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Psychophysiology of arterial baroreceptors and the etiology of hypertension

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Abstract

Arterial baroreceptors are sensitive to blood pressure dependent blood vessel dilation. They play a key role in the short term regulation of blood pressure. Their impact on psychological and psychophysiological aspects is of increasing interest. The review focuses on experimental techniques for the controlled baroreceptor manipulation. Results from the application of these techniques show that baroreceptor activation influences the cardiovascular system as well as central nervous functioning: Behavioral and electrophysiological measures of arousal, low level reflexes and pain responses are modulated through baroreceptor manipulation. The observation of an overall dampening ('barbiturate like') effect of baroreceptor activity led Dworkin et al. formulate the theory of learned hypertension: Subjects might experience blood pressure dependent baroreceptor activation as stress and pain relieving. High blood pressure periods become negatively reinforced. Phasic high blood pressure might develop as a coping strategy. Data from a longitudinal human study supporting this theory are reported.

Keywords: Baroreceptors; Learned hypertension; PRES; Pain; Blood pressure

1. Introduction

The central nervous system receives continuous information about changes in blood pressure through the pressure or baroreceptors. They play an essential role in blood pressure regulation. Investigating the physiological characteristics of the arterial baroreceptors in dogs, the physiologist Koch (1932) made unexpected

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observations; baroreceptor stimulation not only led to cardiovascular regulatory responses, but when prolonged, put the animal to sleep. The ancient Greek scholars must have been aware of this effect of baroreceptors in the carotid artery, as 'carotis' means 'deep sleep'. The other name of this artery, 'arteria lethargica' points to the calming effect, a massaging or rubbing in the region of the carotid sinus (which stimulates the baroreceptors) may have.

Here, we review the extrahomeostatic effects of baroreceptor firing, i.e., effects that go beyond immediate regulation of blood pressure. In particular, different methods of experimental baroreceptor stimulation and the link to hypertension are discussed in a model describing how learning mechanisms can contribute to hypertension.

2. The physiological basis: from the arterial baroreceptors into the brain

2.1. The arterial baroreceptors

A variety of receptors transmits information about cardiovascular status to the brain. The pressure receptors that respond to the tension of the arterial walls, the arterial baroreceptors, are located near the output of the heart (in the aortic branch) and in the carotid arteries where they monitor the pressure in the vessels that are essential for the brain's blood supply (Fig. 1).

There exist a number of histologically discriminable baroreceptors in the wall of the arteria carotis communis (Fig. 1). Three different types have been identified by means of electron microscopy (Rees, 1968). The afferent information is transmitted via both myelinated and unmyelinated fibers (Widdicombe, 1974). Another cluster of receptors is located in the aortic branch (Paintal, 1973, 1977) and still others are found in the walls of the larger artieries.

Baroreceptors respond both to blood pressure level and to its change (i.e., firing increases when blood pressure rises, the more so, the higher the existing pressure). Thus, there is an increase in the firing rate in the course of the heart cycle during every systole. The adaptation to a tonic enhancement is slow, allowing increased firing rates for hours (Korner, 1971). Typically, the firing threshold for humans is around 60 mmHg in the carotid artery. Firing here is continuous, with the firing rate being modulated by blood pressure.

Finally, baroreceptors have been identified at various locations in the heart. The type A receptors in the atrium fire maximally during the arterial systole while the atrial type B receptors respond to filling.

2.2. The afferent pathway

The afferent pathways of the sympathetic (from receptors in the heart) and parasympathetic fibers (vagal nucleus from arterial baroreceptors) lead to the nucleus of the solitary tract within the medulla oblongata. This nucleus tractus solitarius interconnects vegetative fibers with efferent fibers from the reticular

formation. The rostral part of the reticular formation has been described as the head of the autonomic nervous system (Rohen, 1978) from which ascending input is transmitted to the lateral prefrontal and to the insular cortex. The hypothalamus receives direct input from the nucleus tractus solitarius, but also visceral information via the thalamus. The thalamus receives baroreceptor input via the reticular formation. Rutecki (1990) suggests that the connection between the thalamus and the insular cortex mediates important visceral reflexes and this connection has been mentioned as the possible link to conscious perception of visceral sensations (Elbert and Schandry, 1998).

Specific cardiovascular information reaches cortical areas mainly via the thalamus, the hypothalamus and the tegmentum. In addition to widespread innervation

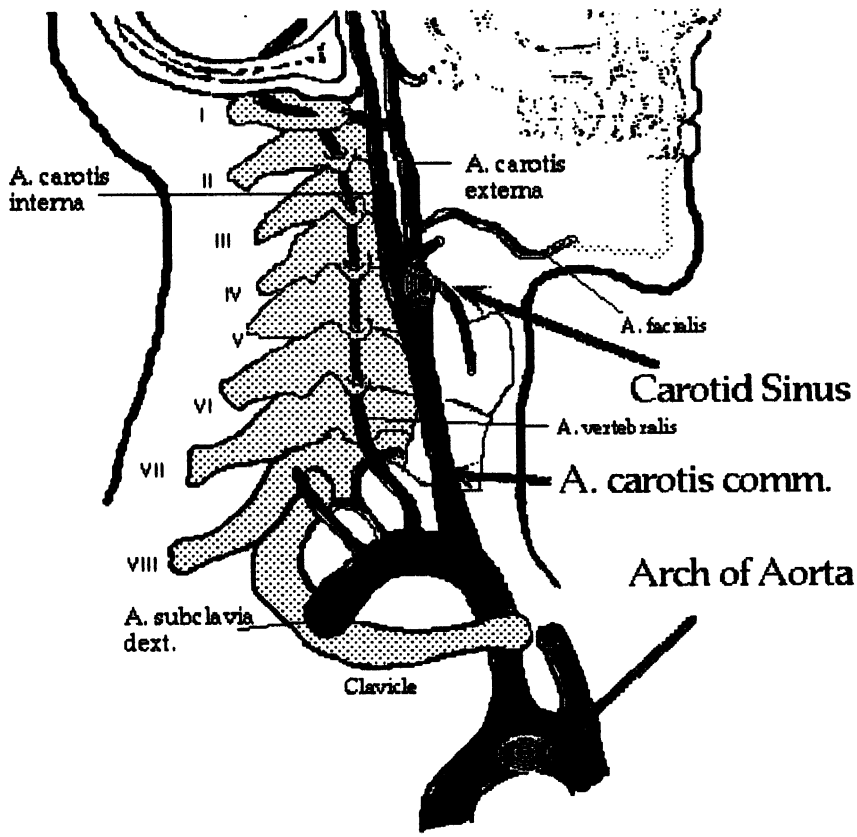

Fig. 1. The functionally most important areas of the baroreceptors are located in the aortic arch and the carotid sinus. The carotid sinus also includes chemoreceptors, which measure (pO_2, pCO_2 and pH). The afferents of the carotid baroreceptors travel within the Carotissinusnerve (a branch of the nucleus glossopharyngeus). Those in the aortic arch are innervated by the N. depressor sinister, those in the Truncus brachiocephalicus by the nucleus depressor dexter. The afferent pathways of the baroreceptors are predominantly ipsilateral (Morest, 1967).

