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RAPID RESETTING OF HUMAN BAROREFLEX WORKING RANGE: INSIGHTS FROM SYMPATHETIC RECORDINGS DURING ACUTE HYPOGLYCAEMIA

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SUMMARY

1. Human muscle nerve sympathetic activity (MSA), which is governed by baroreflexes and involved in blood pressure homeostasis, is increased during acute insulin-induced hypoglycaemia.

2. To elucidate the detailed relationship between MSA and blood pressure during hypoglycaemia, 0·15 i.u. (kg body weight)$^{-1}$ regular human insulin was given intravenously to eight fasting, healthy volunteers. Microneurographic recording of MSA in the peroneal nerve was made with simultaneous monitoring of arterial blood pressure by a finger cuff (Finapres). The course of MSA and blood pressure was monitored for 30 min before and 60 min after insulin injection. In three subjects control recording without insulin injection was made for the same duration.

3. Stimulus–response regression lines were constructed by plotting diastolic blood pressure against the occurrence frequency of MSA for the period of initial rest, the period of maximal MSA outflow during hypoglycaemia and the period of glucose counter-regulation. The control experiments were analysed for the corresponding periods.

4. The stimulus–response line was stable throughout the control experiments, whereas it was shifted either to the left or to the right during hypoglycaemia, and regularly shifted to the left (i.e. towards a lower blood pressure) during glucose counter-regulation, without change of slope.

5. It is concluded that the changes in MSA during acute hypoglycaemia are not secondary to baroreflex regulation but instead are characterized by acute resetting of the baroreflex working range without change of sensitivity.

INTRODUCTION

Acute insulin-induced hypoglycaemia in human beings is accompanied by a strong increase in muscle nerve sympathetic activity, MSA (Fagius, Niklasson & Berne, 1986). MSA is primarily regulated by baroreflexes and is involved in cardiovascular homeostasis (Wallin & Fagius, 1988). At rest there is a close dynamic relationship between (predominantly diastolic) arterial blood pressure and MSA with a fall in blood pressure inducing increase in MSA and a blood pressure elevation inhibiting

the outflow of MSA (Sundlöf & Wallin, 1978; Eckberg, Rea, Andersson, Hedner, Pernow, Lundberg & Wallin, 1988). Acute hypoglycaemia in healthy subjects is known to induce a slow change in blood pressure, mainly characterized by an increase in pulse pressure, coinciding with and following the nadir of blood glucose (Hilsted, Bonde-Petersen, Norgaard, Greniman, Christensen, Parving & Suzuki, 1984; Frandsen, Berne, Fagius, Niklasson, Christensen & Hilsted, 1989).

Thus, it is possible that the increase in MSA during acute insulin-induced hypoglycaemia might be a secondary phenomenon following baroreflex responses to blood pressure fluctuations. On the other hand the enhanced MSA might be a primary event, elicited by neuroglucopenia; if so it may involve an acute resetting of the blood pressure level at which the baroreflex are inhibiting the outflow of MSA.

To elucidate this matter more precisely, sympathetic nerve recording and non-invasive continuous monitoring of blood pressure was carried out during insulin-induced hypoglycaemia in healthy volunteers, and the relationship between blood pressure and MSA was subjected to a detailed analysis.

METHODS

Recordings of peroneal nerve MSA were made with microneurography (Wallin & Fagius, 1988) in eleven healthy, non-smoking subjects of normal weight, seven women and four men, aged 24·3 ± 1·6 years (means ± S.E.M.). Informed consent was received from all subjects from all subjects and the study was approved by the Ethics Committee of the Medical Faculty of the University of Uppsala.

Nerve recordings

A tungsten microelectrode with an uninsulated tip of about 5 μm diameter was inserted through the skin at the right fibular head into the underlying peroneal nerve. A low-impedance reference electrode was placed subcutaneously 2 cm away. The nerve was localized with the aid of electrical stimuli through the recording electrode. An electrode position within a muscle nerve fascicle was identified by muscle twitches without concomitant skin paraesthesiae following electrical stimuli, and by the appearance of afferent muscle spindle activity when the appropriate muscle was passively stretched.

