and inhibits steroidogenesis (6), and induces histamine release from mast cells (26) and neuropeptide Yexpression in Leydig cells (1, their Ref 137; see also 1, their Ref 119 for Leydig cell-derived IL-1).*

Other abbreviations and respective references: SP - substance P (1, 16, 17, 19), VIP - vasoactive intestinal peptide (6, 16, 17), MT - melatonin (27), T - testosterone (7), CA - catecholamines (28), SCF - stem cell factor (mast cell growth factor, c-kit ligand) (22), LIF - leukemia inhibitory factor (19, 23), TNF-a-tumor necrosis factor-a (10, 19, 29), 5-HT - 5-hydroxytryptamine (serotonin) (30), ATP - adenosine 5'~triphosphate (24, 25), A - adenosine (24, 25).

(35). These may have some therapeutic potentials for diseases of the male reproductive organs (1, 30, 36, 37).

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