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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.

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 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

Abbreviations: AD, atopic dermatitis; CGRP, calcitonin gene-related peptide; DRG, dorsal root ganglion; GR, glucocorticoid receptor resistance; HPA, hypothalamus-pituitary-adrenal; NGF, nerve growth factor; PACAP, pituitary adenylate cyclase-activating polypeptide; SP, substance P; TRPV1, transient receptor potential cation channel subfamily V member 1.

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exhaustion, disrupting homeostasis and leading to disease (Selye, 1946). McEwen more recently put forth the concept that the organism strives towards a homeostatic balance termed "allostasis", and the collection of stressors are represented by "allostatic load", which depending on each individual may lead to adaptation or disease. This framework allows us to understand that stressors may be positive or negative depending on the subject's ability to interpret them and cope, depending on the magnitude of the stressor; the psyche, past history, makeup of the individual and the individual response of the Hypothalamic-Pituitary-Adrenal Axis (HPA). Among the latter, the inability to secrete appropriate levels of cortisol would lead to diseased states (McEwen, 1998).

Animal studies have contributed to elucidating the physiologic immune/endocrine underpinnings of either brief or sustained adverse conditions, showing in general that *acute* stressors (minutes to 2–3 h) are beneficial to survival, enhancing cutaneous immune functions, redistributing leukocytes to prevent infections and promoting wound healing; while *chronic* stressors have in general deleterious effects on immunity and immune-surveillance (Dhabhar, 2000; Dhabhar and McEwen, 1997) (reviewed in Dhabhar (2013)). For example, *chronic* restraint stress facilitates UV-induced skin cancers (Parker et al., 2004), whereas *acute* stress promotes resistance to these same tumors (Saul et al., 2005). Although most studies point towards the immunosuppressive role of chronic stress, the effects are not homogeneous, and the results may be contradictory depending on the measured outcomes, the characteristics of the stressor (physical, psychological, controllable or uncontrollable) and the specific characteristics of the studied individual (species, sex, age, diet, submissive or dominant) (Moynihan, 2003; Shi et al., 2003). Murine studies have shown contradictory results when evaluating the effects of stress on the development/worsening of atopic dermatitis (AD); some found that as seen in humans (Wright et al., 2005), prolonged water avoidance stress induced the disease in genetically susceptible mice (Amano et al., 2008), and mediated by the upregulation of substance P (SP) stained cutaneous nerve fibers in mice exposed to sound stress (Pavlovic et al., 2008). More recentlyLin et al. (2014) reported improvement of allergic contact and atopic dermatitis in mice exposed to 18 h of restraint stress. It is important to reiterate that the various animal models of chronic stress (Campos et al., 2013; Avitsur et al., 2009) may show different and sometimes opposing results depending on the nature of the stressor, particularly when comparing physical (restraint, cold water) with social defeat stress. Commonly applied murine physical stress paradigms, such as prolonged restraint, disrupt the circadian rhythms, feeding, drinking and socialization, leading to a situation that is rarely encountered in the animal's life in the wild. Because stress experienced by humans is mostly of social origin (Stress Statistics, 2017), we chose to examine the effects of a chronic defeat stress model (sensory contact social stress), currently considered the one that most resembles the stressors that lead to human psychopathological disorders (Hammels et al., 2015; Bartolomucci et al., 2004) on mice genetically modified to express a psoriasiform phenotype. Paradoxically, contrary to the clinical experience of many patients suffering from psoriasis, who worsen under stress, we found that the stressor mitigated the development of the skin disease in these mice.

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 psoriasiform dermatitis in essentially 100% of mice, and thick plaques within a few months, microscopically showing a psoriasiform dermatitis with neutrophillic abscesses (Poligone, 2012). This genetic background has previously been shown to develop an IL-17 dependent psoriasiform 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 acclimatize 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 psoriasiform dermatitis in Rochester mice, housed in regular cages at a

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