Increase of sympathetic outflow measured by NPY and decrease of the hypothalamic-pituitary-adrenal axis tone in patients with SLE and RA – Another example of uncoupling of response systems

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Running title: Sympathetic tone / HPA axis activity in SLE and RA
ABSTRACT

Objective: Short-term inflammation stimulates the sympathetic nervous system (SNS) and the hypothalamic – pituitary – adrenal (HPA) axis. The activity of the HPA axis is reduced in chronic inflammatory diseases, however, the behavior of the SNS is not similarly understood. This study was initiated to study in parallel the tone of both endogenous response system in patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA).

Methods: A total of 32 patients with SLE, 62 with RA, and 65 healthy subjects (HS) were included. In order to measure the tone of the HPA axis, plasma ACTH and serum cortisol were determined. Serum neuropeptide Y (NPY), a relatively stable sympathetic co-transmitter of norepinephrine, was used to evaluate the sympathetic outflow.

Results: SLE patients demonstrated increased NPY levels as compared to HS irrespective of prior prednisolone treatment (p<0.001). In RA patients, only those with prednisolone (pred) treatment demonstrated increased NPY levels as compared to HS (p=0.016). Daily prednisolone dose correlated positively with serum NPY in RA (R_{Rank}= 0.356, p=0.039). In contrast, in SLE and RA, plasma ACTH levels were generally decreased as compared to HS which reached the significance level in SLE with pred, and in RA with/without pred. Similarly, serum cortisol levels were also decreased in SLE with/without pred, and in RA with pred. The ratio of NPY/ACTH was increased in SLE and RA irrespective of prior prednisolone treatment. The ratio of NPY/cortisol was increased in SLE with/without pred, and in RA with pred. Twelve weeks of anti-TNF antibody therapy with adalimumab did not decrease NPY levels in RA irrespective of prednisolone treatment.

Conclusions: This study demonstrates an increased outflow of the SNS and a decreased tone of the HPA axis in SLE and RA patients. Low levels of cortisol in relation to SNS neurotransmitters may be proinflammatory because cooperative antiinflammatory coupling of the two endogenous response axes is missing.

INTRODUCTION

During acute inflammation in humans and animals, activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS) was observed. In chronic inflammatory diseases such as SLE or RA, the HPA axis demonstrates marked alterations: 1. There is inadequate secretion of adrenocorticotropic hormone (ACTH) relative to circulating cytokines. 2. Patients have inappropriately low spontaneous and stimulated cortisol secretion in relation to inflammation. During a long-term inflammatory disease such as RA and SLE, adrenal androgens dramatically decrease. The reasons for these changes are only partly understood but striking changes on all levels of the HPA axis seem to play a role. For example, during repetitive administration of IL-6 over three weeks, the stimulatory capacity of IL-6 on the central level is normally lost but stimulation of the adrenal glands remains relatively stable.

At this point, the question arises as to what happens with the SNS in chronic inflammatory diseases. Some studies indicated that patients with chronic inflammatory diseases have an elevated activity of the SNS. Such an increased sympathetic tone may be a consequence of hypothalamic changes with an observed shift from CRH to vasopressin, which has been demonstrated in experimental arthritis. However, all these studies have not investigated the tone of the HPA axis in parallel. Thus, a possible preponderance of one system over the other was not investigated.

Why can it be important that the activity of the HPA axis and the SNS are upregulated in parallel, and what would happen if uncoupling of these axes appears? Release of cortisol is typically coupled to release of norepinephrine, which leads to stronger signaling through the β-adrenoceptor. Several studies have shown cooperativity of cortisol and norepinephrine on a molecular level. This permissive effect of cortisol is due to β-adrenoceptor up-regulation and stabilization of the cyclic AMP (cAMP) / protein kinase A / cyclic AMP responsive element binding protein (CREB) signaling pathway. In patients with asthma, this has led to a more effective combination therapy with local glucocorticoids and local β-adrenergic agents as compared to either substance alone. Thus, it seems that instant coupling of the two stress axes and their mediators is important for cooperative effects. Cooperation may be important in chronic inflammatory diseases to efficiently downregulate inflammation in the periphery.

