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Microneurographic Analysis of Sympathetic Outflow to the Skin in Patients with Postoperative Hypothalamic Dysfunction after Suprasellar Tumors

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Abstract: In patients with suprasellar tumors, the tumor itself and also its surgical resection may produce hypothalamic dysfunction including thermoregulatory disturbances. We quantitatively evaluated skin sympathetic nerve activity (SSNA) using microneurography in eight patients with hypothalamic dysfunction following resection. SSNA, skin blood flow by laser Doppler, sweating, blood pressure, and pulse rate were monitored during changes of core (tympanic) temperature, in the patients and seven healthy controls. Core temperature was decreased by 0.3°C and increased by 0.5°C relative to baseline using a cooling/heating blanket. Argumentation of SSNA by cooling did not differ between patients and controls. An increase of SSNA upon heating was absent in patients but present in controls. Skin blood flow during heating increased significantly in controls but not in patients. Our results indicated that the patients had impaired heat loss during body temperature elevation. Microneurography is a sensitive measure of hypothalamic autonomic function.

Key words: microneurography, skin sympathetic nerve activity, suprasellar tumor, hypothalamus, thermoregulatory disturbance

Anhidrosis or intolerance of cold or heat exposure, often accompanied by uncontrollable weight gain, is a characteristic symptom in patients with suprasellar tumors such as craniopharyngioma, optic or hypothalamic glioma, germ cell tumor, or pituitary adenoma.[1-5] Since surgical resection of these tumors frequently worsens thermoregulatory symptoms, this form of autonomic dysfunction has been estimated to result from hypothalamic damage.

Skin sympathetic nerve activity (SSNA) regulates sweat glands and precapillary sphincters of arterioles. These sudomotor and vasoconstrictor/vasodilator/functions contribute to human thermoregulatory control.[6] Changes of ambient or body temperature influence the input to the hypothalamus, which alters sympathetic outflow patterns to maintain core temperature. SSNA contains both vasoconstrictor/vasodilator and sudomotor components in a ratio that varies with ambient temperature change. With cold exposure, SSNA is associated mainly with vasoconstrictor SSNA, with heat exposure, both sudomotor and vasodilator components act synchronously.[7,8]

In the present study, we used microneurography to evaluate sympathetic function in patients with hypothalamic dysfunction. SSNA induced by temperature changes was monitored in the peroneal nerve innervating the dorsum pedis, since SSNA via the peroneal nerve is more thermally dependent than tibial nerve SSNA.[9]

Clinical Materials and Methods

Subjects

Eight patients who had undergone surgical resection of suprasellar tumors involving the hypothalamus (craniopharyngiomas in seven and a massive pituitary adenoma in one) were studied. All patients showed symptoms of hypothalamic dysfunction such as diabetes inspidus, uncontrollable weight gain, and thermoregulatory dysfunction (sweating disorder or intolerance to cold or heat). Patients included six men and two women ranging in age from 17 to 67 years (mean ± SE, 43.6 ± 5.9).

Seven healthy volunteers without autonomic disturbances served as control subjects. They included six men and one woman, with ages ranging from 28 to 46 years (mean ± SE, 33.9 ± 2.6). The age distribution for the controls was slightly younger than for the patients, but not significantly.

Microneurography and other measurements

Subjects were positioned supine on a bed in a temperature-controlled room with initial ambient temperature of 25 ± 1°C. To achieve rapid change of core temperature, a cooling/heating blanket using circulating water was placed over and under the subject. A tungsten microelectrode was inserted percutaneously into the peroneal nerve without anesthesia to record sympathetic nerve discharges. The nerve discharge was integrated with a time constant at 0.1 second and recorded.

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In addition to SSNA, the following parameters were monitored continuously: electrocardiographic activity (ECG), blood pressure, skin temperatures on the forehead, chest, and calf, tympanic temperature (Tty), and cutaneous blood flow on the plantar aspect of the toe base using a laser Doppler flowmeter (LDF).

Protocol of experiments

After 15 min of rest, data were recorded for 5 min and averaged as the baseline. Then ambient temperature (Ta) was lowered to 10°C, and the blanket was irrigated with 20°C water (cooling period). Temperatures and cardiovascular parameters were recorded at 1-min intervals. Cooling was continued until the tympanic temperature (Tty) had declined 0.3°C from its baseline value. If Tty was not lowered to the target temperature within 90 min, or if the subject complained that the cold was intolerable, cooling was abandoned. The heating period followed; Ta was increased to 36°C, and the temperature of water circulating in the blanket was increased to 42°C. Heating was continued until Tty was 0.5°C above its baseline. Heating was abandoned if the subject complained of intolerable heat. Data obtained from initiation of cooling to the trough of Tty were analyzed as representing the cooling period, data obtained after Tty recovered to the baseline temperature were analyzed as representing the heating period.

