Regional sympathetic function in high spinal cord injury during mental stress and autonomic dysreflexia

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Summary
Centrally mediated sympathetic stimulation of subjects who have suffered a spinal cord injury (SCI) does not activate the decentralized part of the body below the level of the lesion, whereas experimental data indicate an exaggerated response above the level of the lesion. SCI subjects may exhibit an autonomic dysreflexia reaction following afferent stimulation below the level of the lesion. In order to investigate the function of the sympathetic nervous system above and below the level of the lesion, regional noradrenaline spillover was measured by means of steady-state isotope dilution technique above (forearm) and below (leg) the level of the lesion at baseline, during mental stress and following bladder stimulation in nine SCI subjects (mean age 41 years; level of injury C7–T4; mean duration of injury 13.8 years). The results from the SCI subjects were also compared with those from 10 weight- and age-matched control subjects, both at rest and during mental stress. Body composition was determined by dual energy X-ray absorptiometry scanning and arm/leg blood flow by occlusion plethysmography. At baseline, total and regional noradrenaline spillover did not differ between the groups. Mental stress increased mean arterial pressure in both groups. Heart rate (76 versus 64 beats/min; P < 0.05) and arm noradrenaline spillover (2.73 versus 1.71 pmol/min/100 g; P < 0.05) increased more in spinal cord injury subjects than in control subjects, whereas total body (2826 versus 3783 pmol/min; P < 0.01) and leg noradrenaline spillover (0.23 versus 0.41 pmol/min/100 g; P < 0.05) increased only in the control group. During bladder stimulation, SCI subjects reacted with a marked increase in mean arterial pressure and leg noradrenaline spillover (from 0.06 to 0.91 pmol/min/100 g; P < 0.05) and their leg blood flow decreased. Regional and total noradrenaline clearance were similar in the two groups. In conclusion, peripheral afferent stimulation below the level of the lesion in spinal cord injury subjects gives rise to a marked noradrenaline spillover from the decentralized part of the sympathetic nervous system suggesting a remaining, but qualitatively altered, neuronal function. Centrally mediated stimulation induced an exaggerated response above the level of the lesion.

Keywords: sympathetic nervous system; paraplegia; noradrenaline; autonomic dysreflexia; mental stress

Abbreviations: CI = confidence interval; SCI = spinal cord injury

Introduction
The decentralization of the sympathetic nervous system following a spinal cord injury (SCI) affects the cardiovascular, thermoregulatory, gastrointestinal, urinary and reproductive systems (Mathias and Frankel, 1992). Centrally mediated sympathetic stimuli do not activate the decentralized part below the level of the lesion (Corbett et al., 1971), whereas some data indicate an exaggerated responsiveness above the level of the lesion (Maiorov et al., 1997). A visceral or noxious stimulus below the level of the lesion sometimes gives rise to so-called autonomic dysreflexia in SCI subjects with lesions above the fifth thoracic level (T5) (Guttmann and Whitteridge, 1947). The reaction is characterized clinically by an immediate and marked increase in blood pressure, a baroreflex mediated decrease in heart rate, sweating above the level of the lesion and a pounding headache (Kewalramani, 1980). Further, the reaction involves vasoconstriction in...
Table 1 Subject characteristics

<table>
<thead>
<tr>
<th></th>
<th>SCI subjects (n = 9)</th>
<th>Control subjects (n = 10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>41 (31–51)</td>
<td>31 (26–36)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>74.9 (64.5–85.3)</td>
<td>79.4 (74.1–84.6)</td>
</tr>
<tr>
<td>Lean body mass (kg)</td>
<td>49.7 (43.5–56.0)*</td>
<td>58.3 (53.0–63.6)</td>
</tr>
<tr>
<td>Arms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>9.9 (8.4–11.4)</td>
<td>9.3 (8.2–11.5)</td>
</tr>
<tr>
<td>Lean weight (kg)</td>
<td>7.3 (6.4–8.2)</td>
<td>7.5 (6.6–8.3)</td>
</tr>
<tr>
<td>Legs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>21.1 (18.2–24.0)*</td>
<td>25.7 (23.8–27.7)</td>
</tr>
<tr>
<td>Lean weight (kg)</td>
<td>14.1 (11.9–16.3)**</td>
<td>20.7 (18.8–22.6)</td>
</tr>
<tr>
<td>Lesion level</td>
<td></td>
<td></td>
</tr>
<tr>
<td>C7</td>
<td>2 (sensory block incomplete in one subject)</td>
<td></td>
</tr>
<tr>
<td>T3–T4</td>
<td>7 (sensory block incomplete in one subject)</td>
<td></td>
</tr>
<tr>
<td>Duration of injury (years)</td>
<td>13.8 (8.7–19.0)</td>
<td></td>
</tr>
</tbody>
</table>