This study aimed to investigate the tone of the SNS in SLE and RA patients by using neuropeptide (NPY), the relatively stable sympathetic co-transmitter of norepinephrine. NPY is an excellent indicator of sympathetic activity, which is more stable and has a significantly longer half life in plasma. The correlation between NPY and norepinephrine release has been demonstrated in situations such as obstructive sleep apnea syndrome, experimental stress, hypertension, surgery, hypoxia, and exercise. It is important to mention that the characteristics of norepinephrine and NPY release is not always identical; Norepinephrine is released at low exercise levels whereas NPY is released at higher exercise levels. This reflects the differential release of norepinephrine and NPY from nerve terminals because norepinephrine is released at low stimulation frequencies whereas norepinephrine and NPY are released together at higher stimulation frequencies. Furthermore, since NPY is produced in the
sympathetic neuron in paravertebral ganglia it needs to be transported to the peripheral nerve ending. Thus, NPY in contrast to locally produced norepinephrine is only available depending on production in the neuronal soma and transport rate. However, when NPY is elevated its most important source is the sympathetic nerve terminal. To our knowledge, NPY has never been investigated in the serum or plasma of patients with RA and SLE. In parallel to the SNS, we studied the HPA axis tone focussing on ACTH and cortisol. Since administration of prednisolone to healthy subjects increases the SNS tone, we separately analyzed patients with and without prior prednisolone therapy. Furthermore, in RA patients, we investigated the effect of 12 weeks of anti-TNF therapy with adalimumab on NPY serum levels.

PATIENTS AND METHODS

Patients, anti-TNF therapy, and healthy subjects
We enrolled 32 Caucasian patients with SLE according to the criteria of the American College of Rheumatology. In these patients, clinical activity was assessed by the SLEDAI. In order to simultaneously study patients with another chronic inflammatory disease, we included 62 Caucasian patients with diagnosed RA fulfilling the American College of Rheumatology criteria. Clinical variables of disease activity included the number of swollen and tender joints and erythrocyte sedimentation rate. Basic characteristics of both disease groups, including therapy, are demonstrated in Table 1. All patients without prednisolone did not receive glucocorticoids during a period of 6 months before study entry, whereas patients with prednisolone had stable therapy over several weeks before study entry.

Some patients with RA (16 with and 16 without parallel prednisolone) were treated with adalimumab (Abbott S.p.A., Campoverde di Aprilia, Italy) according to the inclusion criteria of the Adalimumab Research in Active RA study (ReAct). These RA patients received additional methotrexate (stable throughout this study) but no other immunosuppressive drugs. Patients were assigned to receive single self-injections of adalimumab subcutaneously at 40 mg every other week. Efficacy assessments demonstrated excellent response according to ACR and EULAR response criteria (data not shown; F.A., P.S.-P., see ref. 45). A baseline, blood sample was taken 1 to 2 weeks before the start of adalimumab therapy. Anti-TNF antibodies were infused on weeks 0, 2, 4, 6, 8, 10, and 12. These patients were clinically investigated and blood was drawn on the baseline day, and on weeks 2, 6, and 12.

For comparison, 65 Caucasian healthy subjects (HS) were recruited, and health status was verified by means of a 33-item questionnaire as previously described. Fertile women (HS and patients) were not taking contraceptives and they were in the early to mid follicular phase of the menstrual cycle. Due to the different age and gender in the disease groups, subgroup analyses were carried out in order to correctly compare the different groups of patients to healthy subjects. The subgroups were matched according to age and gender (Table 1). Since serum levels of adrenal hormones are largely independent of gender, male and female subjects were not further separated into subgroups.

The study was approved by the Ethics Committee of the University Hospital of Regensburg, Germany, and for the adalimumab study approval was obtained from the Ethics Committee of L. Sacco University Hospital, Italy.

Laboratory parameters
In all subjects, blood was drawn between 08:00 and 10:00 in the morning when the patients visited the outpatient clinic. The blood was immediately centrifuged and serum or plasma were stored on – 80°C. We used radioimmunoanalytical assays for the quantitative determination of serum levels of NPY (Euro-Diagnostica AB, Malmö, Sweden, via IBL, Hamburg, Germany; detection limit: 6 pmol/l). Although the behaviour of plasma ACTH and serum cortisol are known in SLE and RA patients, we measured these hormones in order to calculate ratios of serum NPY / plasma ACTH and serum NPY / serum cortisol. These ratios should give an impression of the interrelation of the two hormones included. We used a radioimmunoanalytical assays for the quantitative determination of serum levels of cortisol (Coulter Immunotech, Marseilles, France, via IBL; detection limit: 10 nmol/l) and an enzyme immunoassay to detect plasma ACTH (Sangui BioTech, Inc., California, U.S.A., via IBL; detection limit: 0.1 pmol/l). For all assays, intraassay and interassay coefficients of variation were below 10%.