When a muscle nerve fascicle was found, minute adjustments of the electrode position were made until the characteristic multi-unit bursts of MSA (see Fig. 2) were encountered. The criteria for the sympathetic origin of the signal recorded have been established previously and are in brief (Wallin & Fagius, 1988): (a) the impulses are efferent, as shown by applying an anaesthetic agent proximal or distal to the recording site; (b) the impulses are conducted at approximately 1 m s^{-1}; (c) the activity is reversibly abolished by the intravenous administration of a ganglion blocking agent; and (d) the activity is intimately related to changes in blood pressure. At a given recording attempt MSA is identified from its characteristic appearance in sequences of spontaneous, pulse-synchronous bursts (see Fig. 2) and its typical response to a Valsalva manoeuvre (Wallin & Fagius, 1988).

Minor discomfort may be experienced by the subject during the search for a recording position, but once this is obtained nothing is felt during the continuous recording. Transient slight paraesthesiae in the innervation zone of the nerve may occur a few days after the experiment (Eckberg, Wallin, Fagius, Lundberg & Torebjörk, 1989). This was not reported by any of the subjects of the present study in a follow-up by letter.

The nerve signal was amplified in two steps, with a total gain of 50000×, and fed through a 700–2000 Hz bandpass filter and an amplitude discriminator for optimal signal-to-noise ratio. A resistance–capacitance integrating network with time constant 0·1 s delivered a mean voltage neurogram, which was used for display and analysis of the nerve activity (cf. Fig. 2).

Continuous monitoring of finger arterial blood pressure was made non-invasively with a cuff applied to the right middle finger (Finapres, Ohmeda, Englewood, CO, USA; Imholz, van

Montfrans, Settels, van der Hoeven, Karemaker & Wieling, 1988). The hand was positioned at the heart level. The device delivered a continuous blood pressure signal (cf. Fig. 2) as well as a digital display of systolic and diastolic blood pressure values, the latter being the average of measurements every two seconds.

Electrocardiogram (ECG) was recorded by chest surface electrodes.

General experimental procedure

The experiments were carried out in the morning, with the subjects arriving at 8 am after fasting from midnight. They emptied their urinary bladder immediately before the experiment, since bladder distension is known to cause elevation of blood pressure with concomitant increase in MSA (Fagius & Karhuvaara, 1989). The subject was lying comfortably supine on a bed in an ambient temperature of about 23 °C.

After insertion of separate cubital indwelling catheters for insulin injection and blood sampling, the Finapres cuff for blood pressure monitoring was applied. We have observed a drift upwards of the blood pressure values obtained from this device during the first 10–15 min after its application. To prevent this tendency from causing bias, the blood pressure was measured continuously during the search for a suitable intraneural recording position, which comprised 10 min of technical preparation and 10–45 min active exploration of the nerve.

When an electrode position recording MSA with an acceptable signal-to-noise ratio was obtained, nerve activity, blood pressure, and ECG were monitored during 30 min of supine rest before a rapid intravenous injection of regular human insulin, 0·15 i.u. (kg body weight)$^{-1}$ (Actrapid Human, Novo Nordisk, Bagsvaerd, Denmark), was given to eight subjects. Blood samples for plasma glucose analysis were drawn at −15, 0, 15, 22·5, 30, 45 and 60 min in relation to the insulin injection.

Three subjects served as controls. They underwent the same recording procedure during 90 min of supine rest; no indwelling catheters were applied.

Analysis procedure

The mean voltage neurogram, finger arterial BP and ECG were written out on paper, 2·5 mm s^{-1}, with an ink-jet recorder (see Fig. 2) (Siemens-Elema, Stockholm, Sweden). The bursts of MSA, time-locked in the cardiac rhythm were counted manually in 6 min periods surrounding −15, 0, 15, 22·5, 30, 45 and 60 min in relation to the insulin injection. The outflow of MSA was expressed as bursts min^{-1}. Heart rate was obtained from the same paper display.