SCI = spinal cord injury. Data are presented as means, with 95% CIs in brackets. *P < 0.05 and **P < 0.01: significant differences between groups.

skeletal muscle and skin vascular beds below the level of the lesion (Corbett et al., 1971, 1975) and a presumed vasoconstriction and/or inability to dilate the splanchic vascular bed (Kewalramani, 1980).

Microneurographic recordings in SCI patients show reduced sympathetic nerve activity below the level of the lesion at baseline and only a weak activation during induced autonomic dysreflexia (Wallin and Stjernberg, 1984; Stjernberg et al., 1986), whereas renal sympathetic activity in spinal rats shows a marked increase during autonomic dysreflexia (Maiorov et al., 1997). Plasma noradrenaline determinations have yielded varying results in SCI patients, with baseline concentrations reported to be low (Mathias et al., 1976a) or normal (Karlsson et al., 1997b), whereas both unaltered (Krum et al., 1992) and increased (Mathias et al., 1976a) venous plasma noradrenaline concentrations during peripheral afferent stimulation have been reported.

The plasma noradrenaline concentration only partially reflects sympathetic nerve activity; following release from the neuron, noradrenaline is subject to neuronal as well as extraneuronal uptake before reaching the vascular bed. It is possible to determine the noradrenaline clearance and spillover in the whole body as well as regionally by steady-state infusion of radiolabelled noradrenaline (Esler et al., 1979, 1984). This technique was utilized in the present study to evaluate noradrenaline spillover and removal in the total body, in arms and in decentralized legs in nine SCI subjects with lesion at levels C7–T4. In this group, the major part of the body is sympathetically decentralized, although innervation of the heart and the arms is preserved at least in the subjects with a thoracic lesion. In order to evaluate the ability of centrally mediated sympathoexcitatory stimuli to affect noradrenaline spillover, the group was investigated at baseline and during mental stress, and then compared with a weight- and age-matched control group of 10 able-bodied subjects. SCI subjects were also investigated during peripheral afferent stimulation (bladder percussion). By combining noradrenaline spillover data with regional body-composition data from dual energy X-ray absorptiometry scanning (Mazess et al., 1984), we were able to correct for group differences in regional body composition.

The following questions were addressed. (i) Do regional noradrenaline spillover and noradrenaline extraction differ between SCI and control subjects at baseline and during centrally mediated sympathoexcitatory stimulation? (ii) Does peripheral afferent stimulation in SCI subjects affect noradrenaline spillover below the level of the lesion?

Methods

Subjects

The Human Ethics and Isotope Committees at the University of Göteborg, Sweden, approved the study and all subjects gave informed consent to participate. The experimental groups comprised nine SCI subjects and 10 weight- and age-matched control subjects. The SCI group consisted of two subjects with a lesion at C7 and seven with a lesion at T3–4. The neurological classification was performed according to the ASIA (American Spinal Injury Association) scoring (Ditunno et al., 1994). Two subjects showed sensory sparing below the level of the lesion (ASIA grade B). We found no difference between the subjects during baseline, mental stress or peripheral afferent stimulation that could be attributed to the level of the lesion or completeness of injury. Body composition was investigated by means of dual energy X-ray absorptiometry scanning (Mazess et al., 1984) [Lunar DPX (L) Scanexport Medical, Helsingborg, Sweden]. The method measures fat mass, lean mass and bone mineral content directly, and has been validated against other body composition methods (Haarbo et al., 1991; Spungen et al., 1995; Bosaeus et al., 1996). Body composition was calculated in arms, legs, trunk and head (Table 1). The SCI group had a lower lean body mass, a lower leg weight and a lower lean...
weight in the legs than able-bodied control subjects. None
of the subjects had any ongoing disease. Three subjects in
the SCI group used drugs to stem urinary leakage
(probantelinbromide) and reduce spasms (baclophen).