Presentation of data and statistical analysis
The data are given as box plots with the 5th, 10th, 50th (median), 90th, and 95th percentile. Group medians were compared by the non-parametric Mann-Whitney test, correlations were calculated by Spearman rank correlation analysis (SPSS / PC, V.11.5, SPSS Inc., Chicago, USA). A decrease or increase of a variable over time (during adalimumab therapy) was tested by means of the non-parametrical Friedman test (SPSS). p<0.05 was the level of significance.

RESULTS

NPY serum levels in patients with SLE, RA, and in healthy subjects
Figure 1 demonstrates higher NPY serum levels in SLE patients than in healthy subjects irrespective of prednisolone treatment (Fig. 1A). In RA, only patients with prior prednisolone demonstrated elevated NPY serum levels as compared to healthy subjects (Fig. 1B). Since age-matched healthy subjects had relatively high NPY serum levels, no difference was noted in comparison to RA patients without prednisolone therapy (Fig. 1B).

The results of elevated NPY levels in prednisolone-treated RA patients prompted us to study the interrelation of daily prednisolone dose and NPY serum levels. It is obvious that prednisolone dose correlated with NPY serum levels in RA patients but not in SLE patients (Fig. 1C,D). However, plasma NPY levels did not correlate with typical markers of disease activity such as tender joint score in RA (without prednisolone: RRank = 0.111, n.s.; with prednisolone: RRank = 0.227, n.s.), swollen joint score in RA (without prednisolone: RRank = 0.010, n.s.; with prednisolone: RRank = 0.356, p=0.088), and SLEDAI in SLE (without prednisolone: RRank = 0.023, n.s.; with prednisolone: RRank = 0.044, n.s.).

Plasma NPY levels were not different between male and female patients with or without prednisolone (data not shown). Therapeutics such as NSAID, methotrexate, azathioprine, and leflunomide did not influence serum NPY levels in RA or SLE patients (data not shown).

### Relation of NPY serum levels and HPA axis hormones

In order to study the relation between NPY and HPA axis hormones, molar ratios of NPY / ACTH and NPY / cortisol were calculated. These ratios express a possible preponderance of the SNS over the HPA axis or vice versa. As expected, SLE and RA patients with prior prednisolone demonstrated decreased ACTH levels (Fig. 2A,B). In addition, also RA patients without prior prednisolone therapy demonstrated decreased ACTH levels in comparison to healthy subjects (Fig. 2B). The ratio of NPY / ACTH was significantly higher in SLE and RA patients than in healthy controls irrespective of prior prednisolone treatment (Fig. 2C,D). In RA patients, prednisolone treatment increased this particular ratio (Fig. 2D).

With respect to cortisol, patients with SLE demonstrated decreased serum levels irrespective of prior prednisolone treatment (Fig. 3A). In RA, only those patients with prior prednisolone therapy demonstrated decreased cortisol serum levels (Fig. 3B). The ratio of NPY / cortisol was increased in both SLE patient groups irrespective of prednisolone treatment (Fig. 3C). In addition, it is obvious that SLE patients treated with prednisolone had an increased ratio of NPY / cortisol as compared to untreated patients (Fig. 3C). In RA, only patients with prior prednisolone demonstrated an increased ratio of NPY / cortisol as compared to healthy subjects (Fig. 3D).

Above-mentioned ratios were not different between male and female patients with or without prednisolone (data not shown). Therapeutics such as NSAID, methotrexate, azathioprine, and leflunomide did not influence serum NPY levels in RA or SLE patients (data not shown).

### Influence of anti-TNF therapy in RA on NPY serum levels

Twelve weeks of anti-TNF therapy did not change NPY serum levels irrespective of prednisolone treatment (Fig. 4). Again it is obvious that RA patients with prednisolone had increased serum NPY levels as compared to untreated RA patients (Fig. 4). In addition, neither the ratio of serum NPY / plasma ACTH nor the ratio of serum NPY / serum cortisol changed during 12 weeks of anti-TNF therapy (data not shown).

### DISCUSSION

Using NPY as reliable read-out parameter of the SNS activity, we were able to demonstrate an increased SNS outflow in relation to the HPA axis tone in all SLE patients and in prednisolone – treated patients with RA. With respect to the ratio of serum NPY / plasma ACTH, also RA patients without prednisolone demonstrated a preponderance of the SNS over the HPA axis.