The general course of blood pressure (cf. Fig. 1) was calculated as the mean of 12–15 consecutive digital readings from the Finapres display every 7·5 min.

From each experiment, 200 consecutive heart beats during the period of initial rest, during the maximal outflow of MSA during hypoglycaemia (i.e about 30 min after the insulin injection, cf. Results), and during the spontaneous glucose recovery (counter-regulatory) phase, (i.e. about 55 min after insulin injection) were selected for detailed blood pressure analysis. The criterion for selection was that the section should be a sample of the mean sympathetic outflow representative of the period under analysis. The selected periods were written out on the ink-jet recorder with a high gain of the BP signal. From this print-out diastolic blood pressure for every heart beat of the period under analysis ($n = 200$) was measured in mmHg on a digitizing board (Hipad, Houston Instruments, Austin, TX, USA) connected to a computer (Digital Micro VAX II, Digital Equipment, Maynard, MA, USA).

For each heart cycle, thus represented by its diastolic blood pressure value, the occurrence or not of a burst of MSA was noted. From the percentage of heart beats associated with a burst of MSA at a given diastolic blood pressure level a stimulus–response regression line for each analysed period was constructed (cf. Figs 2 and 3). Diastolic blood pressure was chosen for this analysis, since it has previously been shown to be the major determinant for the appearance of bursts of MSA (Sundlöf & Wallin, 1978; Fagius & Karhuvaara, 1989).

The control experiments were analysed in an identical way for the corresponding time periods.

Blood chemistry

Plasma glucose was measured with a glucose oxidase technique using a glucose analyser (Beckman model 2, Beckman Instruments Inc., Palo Alto, CA, USA).

Statistical analysis

Results are expressed as means ± S.E.M. For statistical evaluation analysis of variance (ANOVA) with Dunnet's *t* test for multiple comparisons, linear regression analysis with *t* test of the correlation coefficient, and Student's *t* test for unpaired observations were applied.

RESULTS

All subjects receiving insulin developed the characteristic symptoms of an acute hypoglycaemic reaction (palpitations, feeling of hunger and warmth, sweating and, in a few, a feeling of drowsiness). Fasting plasma glucose was 4·9 ± 0·1 mmol l^{-1}, and after the insulin bolus a nadir value of 1·8 ± 0·1 mmol l^{-1} was reached before glucose counter-regulation took place. The 60 min plasma glucose level was 3·1 ± 0·2 mmol l^{-1} (Fig. 1).