through the reticular formation, the prefrontal cortex, the insula, and somatosensory areas also appear to process specific cardiovascular input. Evidence to support this, although limited, comes from electrophysiological and neuroanatomical studies.

3. Techniques to alter baroreceptor activity in humans

In order to portray the direct consequences of baroreceptor firing on central nervous processes and behavior, experimental approaches are needed that vary baroreceptor activity as the independent variable and provide monitoring of neurophysiological and behavioral dependent measures. Techniques, which allow the manipulation of baroreceptor activity, vary with respect to their specificity. A specific manipulation technique handles the independent variable (here the baroreceptor activity) but has no direct effect itself on any of the dependent variables. Less specific methods produce variations in baroreceptor output, but have additional unwanted impact on the dependent variables through mechanisms other than the alteration in baroreceptor activity. In this case, the changes in any particular dependent variable, which are observed in response to the experimental variation, may not causally be attributed to alterations in baroreceptor firing rate. In addition, enhanced firing rates result in the baroreceptor reflex, which causes the heart rate to drop and the blood vessels to dilate, so that hemodynamic changes may then exert their 'secondary' effects on cerebral and behavioral variables. Although specific stimulation of a particular set of baroreceptors and stringent control conditions (including the suppression of the baroreceptor reflex) can be accomplished in invasive animal experiments, such controlled experiments are difficult to achieve in humans. Therefore, human studies must be complimented by animal experiments and the outcome from different activation techniques in both humans and animals should be reconciled. It is unlikely that different methods of baroreceptor activation produce the same indirect effects. Preferably, different methods should be chosen such that secondary effects are opposite — both increasing and decreasing blood flow.

3.1. Pharmacological manipulations of the blood pressure

A frequently applied technique to manipulate baroreceptor activation is the pharmacological variation of the blood pressure. The drug application acts as the independent variable and CNS and behavioral responses constitute dependent variables. Vasoactive substances such as Phenylephrine, which act on the vascular smooth muscles and increase vascular tone (examples in Larbig et al., 1985; Rockstroh et al., 1988), are the pharmacological agents primarily used. These substances elevate blood pressure for minutes or even hours, thus activating the baroreceptors and consequently engaging the baroreceptor reflex. A dependent cardiovascular variable consists of heart rate change, a dominant and easily measured component of the baroreceptor reflex. Pharmacological blood pressure

elevations of about 10 mmHg generally result in a bradycardia of 10–20 bpm. By relating pharmacologically induced blood pressure change to the heart rate change induced by the baroreceptor reflex, the baroreceptor sensitivity can be determined. When vasodilating (Nitroglycerine) and vasoconstricting agents are administered, baroreceptor stimulation as well as reduced baroreceptor firing can be achieved. Furthermore, the application of Phenylephrine in conjunction with a vagal blocker (atropine) may be used to eliminate the baroreceptor reflex and thus exclude indirect effects of baroreceptor firing as a consequence of changes in blood flow e.g. to muscles, to the viscera or to the brain (e.g., Randich and Maixner, 1984). In human experiments, however, such stringent manipulations go beyond the ethical limits.

The pharmacological manipulation, though highly effective in its baroreceptor manipulation, suffers from a major drawback: drugs applied to vary the blood pressure generally also bind to receptors other than those at the blood vessel or in the heart. For instance, the α-sympathomimetica, which are used as vasoconstrictors, generally penetrate the blood brain barrier and bind to adrenergic receptors within the brain. This causes unwanted effects in the central nervous system not related to baroreceptor activation. Only in animals, these effects can been controlled by experimentally denervating the baroreceptor afferents (e.g., Dworkin et al., 1979).

3.2. Conventional neck cuff technique

As baroreceptors are stretch receptors located in the arterial wall, they measure the pressure or stretch difference across the wall, rather than just the pressure inside the vessel. Therefore, the baroreceptors will not only fire when the intravasal blood pressure is enhanced, but also when the extravasal pressure in the surrounding tissue is reduced (i.e., a negative pressure applied there). Applying externally a positive pressure constricts the vessels and reduces the stretching of the wall, mimicking a decrease in the blood pressure within the vessel. The baroreceptors in the carotid sinus can thus be differentially stimulated by noninvasively manipulating the external pressure in the surrounding tissue with helmets or cuffs around the neck and by changing the air pressure within these chambers. Eckberg et al. (1975) developed a neck cuff which surrounds the neck and is easy to apply (Fig. 2).

In the conventional neck cuff technique alternating periods of positive and negative, i.e. subatmospheric pressure are applied. The pressure change may last for several seconds or even minutes. About two-thirds of the cuff pressure is transmitted to the blood vessel (positive pressure: 86%, negative pressure 64%, Ludbrook et al., 1977, cf. Eckberg, 1980), i.e., a 30 mmHg suction around the neck will have the effect comparable to a 20 mmHg rise in blood pressure. By contrasting the effects of negative cuff pressure (simulated blood pressure increases) with positive cuff pressure (simulated drops of blood pressure), distraction effects are kept similar while the specific baroreceptor effect differentiates the two conditions.