Several studies have demonstrated an increased sympathetic tone in patients with chronic inflammatory diseases. However, all these studies have not investigated the tone of the HPA axis in parallel. Thus, the preponderance of one system over the other was not investigated. In a recent study in patients with Crohn’s disease and ulcerative colitis, we were able to observe a very similar phenomenon in a recent study in patients with Crohn’s disease and ulcerative colitis. We termed this phenomenon uncoupling of the SNS and HPA axis in order to emphasize the loss of cooperative activities of these two endogenous response systems. This present study supports uncoupling of the two main response axes in SLE and RA patients. Uncoupling is enhanced in prednisolone-treated patients because prednisolone stimulates the SNS and inhibits the HPA axis even in healthy subjects. Interestingly, 12 weeks of anti-TNF therapy in RA patients only marginally reduced elevated NPY serum levels and SNS dominance. Thus, it seems that uncoupling is enduringly imprinted, and it is obvious that TNF is not the sole and main factor responsible for this phenomenon.

With respect to patients without prednisolone treatment, it is interesting that the uncoupling phenomenon is obvious in our young SLE patients but not similarly in the old RA patients. Similarly, our recent studies in young patients with inflammatory bowel disease demonstrated the uncoupling phenomenon in patients without prednisolone. It may well be that aging has an influence on the uncoupling pheno-
Coupling of the SNS and HPA axis is important to support the β-adrenergic and glucocorticoid receptor pathways, which would lead to stronger cooperative effects than using one system alone. Cooperative activity of both axes is observed in asthmatics when these patients use local glucocorticoids and local β2-adrenergic agents. In these patients, cooperation increases the bronchodilatory effect of each substance alone. A similar cooperativity can be observed in septic shock patients. The combined treatment with norepinephrine and cortisol leads to improved effects on circulation and blood pressure. Similarly, a cooperative effect of cortisol and norepinephrine is also observed in RA patients (see below). In patients with chronic inflammatory diseases, a relative loss of HPA axis hormones in relation to pro-inflammatory cytokines may lead to deficient vasopressive activity of SNS neurotransmitters, which may consequently lead to upregulation of the SNS tone. This may counterbalance the loss of cortisol in the presence of increased circulating vasodilators such as nitric oxide, TNF, and others. These SNS changes may be supported by the observed hypothalamic shift from initially high CRH expression to chronically elevated vasopressin expression, which has been demonstrated during the course of experimental arthritis. This shift to increased vasopressin production can also be viewed as a sign of an increased sympathetic tone in relation to the HPA axis (CRH) because elevated vasopressin levels would support the SNS in stabilizing blood pressure. Apart from effects on bronchodilation and circulation, cooperativity may also lead to stronger antiinflammatory effects. In addition, disease-related factors such as depression, chronic pain, weight gain, and others may add to the uncoupling phenomenon.

In RA patients, we recently demonstrated antiinflammatory cooperativity of norepinephrine and cortisol. The combined administration of norepinephrine and cortisol to cultured mixed synovial cells led to a stronger reduction of TNF, IL-8, and IL-6 secretion as compared to the use of each substance alone. Furthermore, RA patients with prednisolone therapy and presence of synovial sympathetic nerve fibers had decreased histological markers of synovial inflammation as compared to patients without prednisolone therapy or without sympathetic innervation. Thus, high levels of mediators of the SNS together with cortisol at the local site of inflammation may be favorable to dampen inflammation. However, it has been demonstrated that sympathetic innervation is decreased in inflammatory processes such as in the spleen of the lupus lpr/lpr mice, in the synovium of RA patients, and in inflamed islets of diabetic rats. Thus, an elevated systemic tone of the SNS probably would not lead to increased local sympathetic neurotransmitters because sympathetic nerve fibers are lost. In such a situation, local concentrations of sympathetic neurotransmitters are low, which would support the proinflammatory process via α-adrenoceptors (reviewed in ref. 54). Loss of sympathetic nerve fibers and low levels of cortisol and androgens would lead to a proinflammatory microenvironment in inflamed tissue. In support of this notion, it has been repeatedly demonstrated that a higher SNS tone increases circulating leukocytes such as monocytes, NK cells, and neutrophils. Probably, this has been evolutionarily conserved in order to support the immune system in the very early phase of a systemic inflammatory response (help for the innate immune system). However, in patients with chronic inflammatory diseases such a stimulation of leukocyte migration and redistribution is probably unfavorable.