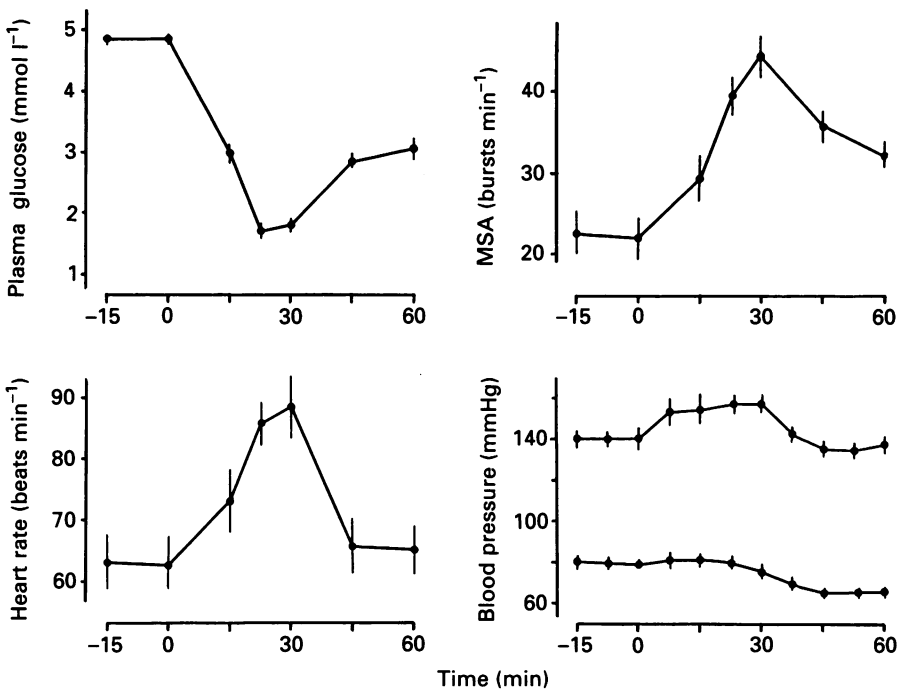

Fig. 1. Course of plasma glucose, muscle nerve sympathetic activity (MSA), heart rate and systolic and diastolic blood pressure in eight subjects given an insulin injection, 0·15 i.u. (kg body weight)$^{-1}$ at time 0. Means ± S.E.M.

MSA and heart rate increased in all subjects as expected, and the time courses of MSA, heart rate and blood pressure are summarized in Fig. 1. Mean outflow of MSA during the period of initial rest was 22·9 ± 2·9 bursts min^{-1}; the range was 10–34 bursts min^{-1}, illustrating the well-known inter-individual variation of MSA at rest (Sundlöf & Wallin, 1977). The peak outflow of MSA at 30 min after insulin was 44·4 ± 2·4 bursts min^{-1} and at 60 min the outflow was 32·4 ± 1·8 bursts min^{-1}. The blood pressure changes were similar to those observed during acute insulin-induced

hypoglycaemia previously (Hilsted *et al.* 1984; Frandsen *et al.* 1989) with an increase in pulse pressure and a relatively late decrease in diastolic blood pressure. The alterations of MSA, heart rate and diastolic and systolic blood pressure were all statistically significant ($P < 0{\cdot}001$; ANOVA).