Despite its noninvasive elegance, this method has a number of problems. First, the cuff and the application of a negative cuff pressure are often described as

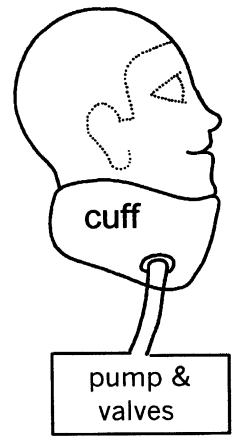

Fig. 2. Schematic drawing of a neck cuff design modeled after Eckberg et al. (1975).

uncomfortable. This problem degrades the specificity of the method. A difference in the comfort of positive and negative pressure results in effects on various dependent variables, some of which interact with, or add to, the baroreceptor mediated effects under study. Second, neck-cuff based baroreceptor manipulation is a selective procedure; stimulating the *carotid* baroreceptors leads to an activation of the baroreceptor reflex, thus lowering blood pressure and, in turn, unloading the remaining baroreceptors (e.g., those located in the *aortic arch).* Third, stimulation affects the receptors in the heart and lung in a nonlinear manner. After a few seconds of stimulation, the 'net' result of overall baroreceptor activity (carotid and aortic) might become unpredictable. For this reason, neck cuff manipulation should be restricted to the study of short phasic effects only — i.e., those taking place within a few seconds.

3.3. Lateral neck suction devices

The neck cuff procedure was modified by Tafil-Klawe et al. (1988), Elbert et al., 1991) with the construction of smaller cuffs which allow the application of a lateralized positive or negative cuff pressure. A negative pressure is used to evoke baroreceptor activation in one of two separate small pressure chambers with a kidney-like shape (about 5 cm in diameter). Baroreceptor inactivation is achieved by applying a positive pressure (e.g., 20 mmHg).

Lateral effects of left and right baroreceptor manipulation could be differentiated: while stimulation of the baroreceptors in the carotid sinus on either side activates the baroreflex arc, the effects were found to differ according to laterality differences in cardiac innervation. Modulation of the firing rate of the *right* carotid sinus nerve produced more pronounced *changes in heart rate*, while the baroreceptors located in the *left* carotid sinus were found to evoke changes in *cardiac contractility* to a somewhat greater extent than those on the right (Tafil-Klawe et

al., 1988). In the study of Elbert et al. (1991), nine out of the ten subjects displayed more pronounced chronotropic effects from pressure manipulation over the right than for those over the left carotid sinus region.

3.4. Cardiac phase related neck suction

In order to increase the specificity of the baroreceptor stimulation methods based on the neck cuff, we developed the PRES technique (Rau et al., 1992). PRES (**p**hase **r**elated **e**xternal **s**uction) refers to rhythmic pressure manipulations that are in phase with the cardiac cycle. Baroreceptor firing occurs synchronously within the heart cycle with a maximum firing during the increase of blood pressure at the beginning of the systole and a minimal firing rate during the diastole. By applying a negative cuff pressure pulse very rapidly during systolic pulse waves with the neck cuff (Fig. 2), the arterial dilation becomes faster and more pronounced (Fig. 3). Barorecep-

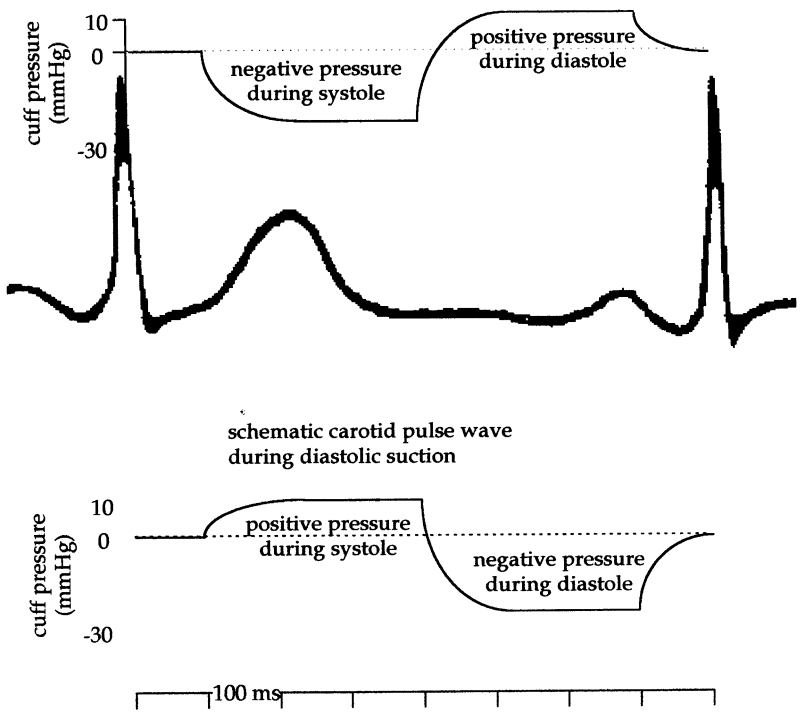

Fig. 3. Schematic illustration of the PRES-technique: the top drawing shows the enhancement of the carotid pulse wave when neck suction is applied during the systole. The differential within one cardiac cycle is increased even more by the positive pressure during diastole. With a reversal of the phase of negative positive pressure sequences with respect to the cardiac cycle, the carotid pulse wave flattens (lower traces) and the baroreceptor firing reduces correspondingly. The scale of cuff pressure corresponds to typically applied magnitudes. The pressure differential created across the arterial wall is estimated to be about $+8$ and -20 mmHg.

tors, which are primarily sensitive to rapid changes of dilation, then respond with enhanced firing. During diastole, a positive cuff pressure is applied which enhances the diastolic narrowing of the carotid artery. In the subsequent systole, another negative cuff pressure pulse is applied, which again results in an increased rate and amount of vessel dilation. Several sequences of systolic suction and diastolic excess pressure are repeated in order to achieve baroreceptor stimulation across seconds. Because rapid cuff pressure changes are distracting to subjects, a control condition must be applied. This control condition simply reverses the cardiac cycle–cuff pressure relationship: during systole, a positive cuff pressure counteracts the systolic blood vessel dilation (Fig. 3, bottom), whereas during diastole a negative cuff pressure antagonizes the naturally occurring reconstriction. As a consequence, the systolic and diastolic variations in blood vessel stretching are reduced during the control condition, a state that may even slightly inhibit overall baroreceptor activity. In two studies, it has been shown that subjects are unaware of the differences between the two conditions (Roberts et al., 1993; Furedy et al., 1992). With this result, PRES fulfills the criterion of nearly perfect specificity. Both the stimulation and the control condition have different impacts on baroreceptor activation but include the identical stimulation of somatic receptors.