**Experimental protocol**

The subjects arrived in the laboratory at 0800 hours after an
overnight fast; they had been instructed to refrain from coffee
and smoking during the 12-h period prior to investigation,
and were investigated supine. A Venflon cannula (Viggo
Helsingborg, Sweden) was inserted into the right radial artery
for blood sampling and blood pressure monitoring. Blood
pressure and heart rate were monitored on an ink jet recorder
(Mingograph 800, Siemens-Elema Ltd, Solna, Sweden). A
blood-sampling catheter was then inserted into the left femoral
vein under fluoroscopic guidance (Seldinger technique) and
placed ~15 cm distally in the vessel. In addition, two cannulae
(Venflon, Viggo Helsingborg, Sweden) were inserted into
deep veins in the cubital fossa and directed 5 cm proximally;
one was used for infusion of [3 H]-noradrenaline tritiated in
position 7 (20 Ci/mmol, New England Nuclear, Boston,
Mass., USA) at a constant rate of ~1.3 µCi/min, the other
was used for blood sampling. The blood samples were
poured immediately into ice-chilled tubes containing reduced
glutathione and EDTA. The tubes were kept on ice until the
end of the investigation.

**Blood flow measurements**

Blood flow in the right forearm and calf was measured by
venous-occlusion strain gauge plethysmography
(Electromedicine, Göteborg, Sweden). Blood flow was
registered four or five times at the end of the resting
periods and resting value was calculated as a mean of these
registrations. During stimulation, blood flow was registered
two or three times during the last minute of stimulation and
the mean of these registrations recorded. Changes in glabrous
skin perfusion on hand and foot were registered by laser
Doppler flowmetry (Periflux, Perimed AB, Stockholm,
Sweden).

Baseline blood flow was recorded four or five times at the
end of the resting period, and baseline values calculated as the
mean of these measurements. Blood samples were collected
simultaneously in radial artery, femoral and arm veins at the
end of the baseline period.

**Centrally mediated sympathetic stimulation**

Centrally mediated sympathetic stimulation was induced by
giving the subjects forced mental arithmetic tests for 5 min.
Blood flow was registered and blood samples collected at the
end of stimulation.

**Peripheral afferent stimulation**

Following a rest period of at least 30 min, peripheral afferent
stimulation was performed in SCI subjects as follows. The
urinary bladder was stimulated to contract by percussion over
the lower abdomen (30–50 taps/min) for 5–6 min. Blood
flow measurements and blood sampling were performed just
after completion of stimulation. In order to ascertain a
reaction during bladder stimulation, we performed this
stimulation with the bladder partly filled. When evaluating
the data and comparing the baseline period before the bladder
stimulation with previous baseline periods, we found signs
of a moderate autonomic activation. A mean of the previous
baseline periods was therefore calculated and used as a
baseline value before bladder stimulation.

**Catecholamine assays**

Blood samples were centrifuged at 4°C and plasma was
separated for storage at ~80°C until assayed. Plasma
concentrations of endogenous noradrenaline were determined
by high performance liquid chromatography with electro-
chemical detection according to Medvedev et al. (1990).
Timed collection of eluate leaving the detection unit, using
a fraction collector (Frac 100, Kabi-Pharmacia, Sweden),
allowed separation of [3 H]noradrenaline for subsequent
counting by liquid scintillation spectroscopy. The inter-assay
coefficients of variation were 9% (3.02 pmol/ml) and 8%
(730 d.p.m./ml) for endogenous and tritiated noradrenaline,
respectively.

**Calculations**

Total body noradrenaline clearance (TB CL) and total body
noradrenaline spillover into plasma (TB SP) were calculated
according to Esler et al. (1979):

\[
TB_{\text{CL}} = I \left[ \frac{[3 \text{H}] \text{NA}_A}{\text{PF}} \right] \text{ml/min}
\]

\[
TB_{\text{SP}} = TB_{\text{CL}} \times NA_A \text{pmol/min}
\]

where \(I\) is the infusion rate of [3 H]noradrenaline (d.p.m./min),
[3 H]NA A is the arterial concentration of radiolabelled
noradrenaline (d.p.m./ml) and NA A is the arterial endogenous
noradrenaline concentration (pmol/ml). The skeletal muscle
noradrenaline spillover in arm and leg (LIMB SP), the
fractional extraction of noradrenaline in arm and leg
(LIMB EX) and arm and leg clearance were calculated
according to Esler et al. (1984):

