

## Does stress influence the course of rheumatic diseases?

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In daily clinical practice, many doctors as well as their patients believe and have the feeling that psychological stress influences the course of rheumatic diseases. Frequently, psychological stress is perceived to worsen the situation in inflammatory rheumatic diseases. However, not many practitioners would be able to explain to a patient how this might happen in more detail. This short review should provide some more information as to how psychological stress can affect disease activity in patients with rheumatic diseases and how stress might be a pathogenetic risk factor for the disease. Furthermore, this review should also give an idea how diseases such as rheumatoid arthritis (RA) might be treated by psychological interventions.

It is clear that psychological stress, originating in the cortex of the brain, must be converted into somatic signals, which can modulate the immune system or pain perception. These somatic signals typically start off in the highest centres of the autonomic nervous system and the endocrine system, i.e., within the hypothalamus. The hypothalamus has close connections to the limbic system, which is responsible for emotionalization of psychological stress (whether it is perceived as positive eustress or negative distress). A stress response results in release of central nervous and peripheral neurotransmitters (i.e. norepinephrine) and hormones (i.e. cortisol), so that an efferent message is sent from the highest centres of the brain to the periphery. These peripheral mediators can then modulate the immune system or pain perception (focus in this review: on norepinephrine and cortisol). If brain-derived signals increase inflammation or enhance pain perception, then stress is perceived as a worsening factor. Five factors are of outstanding importance for the effect of psychological stress on rheumatic diseases:

1. The duration of psychological stress (from minutes to a few days = minor short-lived, versus, weeks to years = major long-standing).
2. The intensity of stress (hassles, versus, catastrophic events).

3. The intactness of the somatic stress response systems in patients with rheumatic diseases (hypothalamic-pituitary-adrenal [HPA] axis and sympathetic nervous system [SNS] axes).
4. The ability of a subject to cope with psychological stress (not discussed, see ref. 1).
5. The type of psychological stress (eustress = positive stress, distress = negative stress) (not discussed).

The above-mentioned items are derived from experiments in animals, experimental studies in healthy humans, and observational studies in patients with RA and other inflammatory diseases. After two decades of intense research, particularly of psychologists and rheumatologists, we start to recognize first concepts, which help to explain the frequently observed worsening of rheumatic symptoms under psychological stress. In addition, we also recognize that long-lasting stress might play a role as a pathogenetic risk factor.

### Minor and major stress modulate arthritis

Major life events (e.g. death of a spouse, severe long-term illness of a spouse, loss of a parent, divorce of parents, death of a parent, severe disease of a parent) are strong stressors, while minor life events are daily hassles with small intensity. The first situation leads to intense release of stress mediators (large time-integral of released neurotransmitters and hormones), whereas in the second situation, only short-lived surges of neurotransmitters and hormones are expected.

In 3000 patients with RA, in 27 independent observational studies on minor stress (summarized in ref.1), minor stress was related to an increase of disease activity. In two prospective studies in RA, disease flare-ups were linked to a higher number of interpersonal minor stressors few days prior to the visit (2, 3). Additionally, a longitudinal study over a period of 5 years showed that RA patients with a higher daily stress level at baseline had a poorer outcome and significantly more bony erosions after 5 years (4). Therefore, long-last-

ing stress may lead to proinflammatory effects because no adequate long-term responses of stress axes (antiinflammatory) are to be expected.

Only five studies on about 150 RA patients did not support the link between minor stress and disease flares (summarized in refs. 1, 5). In contrast, strong major stress, which is likely accompanied by a large and long-lived release of stress axes mediators (large time-integral of released neurotransmitters and hormones), was associated with a decrease in disease activity (see ref. 1). However, these latter studies are inconclusive, and it is fact that major stress has not been studied in a larger group of patients with RA. Only some case reports reporting catastrophic events are available, which presently do not support that major stress, in general, has a disease-ameliorating effect in RA.

The question remains how minor and major stress can elicit completely different effects on immune responses. This necessarily leads to the concept that neurotransmitters such as norepinephrine or stress hormones such as cortisol might have different effects on immune responses at high and low concentrations present during short or extended periods of time, respectively.

### **Opposing effects of cortisol and norepinephrine on immune function at high and low concentrations**

Dexamethasone concentrations of  $10^{-8}$ M to  $10^{-7}$ M, which are biologically equivalent to  $3 \times 10^{-7}$  to  $3 \times 10^{-6}$  M of cortisol, suppressed cytokine secretion *in vitro* (6, 7). The immunosuppressive concept was also confirmed by studies in RA patients under glucocorticoid treatment (8). High doses of glucocorticoids reflect a situation with a large time-integral of released cortisol similar to major stress.

In recent years, the immunomodulating role of this hormone has been critically re-investigated because several studies with lower cortisol concentrations applied *in vitro* and *in vivo* demonstrated immunostimulating effects in humans and rodents (9-11). For example, prior short-term cortisol infusion increased stimulated levels of IL-6 and

TNF in humans *in vivo* (12). Others demonstrated that the short-term influence of glucocorticoids on leukocyte redistribution is probably the most important factor in supporting immune responses (13). We may summarize that short-lived cortisol release leading to a small time-integral of serum cortisol similar to minor stress might increase the immune response.

A very similar paradox emerged for norepinephrine whose immunosuppressive role via  $\beta$ -adrenergic receptors at concentrations of  $10^{-6}$ M to  $10^{-5}$ M has been repeatedly demonstrated (reviewed in ref. 14). Norepinephrine inhibits the RA-relevant TNF secretion from macrophages via  $\beta$ -adrenoceptors at high concentrations (15-17), however, it enhances TNF production via  $\alpha_2$ -adrenergic receptors at low concentrations (15). Moreover, norepinephrine stimulates complement production from macrophages via  $\alpha_1$ -adrenoceptors at low concentrations (18).