The disadvantages of PRES are twofold. First, as with other neck-cuff based procedures, PRES only manipulates the carotid baroreceptors, and second, the cardiovascular effects are moderate and smaller than those of the conventional neck cuff technique. With the latter, a bradycardiac response 10 bpm could be easily achieved. Averaged across subjects, PRES produces about 3–5-bpm heart rate deceleration if the sequence of systolic suction/diastolic excess pressure is applied. With diastolic-suction/systolic-excess pressure, the heart rate remains largely unchanged. Single subjects, however, may show reliable differences of up to more then 15 bpm. (An increment in applied pressure intensities does not necessarily have the capacity to enlarge this effect, as the control condition will eventually turn into a stimulation condition.)

3.5. Electrical stimulation — baropacer

One invasive method of baroreceptor stimulation has been applied clinically. In this method, baroreceptor afferents are electrically stimulated by means of a subcutaneously implanted baropacer, which sends electrical impulses to the nucleus glossopharyngeus. This baropacer is implanted in patients with untreatable hypertension or with myocardial ischemia. When the physician responsible for the treatment activates the baropacer, small drops in both blood pressure and heart rate may be observed. However, when the patient was left blind with respect to the particular stimulation, reliable cardiovascular responses to the maneuver were not detected. This was the case in each of the five patients investigated.[1] This finding (unpublished) casts

[1] The patients were treated at the University Clinic in Bonn, Germany. We thank Professor Dr H. Rüddel for his collaboration.

doubt on the usefulness of this particular device to reliably stimulate the baroreceptors.

3.6. Operant conditioning of phasic blood pressure

A psychological approach to manipulating baroreceptor activity involves the operant modification of phasic blood pressure changes. Blood pressure can be continuously monitored with a device which constantly measures the arterial blood pressure at the finger such as the Ohmeda finapres. From this output, the diastolic and systolic blood pressure (or combinations of both like the mean arterial pressure) can be extracted on a beat to beat basis. By rewarding subjects for increasing the blood pressure in the presence of a discriminative stimulus, subjects can learn to produce phasic blood pressure elevations. In the presence of a second discriminative stimulus, the subject is rewarded for lowering the blood pressure. It has been shown that subjects can learn to reliably produce a differential response in phasic blood pressure in the presence of discriminative stimuli (Elbert et al., 1992). It is assumed that during trials in which blood pressure increases are to be achieved, baroreceptors are activated more than during trials in which blood pressure is left unchanged or even lowered. By contrasting those different trial categories, the effects of baroreceptor activation might be studied. Of course, this technique does not control specificity very well. Successful subjects learn different strategies in order to differentially influence their blood pressure, and these strategies may have non-specific effects on variables to be measured. (The blood pressure changes do not constitute the independent variable; the independent variable is the type of reinforcement schedule.)

3.7. Respiration techniques

By performing the Valsalva maneuver (Levin, 1966; Eckberg, 1980), the intrathoracal pressure can be increased by 40 mmHg and venous return to the heart reduced. The cardiac output and blood pressure consequently drop, activating the baroreflex, which, in turn, increases heart rate and constricts blood vessels. After starting to breath regularly, the combination of normalized cardiac output and constricted blood vessels leads to an immediately strong increase in blood pressure that, via the baroreflex, induces heart rate bradycardia. These heart rate responses, measured as dependent cardiovascular variables, indicate the baroreceptor sensitivity.

For the psychophysiological study of interactions between the cardiovascular and the central nervous system, however, this procedure seems of little value. This is due to the fact that the non-specific effects associated with performing the Valsalva maneuver dramatically interfere with the neurophysiological and/or behavioral effects under consideration. Consequently, the specificity of this task is so limited that it cannot be recommended to apply respiration related techniques for the study of extrahomeostatic baroreceptor effect in humans.

4. Extrahomeostatic baroreceptor effects in humans

An increase in arterial blood pressure stimulates the arterial baroreceptors which in turn elicit the baroreceptor reflex via the neurons in the solitary tract: a reduction in cardiac output and in peripheral resistance reduces blood pressure towards its original level. This reflex may be inhibited through peripheral processes, for example, under conditions of high metabolic demand. In addition, higher brain structures modulate this reflex arc, for instance when threat is detected and fight or flight responses are being prepared.

Given the possibility of strong efferent central nervous control of the cardiovascular system, it seems not sufficient that the brain just monitors the current status of cardiovascular responding. It would be advantageous, for regulatory systemic purposes, if the cardiovascular system could also tune brain dynamics. Particularly under highly strenuous or stressful conditions that may drive the cardiovascular system beyond its limits. The anatomical basis for such an influence has been outlined in the first section of this paper. We refer to baroreceptor effects that are not related primarily to the baroreceptor reflex and therefore are not closely connected to the homeostasis of blood pressure as extrahomeostatic effects.

4.1. Low level reflexes

A series of studies in the first part of the last century (Spychala, 1932; Schweitzer and Wright, 1937; Pinotti and Granta, 1955) observed dampening effects of baroreceptor activation on spinal motoneurons. Schulte et al. (1959) replicated these findings and specified that baroreceptor activation suppresses the activity of γ motoneurons in cats.