Data analysis

In the present study, changes in SSNA burst rate of a subjects were analyzed during cooling and heating periods. A correlation plot was drawn between SSNA burst rate and Tty during the cooling and heating periods, and the slope of the regression line was designated $SSNA/Tty_{cold}$, or $SSNA/Tty_{hot}$ (Fig 1). Changes in other parameters vs. changes in Tty were also plotted, and slopes of regression lines were calculated. These slopes included skin blood flow measured with laser Doppler flowmetry (LDF/Tty), systolic blood pressure (SBP/Tty), diastolic blood pressure (DBP/Tty), and heart rate (HR/Tty). LDF/Tty_{cold} and LDF/Tty_{hot} were slopes of the regression lines between the skin blood flow and Tty during the cooling and heating periods.

Data are expressed as the mean ± SE; they were compared between the patients and the controls using Student's *t* test and between the cooling and the heating periods using Student's paired t test. *P* values less than 0.05 was considered to indicate significance.

Results

Baseline parameters

During the rest period, baseline data for Tty, LDF, and SSNA burst rate did not differ significantly between the patients and the controls (Tty: 36.55 ± 0.085 vs 36.57 ± 0.14°C, LDF: 5.0 ± 1.4 vs 4.6 ± 1.6 ml•min^{-1}•100 g tissue^{-1}, SSNA: 26.8 ± 7.3 vs 26.4 ± 8.8 bursts/min, patients vs controls, mean ± SE). Surface skin temperature (Ts; mean of skin temperatures on forehead, chest, and calf) has a tendency to be lowered in the patients, but the difference was not significant (32.40 ± 0.37 vs 33.09 ± 0.31, patiens vs controls, mean ± SE, p=0.09).

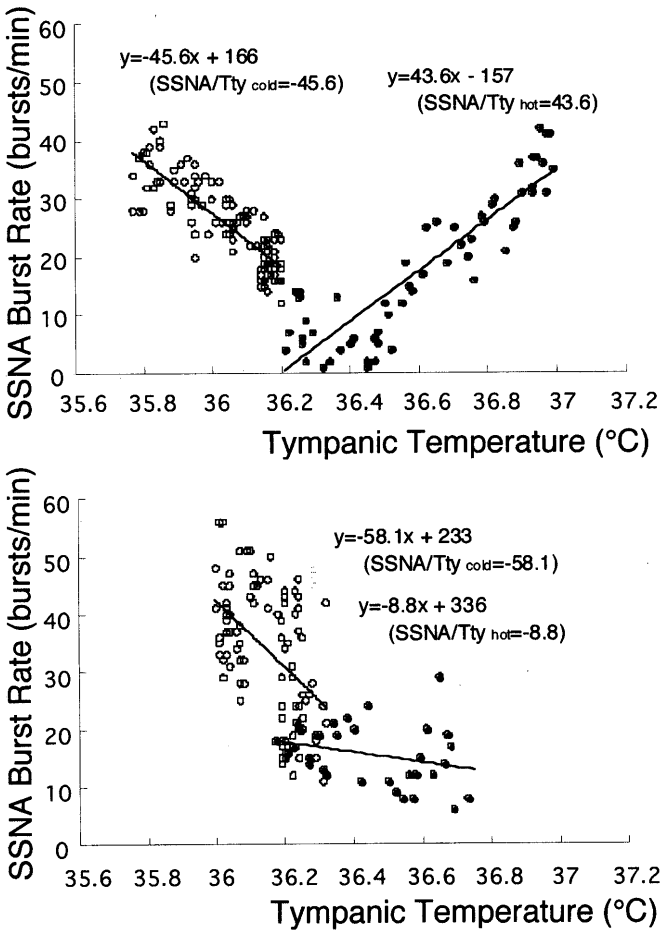

Fig. 1 Correlation plot between tympanic temperature (Tty) and skin sympathetic nerve activity (SSNA) in control 1 (above) and patient 1 (below).
A regression line was drawn for the cooling period (open circles) and for the heating period (filled circles) respectively. Slopes during cooling and heating periods were calculated and determined as $SSNA/Tty_{cold}$ and $SSNA/Tty_{hot}$, respectively.

SSNA and change in core temperature

Tty was lowered in the range of 0.15 – 0.49 (0.3 ± 0.05) °C below the baseline temperature in patients, and 0.3 – 0.45 (0.38 ± 0.02) °C in controls. With cooling of Tty, SSNA burst rate increased in both controls and patients. $SSNA/Tty_{cold}$ was –41.0 ± 13.1 in controls and –38.1 ± 7.7 in patients.