\[
LIMB_{\text{SP}} = \left( [NA_V - NA_A] + NA_A \times NA_{\text{EX}} \right) \times \text{PF} \text{pmol/min/100 g}
\]

\[
LIMB_{\text{EX}} = \left( [3 \text{H}] \text{NA}_A - [3 \text{H}] \text{NA}_V / [3 \text{H}] \text{NA}_A \right) \times \text{PF}
\]

\[
LIMB_{\text{CL}} = LIMB_{\text{EX}} \times \text{PF} \text{ml/min/100 g}
\]

where PF is plasma flow (ml/min/100 g) calculated as blood
flow multiplied by (1 – haematocrit). NA V is the venous
noradrenaline concentration (pmol/ml). [3 H]NA V is the
venous concentration of [3 H]noradrenaline (d.p.m./ml).
Since the individual weights of left and right arms and legs were assessed, it was also possible to calculate total blood flow in arms and legs in ml/min. Accordingly, noradrenaline spillover from arms and legs could be calculated by adding the noradrenaline spillover values from each limb arithmetically. Hence, the values of blood flow, vascular resistance, noradrenaline spillover and noradrenaline clearance are given in relation to 100 g tissue mass and to the whole limb weight.

Statistics
All values are mean with 95% confidence intervals (CIs). The Mann–Whitney U test was used for comparison between groups and the Wilcoxon signed rank sum test was used for comparison within groups. \( P < 0.05 \) was defined as being statistically significant.

Results
Baseline measurements
Mean arterial pressure and heart rate were similar in the groups (Fig. 1). There were no differences in forearm blood flow between groups, either in relation to 100 g or to total limb weights. Leg blood flow was 74% higher and leg vascular resistance was 42% lower among SCI subjects calculated in relation to 100 g but these differences disappeared when related to total limb weight (Table 2).

Total body noradrenaline spillover showed no significant difference between the groups [SCI mean, 2163 (CI, 1233–3094 pmol/min); control mean, 2826 (CI, 1373–4278 pmol/min)] and arterial noradrenaline concentrations were also similar [SCI mean, 1.29 (CI, 0.79–1.78 nmol/l); control mean, 1.26 (CI, 0.82–1.71 nmol/l)]. Total body noradrenaline clearance was similar [SCI mean, 1762 (CI, 1344–2180 ml/min); control mean, 2269 (CI, 1767–2771 ml/min)]. Regional noradrenaline spillover did not differ significantly between arm and leg among SCI subjects, whereas control subjects showed a higher noradrenaline spillover in the arm than in the leg. Fractional extraction of \(^{3}H\)noradrenaline across the leg vascular bed was lower in SCI than in control subjects, whereas there was no difference between the groups with regard to noradrenaline clearance in legs, either in relation to 100 g or to total limb weight (Table 2).

Central stimulation
Mean arterial pressure and heart rate increased in both groups during mental stress (Fig. 1). The SCI group showed a higher heart rate than control subjects (76 versus 64 beats/min, \( P < 0.05 \)) during mental stress. Blood flow increased in arms and legs in both groups following mental stress. This was associated with a decrease in forearm vascular resistance but an unaltered leg vascular resistance in the SCI group, whereas the control subjects presented a decrease in leg vascular resistance [from 79 to 63 mmHg/ml/min/100 g (Fig. 2)]. Skin perfusion increased in the finger in both groups [SCI subjects, +47% (CI, from –9 to +103%); control subjects, +62% (CI, from –4 to +127) (Fig. 2)], whereas none of the groups showed any significant change in toe skin perfusion.

During mental stress, noradrenaline spillover from the forearm vascular bed increased in SCI subjects, reaching a higher value than the control group, which showed an unchanged noradrenaline spillover from the forearm (SCI subjects, 2.73 pmol/min/100 g and control subjects, 1.71 pmol/min/100 g, \( P < 0.05 \)). Total body noradrenaline spillover showed a tendency to increase in SCI subjects (from 2163 to 2646 pmol/min, \( P = 0.06 \)) but it was significantly lower than in control subjects during mental stress. The latter group increased
Table 2 Skeletal muscle blood flow, vascular resistance and noradrenaline kinetics at baseline

