Growth factors

Neuropeptides as mitogens

from Michael R. Hanley

THE current enthusiasm for the study of proliferative growth factors is mostly based on the conviction that they are mitogens, endogenous regulators of cell division. A favourite model for mitogenic signalling is experimentally induced cell division, where both quiescent and normally dividing cell populations are stimulated to divide rapidly and replace damaged tissue. The stimuli for tissue repair are unknown but most speculation has focused on tissue-derived or blood-born mitogens such as platelet-derived growth factor. On page 61 of this issue, however, Nilsson *et al.* report that two related neuropeptides contained in sensory neurones, substance P and substance K, can act as mitogens for connective tissue[1]. This discovery is particularly significant because both peptides may also participate in other aspects of the reaction to injury: sensory signalling and neurogenic inflammation[2]. The discovery has important implications for other peptides found in peripheral nerves and also suggests that neural factors have a previously unsuspected role in the coordination of cell proliferation.

The authors use the standard strategy for identifying potential mitogens; the target cells are isolated in primary culture and the onset of cell division monitored autoradiographically by measuring the incorporation of ^{3}H-thymidine into nuclei after stimulation with the potential mitogen. This permits quantification of responses in a morphologically defined cell population and provides a selective measure of a rapid initial event in mitosis, entry into DNA synthesis. In two connective tissue populations, skin fibroblasts and vascular smooth muscle cells, Nilsson *et al.* show a potent, dose-dependent stimulation of DNA synthesis in the presence of the tachykinin neuropeptides substance P or substance K, but not to another neuropeptide, bombesin.

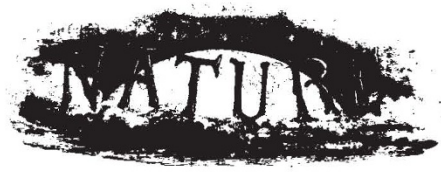
The actions of substance P and substance K seem to be mediated by an authentic tachykinin receptor because their effects are reduced by a specific tachykinin antagonist. Recently, the existence of multiple tachykinin receptors, which may respond to different endogenous peptides, has been suggested[3]. Substance K has a greater potency then substance P, suggesting that a specific subtype of tachykinin receptor[3] is involved in the mitogenic responses, which poses the interesting possibility that the mitogenic effects of tachykinins may be associated uniquely with this class of receptors, and that other cell populations bearing these receptors may also have proliferative responses to tachykinins.

The work of Nilsson *et al.*[1] is the latest contribution to the accumulating evidence that neuropeptides can act as mitogens. For some time, Rozengurt and his colleagues have explored interactions between mitogenic signals in a cell-line model of quiescent cells, serum-starved 3T3 cells. In this system, they have correlated mitogenic activity with the peptides vasopressin[4] and bombesin[5]. Unlike substance P and substance K, however, these peptides have a complicated, possibly synergistic, interaction with other mitogens in 3T3 cells. This difference reflects fundamental differences in the responses of a growth-arrested permanent cell line and a normally quiescent primary culture cell. Nevertheless, the 3T3 model provides a simple prediction that vasopressin and bombesin may be mitogenic for normal cells. Vasopressin has been reported to stimulate DNA synthesis in chondrocytes[6] and bone marrow cells[7]; bombesin, or its mammalian relative gastrin-releasing peptide, can be a growth factor for bronchial epithelial cells[8]. As with the tachykinins, the possibility that these peptides may be endogenous mitogens gains added interest because related peptides occur in mammalian peripheral nerves[9,10], providing ideal local sources.

The tachykinin-stimulated DNA synthesis is neither additive nor synergistic with that elicited by platelet-derived growth factor. In other systems, this observation has been taken as evidence that a common effector mechanism is involved, but it is pertinent to consider whether this explanation is plausible. Elsewhere, the inositol phospholipid pathway, recently delineated in some detail, has been proposed as a common route in the actions of all mitogens[11]. Significantly, the tachykinins, vasopressin and bombesin all stimulate the inositol phospholipid pathway and mobilize cellular calcium, possibly as a direct result of producing the second messenger inositol 1,4,5-trisphosphate, which releases calcium from a non-mitochondrial intracellular pool[11]. Consequently, any receptor acting on the inositol phospholipid pathway may ultimately stimulate cell division. Whether this is a useful generalization for peptides awaits a detailed evaluation of the inositol phospholipid-regulating peptides for their mitogenic activity on target cells. If, as already seems likely, only a subset of such peptide receptors has mitogenic effects, it will be a major challenge to identify any unique aspects of the biochemistry of lipids and second messengers that may correlate with the stimulation of DNA synthesis.

The next logical step will be to evaluate the mitogenic potential of the tachykinins *in vivo*. There are already some preliminary pieces of evidence that strongly support the idea that sensory neurones containing these peptides participate in both normal and stimulated cell growth. A single neonatal dose of capsaicin, the pungent agent of capsicum peppers, permanently destroys a population of sensory neurones that are involved with pain perception and nerve-mediated inflammation[12]. Although this population is chemically heterogeneous, it includes the tachykinin-containing neurones, so neonatal capsaicin treatment provides a method of deleting the cellular influence of tachykinin neurones. Intriguingly, lesions in skin[12] and corneal epithelium[13] frequently result from this treatment. The mechanism of the lesion formation has not been examined in detail but morphological studies suggest that in the cornea the proliferating basal layer of epithelial cells and the normal geometry of cell renewal are severely impaired[12]. Clearly, a specific role for the tachykinins cannot be inferred, but this evidence suggests that a factor from sensory neurones is essential for normal cell turnover in the cornea and, possibly, in the skin.

If corneal damage were to result from the loss of a mitogenic peptide input, could there be a corresponding disorder arising from the local overproduction of a mitogenic peptide? Although skin keratinocytes have not been shown to be targets for tachykinins, there is a large density of tachykinin nerves, presumably of sensory origin, in the basal layers of the epidermis[14], which contains actively mitotic cells that divide to replace the outer layers of skin. Local factors are presumed to regulate keratinocyte proliferation, but little is known about such factors. Psoriasis is a skin disorder in which normal control is lost and the cells proliferate at a greatly increased rate. An expanation for the condition may be that the sensory tachykinins exert a tonic control over normal basal layer cell division, and that, in psoriasis, there is an excessive mitogenic stimulation of keratinocytes. This hypothesis could be conveniently evaluated by the topical use of tachykinin antagonists.



100 Years Ago

REPORTS from Japan state that grave fears were entertained of an outbreak of the long quiescent volcano Fujiyama, and that officials had been sent to investigate the matter. The people living in the neighbourhood believed an eruption to be imminent, because, while the snow on the mountain had begun to melt two months before the usual time, all the wells at the fort became dry, and difficulty was experienced in procuring water. The phenomenon is considered the more remarkable from the fact that the winter has been unusually cold, and that the surface of the snow remains hard, the part nearest the ground being the first to give way. Intelligence has also been received from Java of the eruption of the Semiroo mountain, the most active Javanese volcano.
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