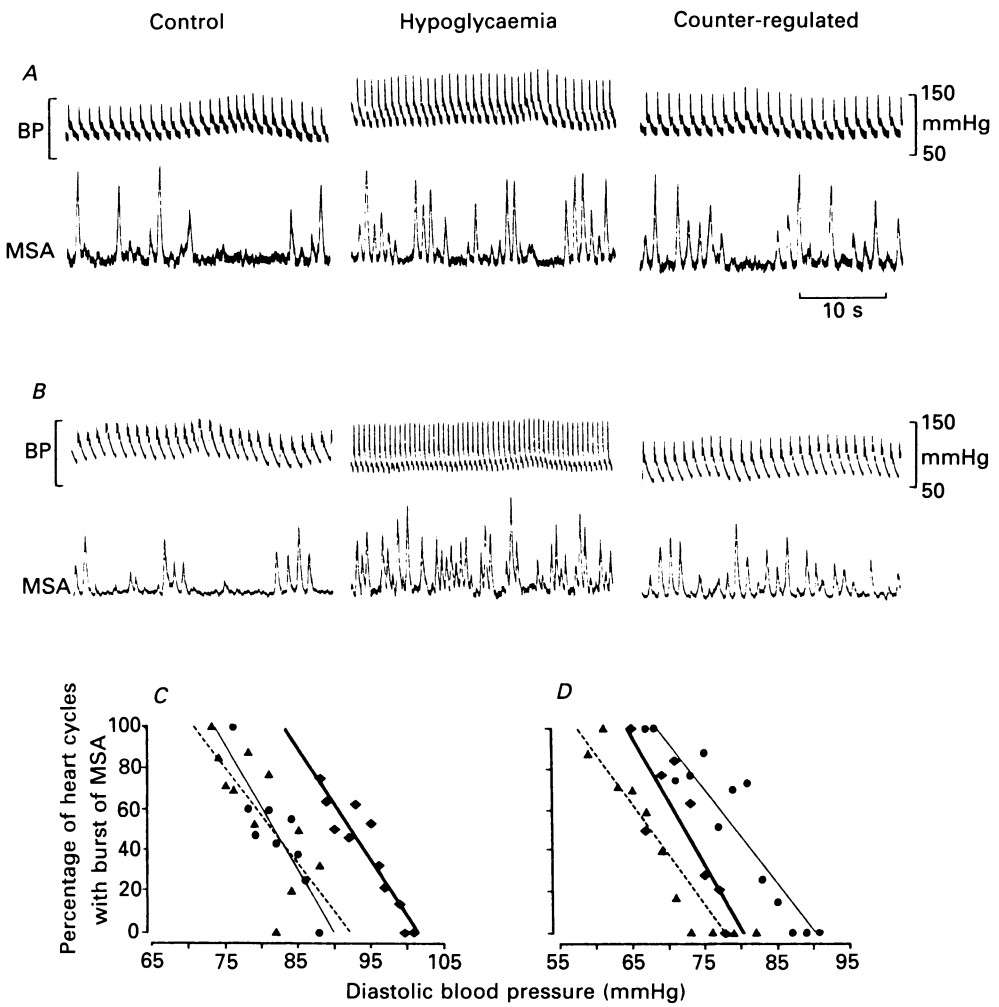

Fig. 2. *A* and *B*, recording examples of muscle nerve sympathetic activity (MSA; mean voltage neurogram) and arterial blood pressure (BP) during initial rest, at the time for maximal outflow of MSA during hypoglycaemia and in the counter-regulatory phase about 25 min after the nadir of plasma glucose in two subjects. *C* and *D*, stimulus–response regression lines for the appearance of MSA at different diastolic blood pressure levels in the same subjects as *A* and *B* respectively. ●——●, initial rest; ◆——◆, hypoglycaemia; ▲---▲, counter-regulation.

The outflow of MSA, heart rate, and blood pressure level remained stable in the three control experiments throughout 90 min of supine rest.

Figure 2 displays examples of recordings from two subjects during initial rest, and