<table>
<thead>
<tr>
<th></th>
<th>SCI subjects</th>
<th>Control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arm</td>
<td>Leg</td>
</tr>
<tr>
<td>Blood flow</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ml/min/100 g</td>
<td>4.31 (0.91–7.64)</td>
<td>2.03 (1.41–7.64)*</td>
</tr>
<tr>
<td>ml/min</td>
<td>440 (87–794)</td>
<td>426 (288–565)</td>
</tr>
<tr>
<td>Vascular resistance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>mmHg/ml/min/100 g</td>
<td>35 (16–54)</td>
<td>46 (29–63)*</td>
</tr>
<tr>
<td>mmHg/ml/min</td>
<td>0.37 (0.15–0.59)</td>
<td>0.22 (0.14–0.31)</td>
</tr>
<tr>
<td>Fractional extraction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>[3H]noradrenaline</td>
<td>0.50 (0.21–0.78)</td>
<td>0.34 (0.21–0.46)**</td>
</tr>
<tr>
<td>Noradrenaline clearance</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ml/min/100 g</td>
<td>0.65 (0.07–1.22)</td>
<td>0.36 (0.13–0.59)</td>
</tr>
<tr>
<td>ml/min</td>
<td>64 (3–126)</td>
<td>76 (22–129)</td>
</tr>
<tr>
<td>Noradrenaline spillover</td>
<td></td>
<td></td>
</tr>
<tr>
<td>pmol/min/100 g</td>
<td>1.56 (0.50–2.62)</td>
<td>0.22 (–0.02–0.46)</td>
</tr>
<tr>
<td>pmol/min</td>
<td>183 (120–245)</td>
<td>53 (–35–245)</td>
</tr>
</tbody>
</table>

All values are mean with 95% confidence interval. *, ** significant difference between groups P < 0.05, P < 0.01, †, †† significant difference between arm and leg within groups.

their total body noradrenaline spillover by 34% from 2826 to 3783 pmol/min (Fig. 3). Leg noradrenaline spillover decreased in SCI subjects, whereas in control subjects it increased from 0.23 to 0.49 pmol/min/100 g, reaching a significantly higher value than in the SCI group (Fig. 3). Fractional extraction and noradrenaline clearance in the lower limbs were unaltered in the SCI group during mental stress, and they remained lower than those in control subjects.

**Peripheral stimulation**

Mean arterial pressure increased during bladder stimulation whereas heart rate did not change significantly (Fig. 1). Forearm blood flow remained unchanged and leg blood flow decreased. The leg vascular resistance increased from 48 to 77 mmHg/ml/min/100 g. Toe skin perfusion showed a reduction by 56% during bladder stimulation (Fig. 2), whereas no reaction was found above the level of the lesion in finger skin perfusion.

Total body noradrenaline spillover showed a tendency to increase during bladder stimulation from 2526 to 3999 pmol/min (Fig. 3). Total body noradrenaline clearance was unaltered [at rest, 1518 (CI 1351–1685 ml/min); bladder stimulation, 1589 (CI, 1119–2059 ml/min)]. Arterial noradrenaline increased almost two-fold during peripheral stimulation [from 1.37 (CI, 0.92–1.82 nmol/l) to 2.55 (CI, 1.44–3.65 nmol/l), P < 0.05]. Leg noradrenaline spillover increased 15-fold during bladder stimulation (from 0.06 to 0.91 pmol/min/100 g; P < 0.05) (Fig. 3). The regional difference in noradrenaline spillover during baseline (related to total limb weight) (arm, 138; leg, 13 pmol/min; P < 0.05) disappeared following bladder stimulation (arm, 174; leg, 201 pmol/min). During bladder stimulation, fractional extraction of noradrenaline across the leg circulation increased and the previous regional difference in noradrenaline extraction disappeared.

**Discussion**

The main findings in our study were as follows. (i) Peripheral afferent (bladder) stimulation in SCI subjects induced a marked noradrenaline spillover below, but not above, the level of the lesion. This suggests that intact sympathetic nerves below the level of the lesion were activated by a spinal reflex arc. (ii) Central sympathetic activation (mental stress induced by forced mental arithmetic testing) increased heart rate and arm noradrenaline spillover more in SCI subjects than in control subjects, indicating an exaggerated sympathetic response above the level of the lesion in SCI subjects. (iii) Noradrenaline spillover, blood flow and vascular resistance in the legs of SCI subjects did not differ from those in control subjects during the baseline, supine condition, in spite of the lack of central sympathetic drive on peripheral sympathetic outflow to the legs. This reflects a low baseline noradrenaline spillover from the legs in healthy subjects as well (Karlsson et al., 1997c) but it may partly be due to a continuous influence of low-intensity peripheral afferent stimuli. (iv) Removal of released noradrenaline in legs did not differ between groups, indicating a normal removal mechanism for noradrenaline in SCI subjects.

