

The Neuroendocrine System, an Opportunity for Immunotoxicologists

by Carroll A. Snyder*

The interrelationship between the neuroendocrine and immune systems was first recognized over 50 years ago. Subsequent investigations have shown that gene products produced by the neuroendocrine system affect the activities of immunologically competent cells. More recent data show that cells of the two systems possess receptors that are identical. Because of these strong interrelationships, it is postulated that compounds that affect the neuroendocrine system will also affect the immune system. It follows that the readily accessible cells of the immune system can be used as surrogates for the less accessible cells of the neuroendocrine system. Moreover, the assays typically used by immunotoxicologists could provide quantitative information regarding dose response, persistence of effects, and surveillance of the extent of exposure for compounds known to be neurotoxicants. Thus, much useful information could be acquired by applying the technique of immunotoxicology to the study of neurotoxicants.

In 1936, Hans Selye published the results of a series of studies which showed that the same sequelae of pathological changes could be produced when rats were exposed to widely diverse stress-inducing agents (1). Repeated acute exposures to physical stressors such as cold temperatures, surgical injury, spinal shock, and excessive exercise induced the same responses as repeated exposures to a number of chemical compounds, including adrenaline, atropine, morphine, and formaldehyde. The responses developed in three distinct stages. The first occurred within 48 hr after the onset of treatment and consisted of a rapid decrease in the sizes of the thymus, spleen, and lymph nodes accompanied by a loss of chromaffin substance and lipid in the adrenals. The second stage occurred shortly after the first and was characterized by greatly enlarged adrenals and hyperplasia of the thyroid. If treatment was continued, there was a transient return to normal appearance and function in the affected organs; however, this was followed by a reappearance of the original responses and ultimately, death. This last phase was considered the third stage of the syndrome. Selye subsequently termed the induction of these diverse physiologic changes "the stress syndrome" (2).

Selye's observations are believed to be the first to clearly show that the organs of the neuroendocrine system and those of the immune system were interrelated. More importantly, from a toxicological perspective, he demonstrated that the same chemical could adversely affect both organ systems.

Selye's findings were an incentive for further studies into the relationship between the neuroendocrine and immune systems. It was subsequently determined that the application of stressors could profoundly affect a number of immune-associated parameters. Among these were susceptibility to Herpes virus, decreased susceptibility to passive anaphylaxis and reduced allograft transplantation immunity [see Wistar and Hildemann (3) for a summary of early studies concerning immunity and stress]. It was further demonstrated that administration of compounds produced by the adrenal cortex such as cortisone and hydrocortisone could mimic the immunosuppressive effects induced by application of stressors (3). Moreover, administration of these compounds could markedly slow the development of spontaneous or X-ray induced thymic lymphoma in mice (4-6). Thus, corticosteroids were found to have profound effects on the activities of both normal and malignant cells of the immune system.

There is now firm evidence that modulation of the immune system by the neuroendocrine system is not mediated solely by corticosteroids. Opioids have been found to be capable of altering a number of responses of both T-cells and natural killer (NK) cells (7-9). Studies with one opioid, β -endorphin, have shown that the immunomodulatory effects of this compound are mediated via specific receptors found on T-cells (7,10). There is evidence that the corticosteroids also modulate the immune response through a specific mechanism rather than by nonspecific cell lysis (11,12). These findings have spurred investigations into the nature of the receptors found on the cells of both the neuroendocrine and immune systems. It now appears that immunologically competent cells possess receptors that are very similar to or perhaps identical to

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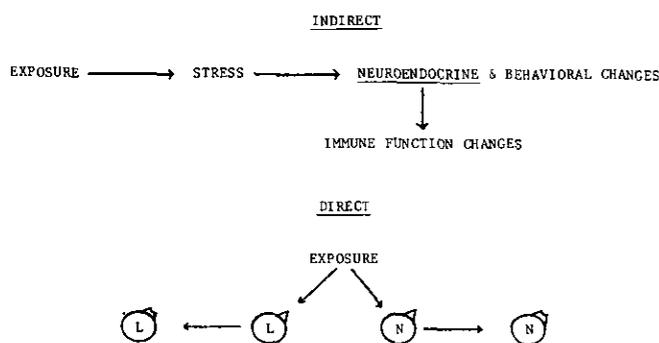


FIGURE 1. Interaction of neurotoxicants with the immune system. Indirect pathway: A compound can affect the immune system by first inducing stress, which, in turn, produces changes in the neuroendocrine system that alter immune function. Immunological assays could be used to monitor quantitative aspects of such exposures. Direct pathway: A compound can interact directly with gene products common to both lymphocytes (L cell) and neuroendocrine cells (N cells). The same type of damage would be produced in both types of cells. Readily accessible lymphocytes can be used as surrogates to assess the molecular damage in the less accessible neuroendocrine cells.

some of the receptors found on neurons and muscle cells (13). For example, the β -receptors long known to be possessed by neurons have recently been found on T-suppressor cells (13).

The interrelationship between the immune and neuroendocrine systems provides an opportunity to apply the quantitative assays routinely employed by immunotoxicologists to the study of compounds that affect the neuroendocrine system. Three areas of study come to mind wherein immunotoxicology assays could be used to assess the activities of neuroendocrine toxicants. The first area concerns exposure to compounds that primarily induce stress that in turn causes alterations of both the immune and neuroendocrine systems (Fig. 1). Such compounds might be termed "indirect neurotoxicants" and might cause stress because of their irritant properties. The neurotoxic effects of such compounds could be monitored by behavioral toxicological assays, but quantitative assessment of their effects such as dose-response information and persistence of effects after exposure might be better assessed by immune function assays.

The second area concerns exposure to compounds that directly alter receptors or other gene products common to cells of both the neuroendocrine and immune systems (Fig. 1). Such compounds might be called "direct neurotoxicants." The more readily accessible cells of the immune system would be useful surrogates for assessing the molecular damage inflicted by direct neurotoxicants on the less accessible cells of neuroendocrine system.

The third area is a variation of the second and consists of using the cells of the immune system for surveillance of the effects of exposure to neurotoxicants. This technique is already being applied to monitor farm workers handling organophosphorus defoliants (14). Although ex-

posures to the defoliants did not induce any clinical effects on the peripheral nervous system, the activity of an esterase common to both lymphocytes and nerve tissue was inhibited by the exposures. Moreover, the extent of inhibition of the activity of the esterase was found to be a function of length and intensity of exposure. Thus, peripheral lymphocytes were used to determine the extent of exposure to compounds known to produce neurotoxicity (14).

In summary, it seems that the application of immune function assays to the study of compounds known to be neurotoxicants would provide much useful quantitative toxicological information as well as continue the study of the interrelationships between the immune and endocrine system described by Hans Selye over 50 years ago.

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