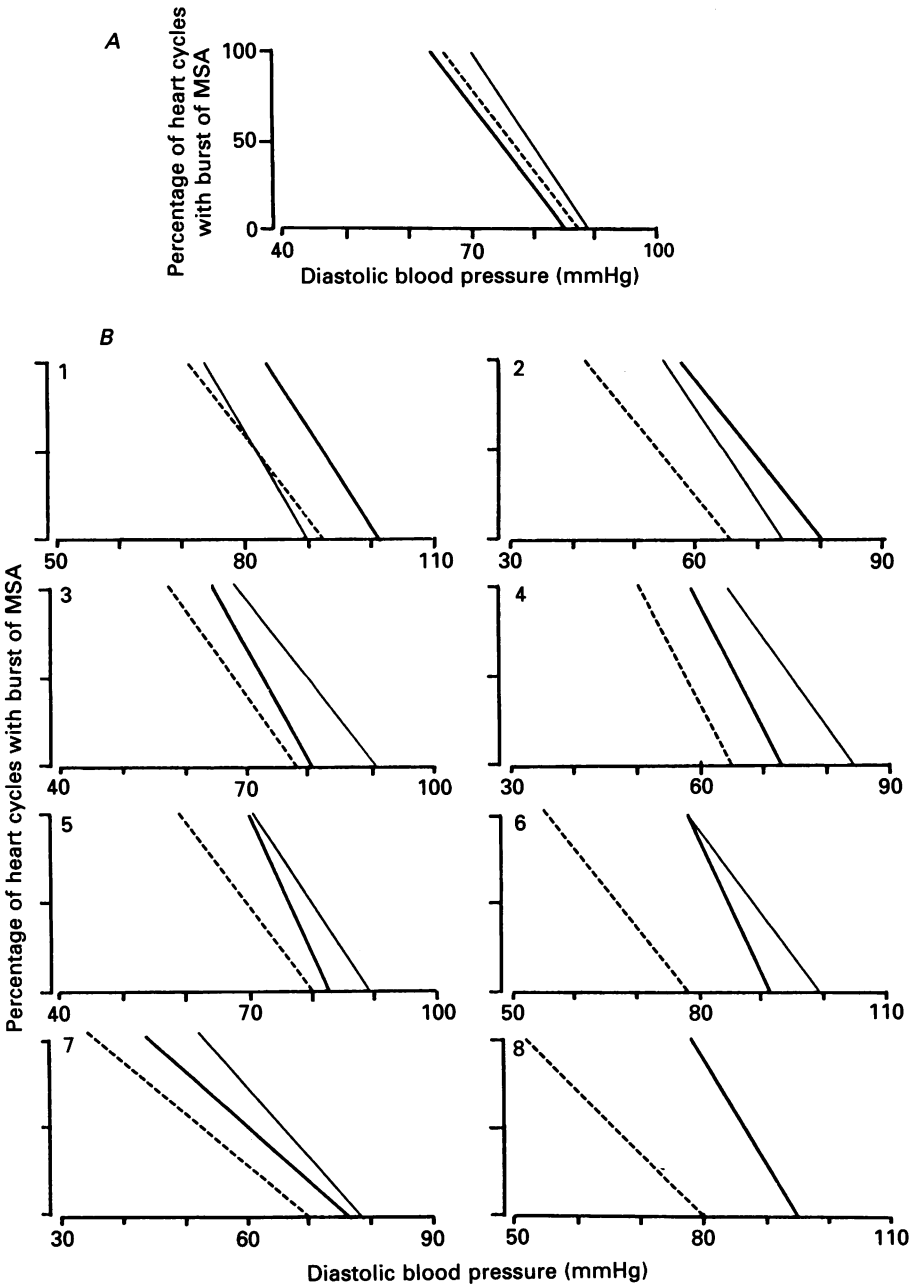

Fig. 3. Stimulus–response regression lines for the appearance of MSA at different diastolic blood pressure levels, *A*, in one control subject during 90 min rest and, *B*, in eight subjects receiving insulin injection (numbered 1–8). ————, initial rest; ——, hypoglycaemia, ~ 30 min after insulin injection; ------, counter-regulatory phase, ~ 55 min after insulin injection; corresponding time points in the control subject. In subject No. 8 no stimulus–response line could be constructed for the period of initial rest, due to too low outflow of MSA; the blood pressure at which MSA occurred was higher at initial rest than during hypoglycaemia in this subject as in subjects 3–7.

in the hypoglycaemic and counter-regulatory phases. Both subjects exhibited an increased pulse pressure during hypoglycaemia, the diastolic blood pressure level being higher than during initial rest in one (Fig. 2*A*) and lower in the other (Fig. 2*B*. In both a reduction of the diastolic blood pressure level occurred during glucose counter-regulation; in the second subject (Fig. 2*B*) to a level that was lower than that

TABLE 1. Mean diastolic blood pressure of heart cycles associated with a burst of MSA during initial rest, hypoglycaemia and in the counter-regulatory phase in each subject and during corresponding time periods in three control experiments

				Statistical significance		
Subject No.	I: Initial rest	II: Hypoglycaemia	III: Counter-regulation	I–II	I–III	II–III
1	81±1	93±1	79±2	***	n.s.	***
2	69±1	71±1	56±1	n.s.	***	***
3	76±1	70±1	64±1	**	***	***
4	78±1	64±1	57±1	***	***	***
5	80±1	76±1	69±1	*	***	***
6	89±1	83±1	64±1	***	***	***
7	69±1	64±1	60±1	**	**	***
8	89±1	86±1	64±1	n.s.	***	***
Control subject No.	I: Rest I	II: Rest II	III: Rest III			
1	80±1	76±1	77±1	*	n.s.	n.s.
2	73±1	72±1	73±1	n.s.	n.s.	n.s.
3	75±1	75±1	76±1	n.s.	n.s.	n.s.

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$; t test for unpaired observations. n.s. not significant. Control subject No. 1 is identical to the one illustrated in the top of Fig. 3.

at initial rest, a pattern that was seen in all subjects but the one illustrated in Fig. 2*A*. It can be seen in the examples of Fig. 2 first that the ordinary pulse synchrony of the bursts of MSA was preserved, and secondly that MSA tended to occur predominantly in association with minor transient reductions in diastolic blood pressure whereas inhibition followed a rise in pressure, as seen at normal rest.