In conclusion, during acute minor stress a short rise of cortisol and norepinephrine can be observed (low concentrations of these mediators), while during major stress a huge release of cortisol and norepinephrine is expected. It is interesting that cortisol and norepinephrine act at similar concentrations in order to exert either immunostimulatory or immunoinhibitory effects. The transition point for these differential effects is approximately  $10^{-7}$  mol/l for serum cortisol and norepinephrine in the tissue. In addition, release of cortisol is coupled to release of norepinephrine, which leads to stronger signaling through the  $\beta$ -adrenoceptor (leading to cooperativity of cortisol and norepinephrine, e.g. ref. 19).

These findings give a first indication how short-lived minor stress might have opposing effects on immune parameters as compared to major stress. However, the question appears whether or not stress axes are intact in patients with RA.

### **Response of stress axis in patients with RA**

The responsiveness of the HPA axis is diminished in relation to ongoing inflammation (20-22). Circadian rhyth-

micity is disturbed in patients with RA (23). On the basis of these defects, RA patients as compared to controls do not mount a significant ACTH response upon controlled minor psychological stress, which is also visible in form of inadequate cortisol secretion (24, 25). It has been demonstrated that controlled exercise-induced release of cortisol was markedly decreased in patients with RA as compared to controls (26). These data suggest that chronic stress in RA reduces the stress response (cortisol production) and might induce a worsening of the diseases. A subpopulation of patients with RA demonstrated impaired hypothalamic-pituitary regulation during a dexamethasone test (27), which indicates a disturbance on the hypothalamic-pituitary level. In addition, controlled adrenaline infusion, simulating a stress response, leads to a fast decrease of cortisol serum levels in RA but not in controls (28). Although the HPA axis is relatively robust, it seems that minor stress can lead to a paradoxical decrease of HPA axis mediators in RA patients as compared to healthy subjects. This would yield an overall proinflammatory situation during short-standing minor and, probably, long-standing major stress. Similar investigations have not been performed with major stress paradigms (ethical problem!).

With respect to norepinephrine and the SNS, a loss of  $\beta$ -adrenoceptors on peripheral immune cells has been described in RA patients (29). In contrast to the typically available  $\beta_2$ -adrenoceptors on immune cells, there seems to be up-regulation of  $\alpha_1$ -adrenoceptors in patients with arthritis, which results in increased IL-6 secretion (30). These  $\alpha_1$ -adrenoceptors are up-regulated by proinflammatory cytokines such as TNF and IL-1 $\beta$  (30). Due to this *beta-to-alpha adrenergic shift*, norepinephrine may not exert its typical immunosuppressive activities on macrophages, neutrophils and NK cells via  $\beta_2$ -adrenoceptors. In contrast, proinflammatory responses via  $\alpha$ -adrenoceptors are expected. These phenomena are accompanied by a significant loss of sympathetic nerve fibers in inflamed RA synovial tissue (31). This

would support a local proinflammatory situation due to an inflammation-induced *beta-to-alpha adrenergic shift*. The loss of sympathetic nerve fibers is paralleled by a slightly increased innervation with proinflammatory sensory nerve fibers (31). In the presence of inflammation-induced central sensitization of pain pathways (32), this can lead to an overall increased pain perception. Particularly in stress situations, these factors would support a proinflammatory environment and would increase pain perception in RA. The role of gonadal hormones is not subject of this short review due to space constraints. However, we might say that these hormones most probably play an additional important role (33, 34).

### Stress and immune responses in RA

The described changes of the HPA axis and of the SNS can lead to proinflammatory reactions during minor stress in RA. It has been shown in RA that interpersonal stressors few days prior to the visit were related to increased numbers of circulating CD3<sup>+</sup> cells and increased serum levels of soluble IL-2 receptors (2, 3). In addition, during the cold pressor test, an enhanced IL-6 production by peripheral blood cells was observed (35). In addition, RA patients demonstrated enhanced IL-6 levels during mental stress before surgery (36). After adrenaline infusion, RA patients demonstrated higher numbers of IL-8 producing monocytes in the peripheral circulation (37). These first studies may give an idea that aberrations of stress axes in RA patients increase proinflammatory signals during minor stress. Similar data for major stress are not available but major stress may also lead to proinflammatory effects because no adequate long-term responses of stress axes are expected.

In a recent study, it was evaluated whether stress-related psychological factors and personality disorders might be involved in the development of RA by using a psychometric methodology (38). Twenty-three patients underwent a clinical interview and specific psychometric tests. Major and minor stressful life events preceded RA in

83% of the cases. Sixty percent of the patients showed a correlation between appearance of minor stress events and flare-ups of the disease (increase of inflammatory markers and clinical status). An obsessive compulsive personality was found in 26% of the patients and anxiety in 40%. The high prevalence of major stress events preceding the onset of RA and the presence of personality disorders support the role of altered stress response systems as important pathogenetic factors in the disease (39).

### Conclusions

The emerging concept is as follows: RA patients with insufficient stress axes demonstrate paradoxically decreased stress responses and, consequently, proinflammatory side effects. The loss of an adequate stress response is reflected by low serum levels of cortisol and low concentrations of norepinephrine in the tissue (nerve fiber loss). Thus, minor stress and probably also major stress are not accompanied by an adequate stress response, which leads to inadequately low concentrations of stress axes mediators in relation to inflammation (below the transition point of 10<sup>-7</sup> mol/l). Therapeutically, a reduction of stress episodes or a change of stress management must be implemented (40, 41). In addition, mild exercise and the decrease of the proinflammatory load can normalize stress axes so that minor stress would lead to favorable responses.

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