

DANCE ROUND



WE DANCE ROUND IN A RING AND SUPPOSE, BUT
THE SECRET SITS IN THE MIDDLE AND KXOII'S.

ROBERT FROST

A SUGGESTIVE NEUROTROPHIC POTENTIAL OF MAST CELLS IN HEART AND SUBMANDIBULAR GLANDS OF THE RAT

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• According to the neurotrophic theory (1), the nerve growth factor (NGF) is widely distributed in the effector tissues of peripheral sympathetic and sensory neurons, suggesting that the density of innervation is controlled by effector-derived NGF. Sympathetic neurons require access to NGF for survival throughout life, whereas sensory neurons are dependent on NGF only during restricted period of embryonic development (1). This development-related feature of sympathetic neurons suggests that they crucially depend on plasticity of NGF biology, including secretion, availability, and utilization, to maintain appropriate neuronal function in adult life, and even in old age. While most previous studies on the cellular source of NGF have focused on neuronal and nonneuronal effector cells, it was recently demonstrated that NGF secretion is not only restricted to cells receiving a direct innervation. Immune cells, including mast cells (MC), lymphocytes and macrophages, for example, produce and release NGF (2,3) as well as NGF secretion-inducing cytokines (4,5). Likewise, since the first evidence that NGF treatment causes a significant increase in the number and size of MC has been published by Aloe and Levi-Montalcini in 1977 (6), it has been repeatedly shown that these cells are also NGF-responsive cells (4,5,7), thus providing further evidence for a widely investigated MC-nerve interaction (4,5). Further on this trophobiological line, a

positive correlation of the amount of NGF and expression of mRNA^{NGF} with the density of sympathetic innervation was demonstrated in a variety of organs (8-10). In the rat heart, one such example, the atrium contains a higher amount of NGF corresponding to a denser sympathetic nerve supply compared to the ventricle. Such a correlation was also revealed in the submandibular glands (SMG) and iris (8). Likewise, the density of MC in the ankle joint capsule, which is heavily innervated, is greater than in the capsule of the knee, which is less densely innervated, and the MC number in the synovial joint of spontaneously hypertensive rats, which have increased sympathetic nerve supply, is significantly greater than in normotensive rats (11). A summing-up of the above mentioned data shows that (i) MC are NGF secreting/responsive cells (2,3,5-7) and frequently colocalized with nerves (4,5), and (ii) a higher NGF amount correlates with a denser sympathetic innervation of a tissue (8-10). This, in our eyes, brings into question the sole contribution of the "classical" effector cells to neurotrophic support of sympathetic nerve-innervated tissues. Consequently, we suggest that MC, through their own and/or cytokine-induced NGF secretion, may also be implicated in the neurotrophic potential in these tissues. As a first approach towards verifying this latter hypothesis, we examined by light microscopy the number of toluidine blue-positive MC in sections obtained from formalin-fixed, paraffin-embedded hearts (12) and SMG of rats (n=10). The heart ventricles serving as a "control" tissue displayed the lowest content of NGF and the lowest density of sympathetic nerves (8) among the tissues studied. Our study showed that the number of MC/mm² in heart atria (5.0 ± 0.5) and SMG (10.1 ± 0.7) was significantly (p<0.01) greater than in heart ventricles (2.1 ± 0.1), thus revealing a positive correlation with the NGF level and sympa-

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thetic nerve density found in these tissues (8). These observations appear to be suggestive of some neurotrophic potential of MC in the heart and SMG of the rat. Recent findings demonstrate that (i) remodeling of intestinal mucosal nerve fibers in response to intestinal inflammation is associated with MC accumulation (13), and (ii) decreased density of sympathetic innervation (10) correlates with both numerical decrease of adventitial MC (14) and degenerative changes of smooth muscle cells (15) in cerebral arteries of old rats. These findings are consistent with the present hypothesis. Beginning with the original studies of Levi-Montalcini and Cohen which led to the discovery of NGF in the early 50s (1), it is known that the largest amount of NGF is secreted, both in saliva and bloodstream, by the convoluted tubular cells of the adult male mouse, and that NGF concentration is 10 fold higher in male than in female glands. Hence we aimed at evaluation of whether this sexual dimorphism may also involve the numerical presence of MC. In our ongoing study, no significant difference has yet been found in the number of MC in male as compared with female mouse SMG. Further, since MC are also NGF-responsive cells, there is a possibility that the greater number of these cells in both SMG and heart atria than in heart ventricles may be a result of the significant difference in the amounts of effector-derived NGF, as shown in the respective tissues (8). Also to be considered is an autocrine-positive feed-back mechanism induced by MC-derived NGF (3,5,7), and a possible trophic effect of sympathetic nerves on MC density (11). The functional significance of such effector-to-MC, MC-to-MC, and nerve-to-MC trophic interactions (16) remains, however, to be defined. Further studies in other tissues which also receive a dense sympathetic nerve supply, such as adipose tissue (17), may prove to be useful. Intriguingly, recent experiments on sympathetic nerves in aging rats demonstrate that the extracellular matrix component, laminin, may act in synergy with NGF to regulate neuronal growth and survival in maturity (18,19). Whether the MC-laminin interaction that was recently demonstrated (20,21) may be implicated in such a neurotrophic action is at present unknown. Accordingly, studies using mast cell-deficient mice and their reconstituted variants (22), as well as transgenic animals, either overexpressing or deficient in laminin, could also prove to be useful models in further investigations of MC-nerve interactions in health and disease. At present, however, a suggestive neurotrophic potential of MC, which may constitute an important player in these interactions, remains a "secret sits" in the sympathetic nerve-innervated tissue "and knows" (fig. 1).

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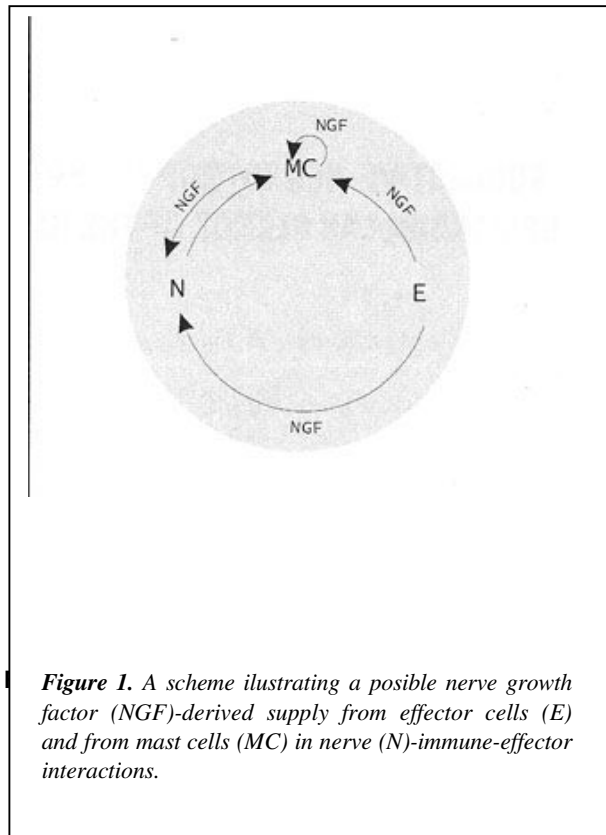


Figure 1. A scheme illustrating a possible nerve growth factor (NGF)-derived supply from effector cells (E) and from mast cells (MC) in nerve (N)-immune-effector interactions.

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