The lower part of Fig. 2 shows stimulus–response regression lines for diastolic blood pressure *vs.* MSA for the two subjects exemplified in this figure, and Fig. 3 shows stimulus–response curves for all subjects given insulin and one control subject (subjects *A* and *C* of Fig. 2 and subject 1 Fig. 3 are identical, and subjects *B* and *D* of Fig. 2 and subject 3 of Fig. 3 are identical). In the control experiments the stimulus–response curves showed a virtually identical position at all periods of analysis (Fig. 3*A*).

During hypoglycaemia the curve was shifted to the right in two subjects, i.e. towards a higher level of blood pressure, whereas it was shifted to the left in five subjects (in one subject, No. 8 of Fig. 3, no stimulus–response line could be constructed for the period of initial rest, due to too low outflow of MSA, but the blood pressure at which MSA occurred was higher at initial rest than during hypoglycaemia also in this subject.

During glucose counter-regulation there was a regular shift of the stimulus–response lines to the left, i.e. to a lower level of blood pressure. In one subject

(Fig. 2*A*; No. 1 of Fig. 3) this meant a return to the initial position, whereas in all other subjects the curve displayed a working range of MSA on a lower blood pressure level than during initial rest.

Table 1 gives the mean values for the diastolic blood pressure of all heart cycles associated with a burst of MSA during the different periods of analysis and it can be seen that most of the shifts shown in Fig. 3 reached a high statistical significance. On the contrary, the control subjects displayed a virtually unchanged blood pressure level at which MSA occurred throughout the experimental course.

The slope of the curve remained similar despite the shifts along the blood pressure axis.

DISCUSSION

The principal finding in the present study was a shift of the stimulus–response curve for diastolic blood pressure *versus* MSA in either direction during hypoglycaemia and a regular shift to the left during the counter-regulatory phase, with the slope of the curve remaining stable. Thus MSA was working with its ordinary properties but at a higher or lower level of blood pressure during hypoglycaemia and at a lower blood pressure level during counter-regulation.

The cardiovascular consequences of acute hypoglycaemia includes a change in blood pressure with a relatively late reduction of diastolic blood pressure, as seen also in the present study, and a reduction of plasma volume, reflected by an increase in haematocrit (Hilsted *et al.* 1984; Hilsted, Bonde-Petersen, Madsbad, Parving, Christensen, Adelhøj, Bigler & Sjøntoft, 1985). These effects, as well as the increase in MSA, are evoked also by intravenous infusion of 2-deoxy-D-glucose, indicating that tissue glucopenia and not insulin *per se* plays the key role for the observed effects (Fagius & Berne, 1989). Attempts to counteract the plasma volume reduction by fluid and colloid substitution during acute hypoglycaemia did not affect the response of MSA, suggesting that the latter is not due to unloading of volume receptors (Frandsen *et al.* 1989).

In previous studies of the response of MSA to acute glucopenia observations of the gross time relationship between increase in MSA and blood pressure changes (detected by intermittent automatic blood pressure measurement) led to the suggestion that the sympathetic reaction is unlikely to be secondary to baroreflex action (Fagius *et al.* 1986; Fagius & Berne, 1989). The present observations confirm that the change of MSA is not a compensatory phenomenon due to baroreflex regulation. Instead the observed relationships represent a conclusive example of acute resetting of the baroreflex working range in humans. Consequently a primary change in peripheral circulation causing the increase in MSA is remote and a direct influence of glucopenia on central sympathetic motoneurones might elicit the reaction.

In experimental animals resetting of baroreflexes is well documented, chronically in hypertension (McCubbin, Green & Page, 1956) as well as within short periods of time in different experimental set-ups, and it has been shown that both reset of the threshold for baroreceptor discharge and central mechanisms can contribute to such a change (Richter, Keck & Seller, 1970; Salgado & Krieger, 1976; Brown, Saum & Yasui, 1978; Tan, Panzenbeck, Hajdu & Zucker, 1989).