As a non-invasive procedure for studying the excitability of the motoneuron pools in human, reflexes can be used (Paillard, 1955). We chose the Achilles tendon reflex (T-reflex) as an indicator of descending modulatory effects of baroreceptor activation (Rau et al., 1993a). The T-reflex was evoked by a tendon tap, stretching the calf muscles. Lengthening the intrafusal fibers of the muscle spindle discharges group Ia afferent fibers, which, in turn, have primarily a monosynaptic link to the motoneurons. This results in a sufficiently large depolarization of the motoneurons and the contraction of the calf muscles. Animal studies (Schulte et al., 1959) demonstrate that the afferent impulses from carotid sinus baroreceptors reaching the brain stem will also radiate to the somatic motor system, either suppressing reticular activation or activating the reticulo-spinal suppressers located in the same gross region. The resulting decrease in spinal motor activity may be caused by fusi motoneurons, which reduce the afferent drive for alpha motoneurons via the gamma-muscle spindle loop and, hence, could express itself in a reduction of the T-reflex. The finding of baroreceptor influenced diminution of the T-reflex could not be attributed to a specific component of the pathway. By applying the PRES technique, we found the greatest T-reflex differences between conditions of highest (elicitation of T-reflex during PRES enhanced systole) and lowest baroreceptor activity (PRES enhanced diastole). Reflexes are suppressed if applied during phases

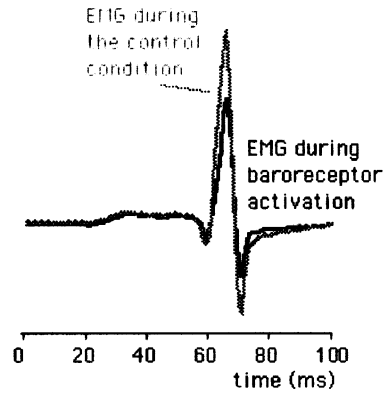

Fig. 4. Effects of baroreceptor manipulation on the Achilles tendon reflex. The reflex is elicited at time zero. The EMG from m. soleus is averaged across 32 trials per condition and displayed here for one subject (data from Rau et al., 1993a).

of maximum baroactivity compared to phases of minimum baroreceptor activity (Fig. 4). In the Rau et al. (1993a) study, baroreceptor stimulation clearly suppressed the Achilles tendon reflex in each of the 12 subjects.

Another example is the baroreceptor modulation of the startle reflex. A startle reflex can be elicited by the presentation of short (50 ms) bursts of loud (e.g., 100-dB (A)) white noise presented via earphones and the amplitude of the EMG response of m. orbicularis oculi serves to assess reflex magnitude. Rau (1989) presented acoustic startle stimuli to 43 normotensive subjects while baroreceptors were manipulated using the conventional neck cuff technique. Startle amplitudes were significantly decreased when elicited during neck suction (Fig. 5).

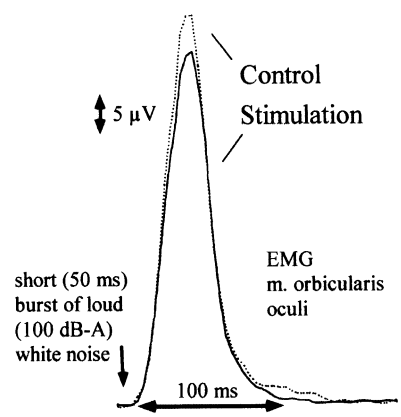

Fig. 5. Grand mean of the startle responses elicited with a 100-dB white noise during baroreceptor activation and during the control condition.

4.2. Baroreceptor input decreases cortical excitability

The influence of baroreceptors on higher central nervous structures was further examined by event-related EEG activity. In several studies, we have used CNV-like brain potentials as markers of cortical excitability. Slow surface-negative potentials are thought to originate in the depolarization of apical dendrites synchronized via thalamic afferents to layer I. Slow negativity has therefore been considered as an indicator of cortical excitability (Elbert and Rockstroh, 1987; Elbert, 1992, 1993; for a review on slow brain potentials see Rockstroh et al., 1989). Typically, a warning stimulus such as a pure tone signals the subject that an imperative stimulus is to follow within a few seconds. Subjects are then asked to respond as fast as possible to the second (imperative) stimulus. Trials are presented some twenty times to allow signal averaging.

The CNV in such a two stimulus paradigm was used to test subjects during an administration of either (1) the blood pressure enhancing Norfenefrin–HCl[2] or (2) a saline placebo (Larbig et al., 1985). CNV-amplitude was significantly reduced during the administration of the Alpha-sympathomimecticum as compared to the placebo (Fig. 6, left column).

This result was validated subsequently in a number of studies with the neck cuff procedure (Elbert et al., 1988; Rau et al., 1988; Elbert and Rau, 1995). The CNV, which develops under control conditions, is markedly reduced when baroreceptors are stimulated (Fig. 6, second column).

Changes in blood flow, blood pressure, or heart rate vary in amplitude and direction for the different methods of baroreceptor stimulation (Fig. 6) and therefore cannot account for the finding of a reduced CNV. However, one could still argue that under both conditions the stimulation is the more distracting procedure and distraction has been known to reduce CNV-amplitude (Rockstroh et al., 1989). To control possible effects of distraction, we performed another CNV experiment by applying the two PRES conditions (Rau et al., 1993b). The CNV amplitude was reduced during the PRES stimulation condition as compared to the PRES control condition. This differentiation is significant over the fronto-central cortical areas, but levels off towards parietal areas. As a third technique, we have employed operant blood pressure conditioning to manipulate blood pressure and, consequently, baroreceptor firing (Elbert et al., 1992). There were two types of trials, one requiring an increase in phasic blood pressure (*'up'*), the other a decrease (*'down'*). Feedback was provided by the outline of a little rocket-ship, which appeared on a TV-screen in front of the subject for eight second intervals. The integral of the mean arterial blood pressure referred to a pre-stimulus baseline (4 seconds) and linearly determined the horizontal position of the feedback stimulus. The arterial blood pressure was measured continuously and non invasively with the Ohmeda finapres device. A letter 'A' or the letter 'B' appeared in the upper left corner, signaling the subject which of the responses (*up* or *down*) would be

[2] Novadral (1-(3′-Hydroxyphenyl)-2-aminoethanol is a sympathomimetic agent with vasoconstrictive effects. There is no known direct effect on the CNS.