**Peripheral stimulation**

The decentralized sympathetic nervous system in the leg was activated during bladder stimulation, as demonstrated by a marked increase in leg noradrenaline spillover associated with
vasoconstriction of the skeletal muscle and skin vascular beds, whereas no such reaction was observed in the arm. The vascular reactions are as those obtained by others (Corbett et al., 1975; Stjernberg et al., 1986), whereas the marked increase in noradrenaline spillover seems contradictory to the limited activation of sympathetic nerve fibres recorded in the peroneal nerve of SCI subjects during bladder stimulation (Stjernberg et al., 1986). However, microneurography registers the electrical activity of sympathetic nerve fibres whereas noradrenaline spillover measures the amount of the transmitter that enters plasma, adjusted for the removal. There may be alterations in the intermediate region that are not visualized by the noradrenaline spillover technique, such as increased transmitter release per nerve impulse, decreased end-organ uptake and degradation or decreased neuronal reuptake. End-organ supersensitivity has been discussed (Mathias et al., 1976b; Stjernberg et al., 1986) when comparing the low nerve activity with the vigorous end-organ response. However, platelet α-adrenoceptor density is normal in tetraplegic subjects (Davies et al., 1982b) in contrast to other autonomic deficiencies presenting denervation supersensitivity (Davies et al., 1982a). Together with our finding of a 15-fold increase in leg noradrenaline spillover, this may indicate that receptor supersensitivity is not inevitably needed to explain the dysreflexia reaction.

Bladder stimulation increased blood pressure whereas heart rate remained unaltered in the SCI subjects. During a dysreflexic episode bradycardia is usually, (Mathias and Frankel, 1992), but not always seen (Scott and Morrow, 1978; Kewalramani, 1980). In the present investigation, the lack of reaction in heart rate may be due to a partly intact sympathetic innervation of the heart in the majority of the investigated SCI subjects. The investigation procedure may have activated these fibres centrally, thereby counteracting the baroreceptor mediated vagal outflow to the heart. Two subjects in the SCI group showed some sensory sparing. When scrutinizing the individual values, we found no difference between their values and the rest of the group during peripheral or central activation.
Noradrenaline spillover in spinal cord injury

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Fig. 3 Total body, arm and leg noradrenaline (NA) spillover during mental stress (left) and bladder stimulation (right) in SCI subjects (filled symbols) and control subjects (open symbols). *P < 0.05, **P < 0.01, significant differences between groups. #P < 0.05, significant difference between baseline and stimulation in SCI subjects. §P < 0.05, significant difference between baseline and stimulation in control subjects. Values are means with 95% CIs.

Furthermore, it is known that subjects with incomplete lesions may exhibit a dysreflexia reaction (Kewalramani, 1980; Thyberg et al., 1992).

In able-bodied subjects, bladder distension increases sympathetic nerve activity in limb nerves (Fagius and Karhuvaara, 1989), but it has limited haemodynamic effects. In our SCI subjects, the marked increase in blood pressure was associated with a rise in arterial noradrenaline concentration, indicating a more widespread sympathetic activation, possibly including the visceral vascular bed. Our findings corroborate recent findings (Maiorov et al., 1997) of a marked increase in renal sympathetic nerve activity in ‘spinal’ rats, i.e. rats with spinal cord lesions at level T5. Furthermore, experimental spinal cord injury is associated with dendrite degradation of sympathetic preganglionic neurones post-injury, followed by signs of sprouting and new synapse formation in the injured medulla (Krassioukov and Weaver, 1995; Krassioukov and Weaver, 1996; Maiorov et al., 1997; Weaver et al., 1997). Such a spinal remodelling may underlie the marked capacity for peripheral afferent stimulation of the sympathetic nervous system arising after spinal cord injury.