Tty rose in the range of 0.3 – 0.79 (0.5 ± 0.08) °C above the baseline in patients, and 0.35 – 0.84 (0.54 ± 0.08) °C in controls. With the Tty increase, the SSNA burst rate increased in controls (Fig. 1, upper panel), however, SSNA burst rate increased slightly in one and decreased in other patients. The

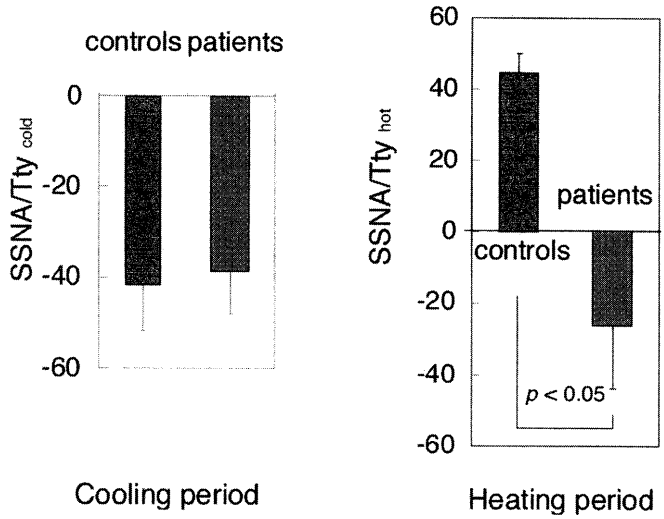

Fig. 2 Changes of skin sympathetic nerve activity (SSNA) during cooling ($SSNA/Tty_{cold}$) and heating ($SSNA/Tty_{hot}$) periods were compared between the controls and patients.
$SSNA/Tty_{cold}$ were not significantly different between controls and patients. $SSNA/Tty_{hot}$ was significantly lower in patients than controls.

lower panel of Fig. 1 shows typical changes in a patient with decreased SSNA. $SSNA/Tty_{hot}$ in the controls and the patients was 45.1 ± 5.4 and –26.0 ± 17.5, respectively. While no difference was present in $SSNA/Tty_{cold}$ between the patients and the controls, $SSNA/Tty_{hot}$ in the patients was significantly lower than in the controls ($p<0.05$, Fig. 2).

Skin blood flow and change of core temperature

In both patients and controls, LDF increased when Tty was elevated. LDF/Tty was 27.6 ± 9.3 in the patients and 20.0 ± 14.0 in the controls. The controls showed a significant increase in LDF during the heating period; (LDF/Tty_{hot} = 35.9 ± 14.6) as compared with LDF during the cooling parid (LDF/Tty_{cold} = -8.3 ± 5.8) ($p<0.05$). In the patients, LDF/Tty_{hot} (15.3 ± 5.8) was higher than LDF/Tty_{cold} (4.0 ± 2.1), but not significantly.

Discussion

To demonstrate the advantages of microneurography for quantitative evaluation of the sympathetic component of hypothalamic function, we examined patients with sympathetic hypothalamic dysfunction after surgical resection of large suprasellar tumors.

In response to cooling or heating input to the hypothalamus, SSNA increased in healthy controls. The SSNA increase induced by cooling input results mainly in constriction of the precapillary sphincter of arterioles. The SSNA increase associated with heating results mainly in vasodilation and in sudomotor activity in sweat glands.[6] In patients, the SSNA response to cooling was preserved, while SSNA did not increase when core temperature was elevated. Also the normal marked increase of skin blood flow during heating was blunted in patients.

The present results demonstrated that sympathetic outflow mediating vasodilation and sweating induced by heating of the core temperature was impaired in the patients with hypothalamic dysfunction. Our results objectively indicated that patients were incapable of heat loss during core body temperature elevation.

Craniopharyngiomas usually originate from the pituitary stalk and compress the anterior hypothalamus from the medial or inferior aspect of the anterior third ventricle.[5] Total removal of these tumors using a lamina terminalis approach requires dissection of the tumor from surrounding structures, which may damage the anterior portion of the hypothalamus.

Animal studies identified thermosensitive neurons in the preoptic area that regulated heat production and heat loss.[10] Zhang et al. reported that heat-sensitive neurons predominanted in the preoptic area relative to cold-sensitive neurons.[11]

Taking the above observations together, the preoptic area would appear to be responsible for impaired sympathetic activity in the patients, explaining elimination of responses to heating.

Responses of sympathetic nerve activity to the skin were examined using microneurography in patients who manifested hypothalamic dysfunction after surgical resection of the suprasellar tumors. In patients, sudomotor and vasodilator nerve activities during heating were markedly impaired compared with responses in controls. This thermoregulatory dysfunction appears attributable to the preoptic lesion. We found microneurography to be an effective and sensitive way to evaluate the sympathetic component of hypothalamic function. In these patients, thermoregulatory dysfunction, including sweating disorders or heat intolerance might be attributed to lack of sympathetic response to core temperature elevation.

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