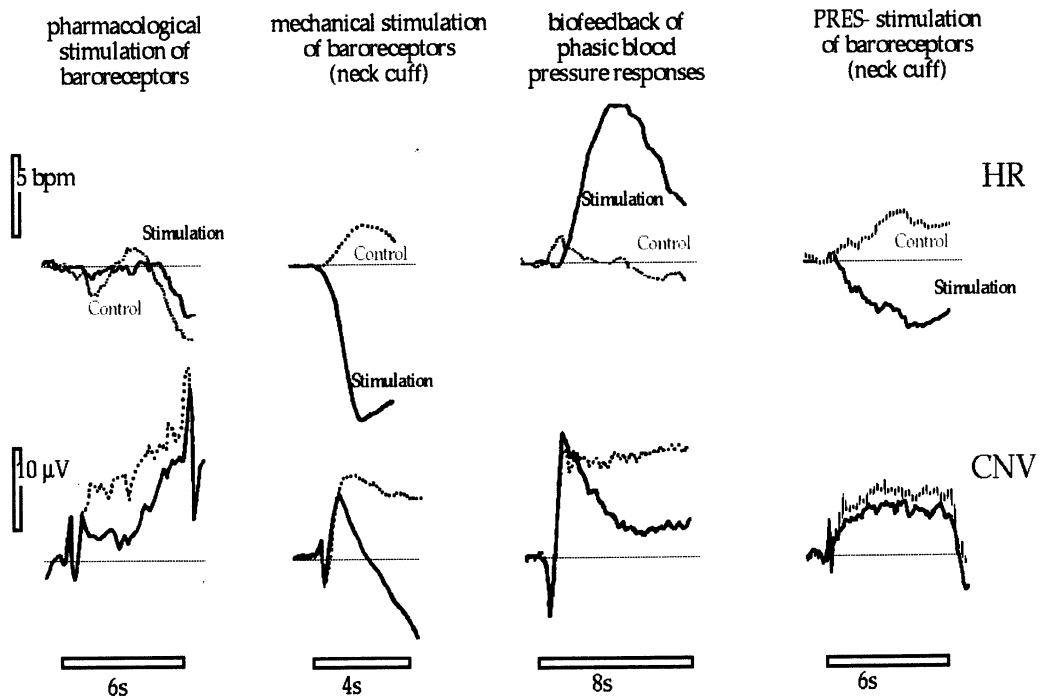

Fig. 6. Comparison of heart rate and slow brain potentials in response to different methods of baroreceptor stimulation and the respective control conditions (see text). Depending on the particular method of baroreceptor stimulation, the heart rate slows down, accelerates or stays the same. For all conditions, however, the slow brain potential is reduced in negativity.

rewarded. The sequence of up- and down-trials alternated randomly and were evenly divided between the two. Subjects participated in a number of training sessions until they had reached at least 15 net win points (win minus lost points). Net win points increased significantly across sessions. Subjects' heart rate accelerated during the first few seconds of up-trials but then, while blood pressure was climbing subsequently with some delay, heart rate started to decelerate (Fig. 6c). The average of the time period 3–8 s, amounted to 7.5 ± 1.7 bpm. During down trials, heart rate tended to decelerate (-0.7 ± 0.6 bpm, $P < 0.001$ for the difference between *up* and *down*). Absolute heart rates were 83.2 bpm during *up*- and 75.0 bpm during *down*-trials ($F(1/13) = 24.5$, $P < 0.001$). Consistent with the predictions from the previous experiments, the precentrally dominant terminal CNV was considerably reduced in amplitude during up-trials (Fig. 6c). Even more pronounced effects were found over parietal and frontal but not prefrontal cortex.

These results support the possibility that intense baroreceptor stimulation provokes a reduction in scalp negativity indicating reduction in cortical excitability. This reduction was obtained regardless of whether the heart rate had increased (as in the biofeedback study), showed no phasic change (under norfenefrin) or decreased as a consequence of the baroreflex elicited by cervical suction or PRES[3].

This impact of baroreceptors on the cortex is lateralized: stimulation of the receptors on the right produces a more pronounced change in heart rate than stimulation on the left, whereas the left carotid sinus was found to alter cardiac contractility to a higher degree than the sinus on the right side (Tafil-Klawe et al., 1988). We replicated these effects and demonstrated that stimulation of the left side reduces negativity to a greater extent over the left than over the right hemisphere (Elbert et al., 1991). Given the ipsilateral projection of the nucleus tractus solitarius, this finding is further support for the view that baroreceptor input dampens cortical excitability as indicated by slow event-related brain potentials. In sum, these results suggest a powerful capacity of baroreceptors to influence cortical excitability.

4.3. Effects on arousal and sleep

Following Koch's observation that baroreceptor stimulation can put dogs to sleep (Dworkin et al., 1979; Dworkin, 1988) manipulated the blood pressure pharmacologically in rats but controlled indirect effects by introducing a group with denervated baroreceptors. Only animals with the baroreceptor innervation left intact were put to sleep, while arousal increased in the animals with baroreceptor deafferented. This result constitutes an elegant demonstration that blood pressure-induced arousal reduction is mediated through the baroreceptors in the carotid sinus.

[3] The relatively small effects using PRES might result from a non-linear relationship of the postulated impact, baroreceptors might have on higher CNS-structures. Baroreceptor firing rates that fall within the range of typical cardiac cycles might not surmount the threshold needed to disrupt higher brain functioning.

Cole (1989) applied body tilting, in combination with the anti-g suit, in order to investigate baroreceptor effects on sleeping behavior in humans. He found a systematic and significant relationship between the cardiovascular manipulations and sleep latency that could be explained by the assumption that activation of pressoreceptors facilitates sleep. By integrating the human and animal results regarding the relationship between arousal and baroreceptor activity, it seems likely that baroactivation decreases arousal and facilitates sleep.

4.4. Subjective report

As mentioned above, subjects cannot distinguish the stimulation and the control condition in PRES. This implies that corresponding alterations in baroreceptor firing are not consciously perceived. It is possible, however, that the subjective rating of their current state may vary with the stimulation type. In a pilot study[4], we obtained ratings of the affective dimensions arousal, valence and dominance. The predicted effect of lower arousal rated during baroreceptor stimulation as compared to the control condition did not achieve significance ($t(18) = 1.12$). Fifteen of the 19 subjects rated themselves as being significantly more dominant ($t(18) = 2.7$; $P < 0.05$) when baroreceptors were stimulated, but the magnitude of the effect was small. The differential rating of the emotional valence (happier during barostimulation $t(18) = 1.43$) was also not significant but correlated with the differential heart rate response ($r = 0.52$, $P < 0.05$), suggesting a more pronounced effect in subjects with stronger stimulatory effects. In sum, these data indicate that baroreceptor activation does not easily penetrate into awareness and that blood pressure is not consciously discriminable.