Central stimulation

Mental stress induced an increase in heart rate and mean arterial pressure in SCI subjects, in contrast to the previous findings of Corbett et al. (1971) who investigated SCI subjects with lesions at C5–C6. Our group consisted of two subjects with lesions at C7 and seven with lesions at T3–T4. An SCI subject with a lesion at C7 has an almost intact motor and sensory function, but is usually considered to be sympathetically decentralized in the arm. However, there were no differences in cardiovascular reactions among our SCI subjects in spite of the differences in the level of the lesion. This finding suggests either a remaining sympathetic innervation of the heart in the whole group or a withdrawal of vagal tone as the mechanism behind the heart rate increase in the subjects with a lesion at C7. The stress-induced increase in arm noradrenaline spillover in the whole group supports the first alternative. It may be difficult to assess the neurological level of the lesion correctly when it is a low cervical one, since C8 function is seen only in finger flexors, and T1 function in finger abductors of the little finger. Consequently, a lesion classified as a C7 lesion may be confused with a T1 lesion with partly preserved sympathetic innervation of the arm and heart. Interestingly, the heart rate reaction and the increase in noradrenaline spillover were more marked in SCI subjects than in control subjects, indicating that the spinal cord lesion also affected sympathetic function above the level of the lesion, findings which are in agreement with studies in experimental spinal cord injury where signs of increased sympathetic activity (Maiorov et al., 1997) and synapse formation have been demonstrated above as well as below the level of the lesion (Krassioukov and Weaver, 1995, 1996).

In control subjects, noradrenaline spillover in the total body
and leg increased whereas no reaction was detected in the arm during mental stress, in agreement with the observed regional heterogeneity during mental stress in microneurographic recordings (Anderson et al., 1987). Although leg noradrenaline spillover in our study increased by almost 75%, its contribution to total body noradrenaline spillover was negligible (from 2.2% to 2.9%). This suggests that the stress-induced increase in total body noradrenaline spillover also emanated from other organs, presumably the splanchnic and renal vascular beds.

**Baseline measurements**

The finding of a similar total body noradrenaline spillover in the two groups may at first seem surprising, since sympathetic outflow to the main part of the trunk, splanchnic organs and lower limbs was decentralized in the SCI subject group. It may be that sympathetic activity is low at rest, as previously suggested by a lack of difference in lipolytic rate (Karlsson et al., 1997a). The ability to detect a difference between the two groups would perhaps require a larger sample population. The lack of difference should also be viewed in the light of regional differences in noradrenaline spillover in neurologically intact subjects. Leg noradrenaline spillover is markedly lower than arm spillover (Karlsson et al., 1997c) and <10% of total body spillover is derived from skeletal muscle and adipose tissue in legs and trunk in able-bodied subjects (Karlsson et al., 1997c). An intact innervation of the lungs in our SCI group may also be part of the explanation for the similar total body noradrenaline spillover in the groups, since noradrenaline spillover from lungs constitutes about one-third of total body noradrenaline spillover (Esler et al., 1984). Total body noradrenaline spillover in SCI subjects with lesions above T1 revealed a significantly lower total body noradrenaline spillover compared with control subjects (Krum et al., 1990). Peripheral afferent stimulation of sympathetic nerves below the level of the lesion may contribute to the normal total body noradrenaline spillover. Frequent episodes of high plasma noradrenaline levels have been demonstrated during 24 h (Karlsson et al., 1997b) and 4 h of continuous plasma noradrenaline monitoring (Levin et al., 1980). A peripheral activating mechanism seems likely, since even vigorous centrally mediated sympato-excitatory stimuli showed only a weak tendency to increase total body noradrenaline spillover in our present study group.

It may be speculated that differences in body composition may affect noradrenaline spillover values. The decrease in lean body mass in SCI subjects might result in altered sympathetic nerve density. The finding of a lower fractional extraction in the leg than in the arm may support this idea. However, the unaltered clearance suggests an intact removal capacity, which in turn indicates an unaltered nerve density. The putative relationship between obesity and sympathetic activity is obscure. Degree of obesity (Scherrer et al., 1994) and fat mass (Spraul et al., 1993) are held to correlate positively with sympathetic activity, whereas weight gain is thought to be related to reduced activity (Spraul et al., 1993). It seems less likely that differences in body composition have affected our results.

In summary, mental (i.e. central) stress activated the sympathetic nerves above the level of the lesion to a higher degree than in control subjects. This may be of importance for the blood pressure regulation in high paraplegia and tetraplegia. Peripheral stimulation activated the decentralized sympathetic nerves below the level of the lesion as shown by a marked increase in noradrenaline spillover in the legs and a pronounced end organ response. This may act as a compensating mechanism for the loss of central activation, in part explaining the lack of difference in total body noradrenaline spillover between resting SCI and control subjects.

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**References**


