Neuroimmune interactions in stress

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Ever since its publication in a 1936 issue of *Nature*, Hans Selye’s pioneer work ‘A syndrome produced by diverse nocuous agents’ became a cornerstone [1]. This brief, dense report tackled the effects of diverse, nonspecific nocuous stimuli (the *stressors*) on distinct physiological systems, constituting phases of a ‘general adaptation syndrome’. Selye’s work built the foundation for the study of the effects of stress and its associated hormones on brain function, behavior, and immunity, crucial to the establishment of what we now study in neuroimmunomodulation. The literature has then accumulated numerous reports ascribing effects on neuroimmune interactions during health and disease to several experimental stressors. The parameters analyzed include changes in brain activity, animal behavior, and immunity. An overwhelming amount of data has gathered from clinical reports and experimental studies and constituted unequivocal, but sometimes controversial, evidence that supports the biological relevance of stress-mediated neuroimmune interactions in health and disease.

Early studies in this area focused particularly on the suppressive effects of stress on immunity and collectively considered stressors as a single, homogeneous group, since their effects used to be considered stereotyped. Nonetheless, the past decades have witnessed the development of novel neuropsychiatry theories on stress and its role in neuroimmunomodulation. This new conceptual framework accounts for differences in stressors regarding their nature or origin (physical or psychological).
and temporal pattern (acute vs. chronic). Moreover, different parameters of immunity, innate and adaptive, have been assessed, adding complexity and variability to previous reports in the field. Altogether, stress assumed a more intricate position as a putative immunomodulator in a wide variety of biological responses. We review here a series of studies performed in our labs that employed specific stressors and their effects on neurochemistry, behavior and immunity (compiled in Table 1). Our major goal is to bring attention to the necessity of dealing with the nature of stressors as variable, complex entities that may lead to differential neuroimmunological effects.

Employing semi-automated analysis of standard parameters of animal behavior such as motor activity and anxiety, in an open-field arena and in the elevated plus maze, respectively, we have focused on the effects of specific stressors on behavior and immunity (compiled in Table 1). Our major goal is to bring attention to the necessity of dealing with the nature of stressors as variable, complex entities that may lead to differential neuroimmunological effects.

### Table 1. Compilation of results obtained with different stressors on brain activity and chemistry, animal behavior, immunity, and corticosterone levels

<table>
<thead>
<tr>
<th>Stressor</th>
<th>Brain activity</th>
<th>Behavior</th>
<th>Immunity</th>
<th>Corticosterone</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inescapable footshock</td>
<td>↑ NA turnover in hypothalamus</td>
<td>anxiety in EPM</td>
<td>↓ macrophage activity and resistance to Ehrlich tumor</td>
<td>↑ plasma levels</td>
<td>2, 3</td>
</tr>
<tr>
<td>Watch footshock on cage mate</td>
<td>↑ NA turnover in hypothalamus</td>
<td>anxiety in EPM</td>
<td>↓ macrophage activity and resistance to Ehrlich tumor</td>
<td>↑ plasma levels</td>
<td>2</td>
</tr>
<tr>
<td>Prenatal footshock</td>
<td>↑ NA turnover in hypothalamus</td>
<td>anxiety in EPM</td>
<td>↓ macrophage activity</td>
<td>↑ plasma levels</td>
<td>4</td>
</tr>
<tr>
<td>Cohabitation with sick cage mate</td>
<td>↑ NA turnover in hypothalamus</td>
<td>↑ motor activity in OF</td>
<td>↓ neutrophil activity, ↓ DTH, ↓ differentiation of dendritic cells</td>
<td>baseline unchanged</td>
<td>5, 6</td>
</tr>
<tr>
<td>Individual housing</td>
<td>↑ NA turnover in hypothalamus</td>
<td>anxiety in EPM</td>
<td>↓ resistance to Ehrlich tumor</td>
<td>baseline unchanged but ↑ after immobilization</td>
<td>7</td>
</tr>
<tr>
<td>Social subordination</td>
<td>↑ NA turnover in hypothalamus</td>
<td>anxiety in EPM and OF</td>
<td>↓ neutrophil and NK cell activity; ↓ resistance to B16F10 metastases</td>
<td>baseline unchanged but ↑ after immobilization</td>
<td>8</td>
</tr>
<tr>
<td>Chemical stressors</td>
<td>↑ NA turnover and c-fos expression in hypothalamus</td>
<td>anxiety in EPM</td>
<td>↓ neutrophil and macrophage activity; ↓ resistance to infection</td>
<td>↑ plasma levels</td>
<td>9, 10</td>
</tr>
</tbody>
</table>

NA = Noradrenaline; EPM = elevated plus maze; OF = open field; DTH = delayed-type hypersensitivity; ↑ = increase; ↓ = decrease.

With decreased activity of peritoneal macrophages and reduced resistance to the growth of the ascitic Ehrlich tumor. Stress effects on behavior and macrophage activity were not found following escapable footshocks, supporting that coping and manageability over the stressor may change its perception by the animal and therefore its effects [2]. Additionally, when inescapable footshock was associated with a rat model of experimental lung inflammation, the stressor exacerbated the effects of ovalbumin-induced asthma-like signals and increased the number of leukocytes in the bronchoalveolar lavage of allergic rats challenged with the antigen [3].