Resetting of the baroreflex can be postulated in a number of well-known physiological and clinical situations in humans, but it has not been directly demonstrated very often. The most commonly used methods for testing baroreflexes in humans are analysis of R–R intervals of the ECG following induction of blood pressure changes by vasoactive drugs or by use of a neck chamber; in the latter case blood pressure reactions can be studied too (Mancia & Mark, 1983). Such studies have shown that chronic resetting, including reduced sensitivity of the baroreflexes is present in hypertension (Bristow, Honour, Pickering, Sleight & Smyth, 1969; Mancia, Ludbrook, Ferrari, Gregorini & Zanchetti, 1978; Zanchetti, 1979). A resetting of the baroreflex control of blood pressure must also be assumed for an understanding of the lack of overt difference in MSA characteristics between normotensive and hypertensive subjects (Sundlöf & Wallin, 1978; Wallin & Sundlöf, 1979).

Acute or short-lasting resetting of the baroreflex control of heart rate and blood pressure has been demonstrated in humans during exercise, whereby loading or unloading of the carotid sinus by the neck-chamber technique exerted similar influence on heart rate and blood pressure during rest and during dynamic or isometric exercise with tachycardia and elevated blood pressure (Bevegård & Shepherd, 1966; Ludbrook, Faris, Iannos, Jamieson & Russel, 1978). Baroreflex regulation of heart rate, tested by administration of vasoactive drugs, was reset during sleep and during dynamic exercise (Bristow, Honour, Pickering & Sleight, 1969; Bristow, Brown, Cunningham, Howson, Strange-Petersen, Pickering & Sleight, 1971).

To our knowledge an acute resetting of the baroreflex has not previously been demonstrated with direct recording of sympathetic nerve signals in humans. There are a number of well-described manoeuvres and physiological conditions, however, characterized by a simultaneous increase in MSA and blood pressure, in which a resetting of baroreflexes must be assumed. These include isometric muscle work (Mark, Victor, Nerhed & Wallin, 1985), the sympathetic response to simulated diving (Fagius & Sundlöf, 1986), the cold pressor test (Victor, Leimbach, Seals, Wallin & Mark, 1987; Fagius, Karhuvaara & Sundlöf, 1989), the response to hypoxia (Hedner, Ejnell, Sellgren, Hedner & Wallin, 1988), and urinary bladder distension (Fagius & Karhuvaara, 1989).

Wallin & Eckberg (1982) demonstrated that MSA responded strongly but adapted very rapidly to neck suction and pressure. The baroreflex adapted to the applied pressure or suction (30 mmHg) within 5 s and reacted at the end of the applied stimulus as if a new stimulus of opposite direction was present. This study involved only the carotid baroreceptors and hence receptors in the aortic arch not affected by the stimulus may have worked in an counteracting way; it was recently convincingly demonstrated that the latter type of baroreceptors play an important role in the regulation of MSA and blood pressure in humans (Sanders, Mark & Ferguson, 1989). However, the study by Wallin & Eckberg (1982) indicates that rapid resetting of baroreflexes to new working ranges would not be unexpected in various physiological conditions.

The slope of the stimulus–response regression lines remained virtually unchanged in the present experiments, indicating that the sensitivity of the baroreflex

regulation of the outflow of MSA was similar irrespective of the blood pressure level at which it operating. Our method for constructing stimulus–response lines is probably not sensitive enough to allow very detailed conclusions about changes of slope (and hence no statistical comparison of the slopes was applied) by the similarity of slopes and lack of consistent change in any certain direction despite an obvious shift of position along the blood pressure axis indicate that the sensitivity of the baroreflex was mainly unchanged during the experiments.

The finding of rapid resetting with stable sensitivity is in agreement with previous conclusions that the primary role of MSA in blood pressure regulation is to counteract blood pressure fluctuations irrespective of the mean pressure level (Wallin & Fagius, 1988). These properties would be physiologically meaningful for a dynamic system capable of stabilizing blood pressure despite short term periods of altered blood pressure level, induced by influences other than the baroreceptors. The same properties will also mean that baroreflexes at least indirectly might contribute to the development of essential hypertension by successive adaptation to higher blood pressure levels, irrespective of the primary origin of these levels.

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