5. Pain and the cardiovascular system

Considerable evidence suggests a link between hypertension and hypoalgesia. A weak but consistent correlation indicates that hypertensive humans as well as hypertensive animals are less likely to perceive pain than are normotensive subjects. Such correlational observations do not allow a determination of whether hypoalgesia is a consequence or a cause of hypertension or whether both hypertension and hypoalgesia result from a third process (e.g., an alteration in endogenous opioid

[4] We presented randomly 45 trials of PRES baroreceptor stimulation and 45-trials of PRES control condition to each of 19 normotensive student subjects. During a particular trial, subjects rated one of three emotional dimensions (arousal, dominance, and emotional valence) on a computerized version of the SAM (Self Assessment Mannekin, Lang, 1980). The rating was performed through a computer mouse, the movement of which would (1) manipulate the activity of a mannequin ranging from quiet to jumpy (low–highly aroused), (2) change the symbol of a person with varying size from extremely small to extremely large (submissive-dominant), or (3) change a sketched face on the computer screen stepwise from happy to sad (affective valence).

system; France, 1999). Studies in animals and humans have repeatedly demonstrated that artificial stimulation of the arterial baroreceptors results in a dampening of pain perception and the behavioral consequences of pain, such as the intensity of avoidance responses. Decreased pain perception can be viewed as a consequence of elevated blood pressure levels.

5.1. Relationship between tonic blood pressure level and pain sensitivity

Zamir and Shuber (1980) elicited pain by application of electrical tooth pulp stimulation in 55 male subjects who had different resting blood pressure levels. In this study, individual pain and sensation thresholds were related to resting blood pressure. The authors reported a significant correlation for both sensation and pain thresholds with tonic blood pressure level. This relationship was more pronounced for systolic than for diastolic blood pressure values. Higher blood pressure was related to higher pain and detection thresholds (less sensitivity). Ghione et al. (1985) as well as Rosa et al. (1986) also reported increased tooth pulp stimulation pain thresholds in hypertensive as compared to normotensive subjects. In the former study, 156 subjects performed pain threshold and detection threshold tasks. These subjects were divided into groups of 80 normotensives, 32 borderline hypertensives and 42 hypertensives. The hypertensive subjects showed the highest detection thresholds, followed by the borderline hypertensives. Both groups had significantly higher detection thresholds than groups of normotensive subjects. Age, gender nor resting heart rate could account for this result. For pain thresholds, a small, but highly significant ($r = .27$, $P < 0.001$) correlation with resting mean blood pressure was found. After the initial experiment, 25 hypertensive subjects were treated with an antihypertensive medication that successfully lowered arterial blood pressure. This blood pressure lowering, however, did not significantly influence the higher pain or detection thresholds.

By applying the neck cuff technique Elbert et al. (1988) studied the impact of carotid baroreceptor stimulation on electrically evoked pain sensation in a group of 10 normotensive and another group of 10 borderline hypertensive subjects. They found a generally higher pain tolerance in the borderline hypertensive subjects as compared to the normotensive ones. Similarly, Bruehl et al. (1992) found subjective pain ratings were significantly correlated ($r = -0.43$) with resting systolic, but not diastolic ($r = -0.11$) blood pressure. Subjects with higher, but still normotensive, blood pressure values reported less pain during this mechanical pain maneuver.

Guasti et al. (1999) demonstrated that normotensive and hypertensive subjects differed with respect to pain threshold. The relationship between pain threshold and ambulatory systolic pressure measured over a 24 h period achieved the strongest correlation ($N = 181$, $r = 0.31$, $P < 0.0001$). While these findings provide support for a role for blood pressure elevation in the modulation of pain sensitivity, they also suggest that the relationship does not explain a great deal of the variance ($\leq 10\%$).

6. Experimentally induced hypertension and pain (animal studies)

In contrast to human correlational studies, Zamir and Segal (1979) performed animal studies, which allowed for stringent experimental control of blood pressure. They produced renal hypertension in male rats by occluding the left renal artery and leaving the right kidney intact. They also included a group of sham operated rats and a third group of rats in which the left renal artery was totally constricted so that the kidney became atrophied and could no longer produce renin. After these surgical interventions, the animals performed hot plate tests with latency to paw lick serving as the dependent variable indicating pain sensitivity. Before the operation, the paw lick latency was identical for all groups of animals. The operation led to a dramatic increase in systolic blood pressure in the experimental animals from 100 mHg (pre-operation) up to 200 mmHg (15 days post-operation). Only experimental animals produced significant blood pressure increases. Changes in paw lick latency perfectly paralleled blood pressure increments: an increase of blood pressure during the first 20 days after the operation was associated with an increase in paw lick latency from around 13 s up to around 22 s. On day 20, the atrophied kidney was removed, followed by a normalization of both blood pressure and paw lick latency in the next 20 days. This data provides convincing evidence of a causal relationship between resting blood pressure and pain sensitivity. Zamir et al. (1980) extended these studies by adding another model of animal hypertension. DOCA–salt sensitive hypertensive rats performed the hot plate test and showed decreased pain sensitivity. Naloxon did not effect blood pressure but abolished the pain decreasing effect of high blood pressure. This latter result suggests that the pain dampening effects of high blood pressure may be linked to the endogenous opiate system.

A number of laboratory animal studies has shown that hypertensive hypoalgesia is reversed by administration of opiate antagonists (reviewed in France, 1999). France argues that these reflect pathophysiological processes that are associated with a genetic predisposition to hypertension rather than a secondary consequence of chronic high blood pressure.

6.1. Barostimulation and pain

Dworkin et al. (1979) intended to test (a) whether pharmacologically elicited blood pressure increases have antinociceptive effects and (b) whether these antinociceptive effects are dependent upon the undisturbed functioning of the arterial baroreceptors. In their study, they surgically deafferented the aortic and carotid baroreceptors in rats. Before and after the denervation, the rats performed a pain avoidance task in which they could avoid electrical shocks by running a specified amount on a running wheel. The blood pressure elevation, which was achieved by applying phenylephrine, led to a significant drop in avoidance behavior in the rats with intact baroreceptor afferents. After denervation, the blood pressure elevation slightly increased the avoidance behavior. These results were replicated by Randich and Maixner (1984), who also controlled for the heart rate changes by additionally

applying atropine and blocking the parasympathetically mediated heart rate decrease. Again, an inhibition of pain avoidance behavior in response to blood pressure elevation was found only in animals with baroreceptors left intact.

