Full-length Article

Chronic social stress Ameliorates psoriasiform dermatitis through upregulation of the Hypothalamic-Pituitary-Adrenal axis

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Abstract

Acute stress is a physiological response of an organism to adverse conditions, contributing to survival; however, persistence through time may lead to disease. Indeed, exacerbation of inflammatory conditions such as psoriasis has been reported to follow stressors in susceptible patients. Because chronic stress cannot ethically be elicited in patients under controlled laboratory conditions, we studied genetically modified mice that naturally develop psoriasiform dermatitis, and subjected them to an ethological chronic social contact stress paradigm. Although we found elevated pro-inflammatory neuropeptide production of substance P (SP), calcitonin-gene-related peptide (CGRP) and nerve-growth factor (NGF) mRNA in the dorsal root ganglia (DRG) as well as pro-inflammatory cytokines in response to the social stressor, stress paradoxically prevented the development of the skin lesions. This effect of stress could be reversed by the treatment with glucocorticoid (GC) receptor blockers, suggesting that it was mediated through the upregulation of corticosterone secretion. Extrapolating to humans, the worsening of disease in susceptible patients with psoriasis could be attributed to a defect in the Hypothalamic-Pituitary-Adrenal (HPA) axis with an impaired production of GC during situations of adversity, thus rendering them unable to counteract the pro-inflammatory effects of chronic stressors.

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1. Introduction

Psoriasis, a chronic papulosquamous skin disease afflicting approximately 3% of the US population (Helmick et al., 2014) is associated with increased levels of distress, depression and anxiety (Rieder and Tausk, 2012). Numerous investigators have found emotional stress an aggravating factor for psoriasis (Seville, 1977, 1978; Rieder and Tausk, 2012), but precisely defining the role of stressors has proven complex, mostly because studies have been retrospective, based on patient recollection and thus subject to bias (Farber et al., 1986; Gaston et al., 1991; Farber and Nall, 1993). Assessment of the effects of chronic stressors on disease progression becomes difficult in the absence of controlled laboratory studies, which ethically cannot be performed in humans.

Psychological stress occurs when the environmental demands exceed the perception of the ability of a subject to cope with them (Cooper and Quick, 2017). The term stress as originally coined by Selye (Selye, 1936) represented the organism's ability to adapt to acute perceived challenges with a stage of alarm (fight-flight) (Canon, 1939), followed by adaptation, and finally, a stage of
2. Methods

2.1. Husbandry

Male homozygous FVB-Tg(KRT14-Vegfa)3Dtm/J transgenic mice on an FVB/N background were reared in isolator cages and housed in an AAALAC-accredited, climate-controlled facility (20°C ± 1°C at 50% humidity), with a 12 h light/dark cycle (white lights on from 18:00 to 06:00 h), and fed ad libitum with a commercial diet and water. These mice have been described elsewhere (Poligone, 2012). Briefly the hemizygous FVB-Tg(KRT14-Vegfa)3Dtm/J (Jackson Laboratories, Bar Harbor, ME) were backcrossed to homozygosity of the transgene, establishing a transgenic mouse that develops in 3–6 weeks severe psoriasisform dermatitis in essentially 100% of mice, and thick plaques within a few months, microscopically showing a psoriasisform dermatitis with neutrophilic abscesses (Poligone, 2012). This genetic background has previously been shown to develop an IL-17 dependent psoriasisform dermatitis (Hvid et al., 2008). To differentiate this mouse from the hemizygous mouse, which has a more variable, less penetrant phenotype, established by Detmar et al. (1998), we refer to it as the Rochester mouse. All studies were the approved by the University Committee of Animal Resources of the University of Rochester (UCAR). Animals were housed together, in standard transparent plastic cages four to a cage. They were randomly assigned to their social conditions, and those in the stress group, moved to the experimental room, which was maintained at a constant temperature of 20°C and a 12-h light:12-h dark cycle (white lights on 20:00–08:00 h local time), and procedures conducted under dim red light.

Eight week old CD-1 mice (Jackson Laboratories, Bar Harbor, ME), allowed to acclimate for 2 weeks were subsequently housed in individual cages in the experimental room.

2.2. Mouse treatments

2.2.1. Selection and training of aggressive mice

Male CD1 mice were selected and trained by means of a series of alternative confrontations (Vegas et al., 2004). Two interactions were carried out with intruder-submissive mice, in order to enable subjects to acquire an experience of winning, with confrontations being extended up until the observation of the first defense/flee behavior; and three confrontations were carried out with intruder mice, with confrontations being prolonged only until the first attack was observed. Finally, the most homogeneously aggressive subjects were selected, with attack latencies of less than 10 s.

2.2.2. Chronic sensory social contact stress

Twenty Rochester mice assigned to the stressed group were exposed to the sensory contact social stress model (Kudryavtseva et al., 1991) during a period of 21 consecutive days. Social interaction involved contact with highly aggressive trained and selected CD1 mice (Vegas et al., 2004). During this period of social stress, the experimental subjects were exposed daily to 3 min of agonistic interaction with a different resident dominant CD1 mouse between 8 and 9 AM. The Rochester mice were exposed to a different CD-1 every day for the 21 days. This interchange of pairs prevented mice from becoming habituated to their dominance–submission relationship, and forced them to re-establish it on a daily basis. As a result, the experimental subordinate mice were repeatedly defeated by a different aggressive resident dominant CD1 mouse every day. After each daily confrontation, mice were separated by perforated transparent partitions, located in the same cage in which the confrontation took place (the cage of the dominant CD1 mouse). This permitted the mice to see, hear, and smell each other (sensory contact), but prevented physical contact (outside the 3 min direct confrontation) for a 24 h period. During the direct interactions, although experimental subjects received some bites, no wounds were evident.

2.2.3. Control intact

This group represents the normal development of the psoriasisform dermatitis in Rochester mice, housed in regular cages at a...
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