Prenatal stress has also been studied in the offspring of mice submitted to footshock during late pregnancy [4]. Juvenile mice from dams stressed during gestational days 15–19 displayed increased motor activity, particularly in the central open field, which suggests increased levels of anxiety-like behavior, even in the absence of altered exploration of the elevated plus maze [4]. Prenatal stress leads to decrease in spreading and phagocytosis by macrophages, along with reduction in nitric oxide secretion [4] and increased serum levels of corticosterone [unpubl].

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![Image](https://via.placeholder.com/150)
Communication between conspecifics also plays a role in stress-induced immunomodulation. Mice watching their cage mates receiving footshock, which can be regarded as a natural psychological stressor, showed similar changes in brain function, behavior, and immunity as their companions [2]. Living with a sick cage mate, a putative rodent model for the caregiver situation in humans, also shed some light on the perception of sickness among conspecifics living in a dyad. Cohabitation with a tumor-bearing sick mate induced an increase in total motor activity, along with increased turnover of noradrenaline in the hypothalamus, but no changes in corticosterone [5, 6]. The companions of sick cage mates also have decreased neutrophil activity [5]. Cell-mediated immunity in these mice seems disturbed, with altered phenotype of dendritic cells. While spleen-derived CD11c+ cells show increased expression of CD80 costimulatory molecule, in vitro differentiation of these cells from bone marrow precursors in the presence of GM-CSF, IL-4 and LPS is partially blunted. Delayed-type hypersensitivity to ovalbumin in these mice is deficient, associated with proliferation of a IL-10-secreting lymphocyte subpopulation [6].

Although sometimes still controversial, individual housing (IH) of rodents can lead to high levels of stress. After being housed in groups, mice were IH for 2 or 3 weeks. Corticosterone levels were similar in resting conditions, but peaked higher in IH animals following a single 30-min immobilization session. Additionally, IH mice spent less time in the open arms of an elevated plus maze, an indicative of higher anxiety levels. Moreover, when challenged with the Ehrlich tumor, these animals died slightly sooner than their counterparts, with higher number of tumor cells in their abdomens [7].

From an ethological standpoint, social stressors are extremely interesting and relevant since they tend to reproduce natural situations of life. The biology of dominant and subordinate mice has been focused in some studies from our group. In a stable hierarchy, subordinate mice display more anxiety-like behaviors in the open field and in the elevated plus maze, consistent with increased noradrenaline turnover in the hypothalamus. Furthermore, circulating neutrophils and NK cells from these mice showed decrease killing activity, when compared to cells obtained from their dominant cage mates. Transfer of B16F10 melanoma cells to subordinate mice lead to increased number of metastases in their lungs [8].

Chemically-induced stress has also been employed as a model of neuroimmune disturbance. Mice treated with picrotoxin, a noncompetitive GABA_A receptor antagonist, have increased serum levels of corticosterone, higher turnover of noradrenaline in the hypothalamus, and increased anxiety in the elevated plus maze. Although not as drastic as the changes in immunity during physical stressors, picrotoxin induced a decrease in neutrophil activity [9]. Cyhalothrin, a synthetic type II pyrethroid insecticide, has also been used with a similar purpose by our group [10]. Treated rats display increased anxiety in the open field, increased c-fos expression and noradrenaline turnover in the hypothalamus, increased serum corticosterone levels, and reduced innate immunity [10] leading to diminished resistance to infection.

The balance between circulating levels of cytokines is crucial for regulating immune responses, and failure of this balance usually leads to disease. Since cytokines may have opposing effects in the brain, and their levels can be influenced by the brain directly or not, by adrenaline and glucocorticoids among other stress hormones, stressors may influence this delicate balance and change immunity.

Glucocorticoids seem a common link between the effects of stress on immunity, and in fact, many of the effects on circulating leukocytes described during stress may be ascribed to increased levels of this hormone. Several changes in immunity during stress are lacking in mice treated with methyrapone, reinforcing the role of glucocorticoids.

Nonetheless, there are cases in which immunity is altered during stress in the absence of altered corticosterone levels, pointing to a possible role of catecholamines. Additionally, stressors seem to strongly suppress Th1 adaptive immune responses, while skewing the balance towards a Th2 pattern of cytokine secretion. Glucocorticoids have long been shown to shift this balance, influencing the polarization of naïve T cells, possibly leading to decreased resistance to infections caused by several stressors, particularly in long-term or chronic conditions. However, not all stressors unbalance the Th1/Th2 (more recently Th1/Th17) equilibrium, hence their effects on adaptive immunity may vary, at least slightly.

Ongoing research in our labs focuses on the role of the sympathetic autonomic nervous system (SNAS) on the neuroimmune interactions during stress and also on the pathways and mechanisms that underlie the responses...
described here. We hope to find a complementary response in the SNAS during stress that would support the lack of participation of glucocorticoids in some cases. Also, the model of immune response employed and its parameters included for analysis may lead to different conclusions in regard to the effects of stress on immunity. We believe the body of evidence accumulated from studies performed by several groups, along with our own, supports that the neuroimmune consequences of stress vary according to several factors such as the nature of stressor, its magnitude and duration, onset, and degree of control over the stressor by the stressed animal.

References