In conclusion, an increased SNS tone in the presence of a defective HPA axis probably supports the ongoing inflammatory process. In addition, an increased SNS tone would support atherosclerosis in patients with chronic inflammatory diseases. These observations may stimulate rheumatologists to properly treat patients with centrally acting drugs in order to inhibit enhanced SNS outflow.

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Competitive Interest Statement
The authors declare that no competitive interest exists.

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Table 1 Basic characteristics of healthy subjects and patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Data are given as means ± SEM, percentages in parentheses, and ranges in brackets.

<table>
<thead>
<tr>
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<th>SLE HS (match SLE)</th>
<th>RA HS (match RA)</th>
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<tr>
<td>number</td>
<td>32</td>
<td>42</td>
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<tr>
<td>age (yr)</td>
<td>38.1 ± 2.1</td>
<td>37.1 ± 1.5</td>
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<tr>
<td>gender female/male</td>
<td>24/8 (75/25)</td>
<td>25/17 (60/40)</td>
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<td>disease duration (yr)</td>
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<tr>
<td>SLEDAI</td>
<td>10.9 ± 1.5</td>
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<td>tender joints</td>
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<td>n.a.</td>
</tr>
<tr>
<td>swollen joints</td>
<td>n.a.</td>
<td>n.a.</td>
</tr>
<tr>
<td>ESR (mm 1st hour)</td>
<td>25.0 ± 3.3</td>
<td>n.m.</td>
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</tbody>
</table>

Medication

<table>
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<th></th>
<th>SLE HS (match SLE)</th>
<th>RA HS (match RA)</th>
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</thead>
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<tr>
<td>prednisolone</td>
<td>20 (63)</td>
<td>34 (55)</td>
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<tr>
<td>prednisolone / day (mg)</td>
<td>9.4 ± 3.4</td>
<td>4.3 ± 0.9</td>
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<td>NSAID</td>
<td>13 (41)</td>
<td>38 (62)</td>
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<tr>
<td>methotrexate</td>
<td>2 (6)</td>
<td>43 (69)</td>
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<tr>
<td>azathioprine</td>
<td>12 (38)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>anti-TNF therapy</td>
<td>0 (0)</td>
<td>38 (61)</td>
</tr>
<tr>
<td>leflunomide</td>
<td>0 (0)</td>
<td>8 (13)</td>
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<tr>
<td>cyclophosphamide</td>
<td>2 (6)</td>
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<tr>
<td>hydroxychloroquine</td>
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<tr>
<td>sulfasalazine</td>
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<td>2 (3)</td>
</tr>
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</table>

Abbreviation: ESR, erythrocyte sedimentation rate; n.a., not applicable; n.m., not measured; SLEDAI, SLE disease activity index.

Figure legends

Figure 1 Serum neuropeptide Y in healthy subjects (HS), patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). A) Comparison of HS and SLE patients. B) Comparison of HS and RA patients. For panels A) and B) data are given as box plots with the 5th, 10th, 50th (median), 90th, and 95th percentile. Abbreviations: RA-, RA patients without prednisolone; RA+, RA patients with prednisolone; SLE-, SLE patients without prednisolone; SLE+, SLE patients with prednisolone. C) and D) Interrelation of daily prednisolone dose and serum neuropeptide Y levels in prednisolone – treated patients with SLE (C) and RA (D). The linear regression line, the rank correlation coefficient and its p-value are given.
Figure 2  Relation of neuropeptide Y and plasma ACTH in healthy subjects (HS), patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). A) and B) demonstrate plasma levels of ACTH. C) and D) demonstrate the ratio of serum neuropeptide Y (NPY) and plasma ACTH. All data are given as box plots with the 5th, 10th, 50th (median), 90th, and 95th percentile. Abbreviations see legend to figure 1.

Figure 3  Relation of neuropeptide Y and serum cortisol in healthy subjects (HS), patients with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). A) and B) demonstrate serum levels of cortisol. C) and D) demonstrate the ratio of serum neuropeptide Y (NPY) and serum cortisol. All data are given as box plots with the 5th, 10th, 50th (median), 90th, and 95th percentile. Abbreviations see legend to figure 1.

Figure 4  Influence of anti-TNF therapy with adalimumab during 12 weeks on serum neuropeptide Y in RA patients. All data are given as box plots with the 5th, 10th, 50th (median), 90th, and 95th percentile.
Increase of sympathetic outflow measured by NPY and decrease of the hypothalamic-pituitary-adrenal axis tone in patients with SLE and RA - Another example of uncoupling of response systems

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