Elbert et al. (1988) observed that baroreceptor manipulation can have differential effects in normotensive and hypertensive subjects. In a group of borderline hypertensive subjects, the baroreceptor stimulation (realized through neck suction) led to a highly significant decrease in pain sensitivity as compared to the baroreceptor inhibition (neck excess pressure). This result was reversed in a group of normotensive subjects who showed a significant sensitization during the baroreceptor stimulation as compared to the baroreceptor inhibition condition.

We also used the PRES technique for the controlled stimulation of the carotid baroreceptors in a group of 11 normotensive and a group of 10 hypertensive subjects (Rau et al., 1994). Mechanical and thermal pain thresholds were tested during three states: rest, the baroreceptor stimulation, and PRES control condition. Thermal pain thresholds were significantly higher in the hypertensive as compared to the normotensive subjects. The baroreceptor manipulation, however, had no effect on thermal pain thresholds. In contrast it led to significantly decreased pain sensitivity when pain was applied mechanically.

Kardos et al. (1994) investigated the effect of baroreceptor manipulation using PRES on electrical pain sensitivity in nine patients suffering from symptomatic myocardial ischemia (pain perception during objectively diagnosed episodes of myocardial ischemia) and in another group of 10 asymptomatic patients (patients reporting no pain during objectively diagnosed myocardial ischemic events). A highly significant antinociceptive effect of the PRES baroreceptor stimulation condition compared to the PRES control conditions was observed in both groups. Droste et al. (1994) reported corresponding effects of PRES baroreceptor manipulation on electrical pain sensation in a group of 14 hypertensive and a group of 14 normotensive subjects.

The outcome of such studies varies with a number of factors. These include the type of baroreceptor stimulation, the type of the particular pain measurement, and task. For instance, a painful condition could be actively escaped in Elbert et al. (1988). In other studies (Kardos et al., 1994), pain stimuli well above pain thresholds were applied without leaving subjects any control over the pain stimulation; subjects simply rated the perceived intensity on an analog scale after each application. No active behavioral escape or control possibility was included in this approach.

Despite these considerable variations in experimental manipulations, there is a converging picture; all studies suggest an antinociceptive influence when baroreceptors are more active, be it through experimental stimulation or in hypertensive conditions.

Baroreceptors show a rapid resetting to altered blood pressure levels and therefore may not necessarily show a higher overall firing frequency in hypertensive patients compared to normotensives. On the other hand, blood pressure amplitude, the diastolic–systolic blood pressure difference, is more pronounced in hypertensive subjects, primarily at the initial stages of the hypertensive development, during

which cardiac output is increased. Cardiac hypertension might be associated with increased blood pressure amplitudes and, consequently, with increased firing rates of the baroreceptors within the cardiac cycle. If this is true, then the described antinociceptive effect should show a strong dependency on the presentation time of the painful stimulus within the cardiac cycle. As hypertension develops, the cardiac output normalizes and blood vessels become involved in hypertensive mechanisms, thus manifesting hypertension into vascular hypertension. At this stage, baroreceptor activation may no longer be enhanced, and hence, higher pain thresholds should no longer be observable in such a group of hypertensives. To our knowledge, this question has not yet been systematically investigated.

7. Significance of the baroreceptor–brain circuitry for a model of learned hypertension

Based on the observation of arousal and pain dampening exerted through baroreceptor activation, Dworkin, Rau, Elbert and colleagues (Dworkin, 1988; Rau and Elbert, 1993; Elbert et al., 1994; Dworkin et al., 1994, 2000) advanced the model of 'learned hypertension'. This theory predicts that learning mechanisms, and operant conditioning in particular, contribute to blood pressure elevations with a possibly catastrophic outcome. The reduction in pain and stress constitutes a reinforcing mechanism, which drives as a reward phasic blood pressure increase in a noxious, stressful situation. Consequently, according to the laws of operant conditioning, the frequency of behavior, which enhances blood pressure, will increase, and those individuals who genetically have baroreceptors that impact powerfully on higher brain functioning are at particular risk for constant elevation of their blood pressure. Extending Dworkin's (1988) original suggestion, the following factors would contribute to the risk for learned hypertension in a particular individual:

(A) Blood pressure elevations exert a strong impact on the discomfort perceived in stressful and painful conditions. The results described in the previous section suggest pronounced inter-individual differences. A genetic origin of these differences may contribute to the known risk for developing hypertension.

(B) The individual is exposed to frequent pain- and/or stressful conditions. An increase in stress, particularly time pressure but also social stress in industrialized societies, may account for more frequent hypertension.

(C) Certain conditions (e.g., stressful conditions) are cognitively processed such that they are perceived as aversive; therefore, suppressing such cognitive operations could be reinforcing. If true, this factor may constitute an important tool for the psychological treatment of learned hypertension — treatment including not only stress management but also cognitive restructured perception of the environment in addition.

(D) Obviously, learning of phasic increases in blood pressure is a mandatory prerequisite for the postulated mechanism to work. However, there exist individual differences, such as ability and strategies to produce blood pressure elevation; these are exemplified in the study of Elbert et al. (1992).

(E) In addition to the previously suggested factors, the transition from acute to chronic conditions needs to be specified. An individual may learn to perform frequent phasic elevations in blood pressure; however, this may not necessarily transform itself into chronic hypertension. Resetting and the rate of adaptation of baroreceptors may play a role, which, again, may differ from subject to subject.

In order to test the model of learned hypertension, we have conducted a prospective longitudinal study (Rau et al., 1993a,b; Elbert et al., 1994). At the beginning of this study, each of 120 subjects was tested using PRES and electrical intracutaneous pain stimulation. With this procedure, the individual pain inhibition was measured in response to baroreceptor stimulation. After this laboratory investigation, subjects were instructed to measure their blood pressure twice daily during a one-week period, using an automatic blood pressure monitoring device. During the same week, subjects rated their subjectively perceived stress and the aversiveness of this stress (B, C) daily. Two years later, the blood pressure and stress record was repeated. Blood pressure changes across the two-year period were then related to individual pain inhibition. Consistent with predictions from the model, there was a significant, correlation between the baroreceptor dependent pain inhibition and the mean blood pressure changes over these 2 years ($r = 0.29$; $P < 0.004$). Taking into account the daily stress of subjects (as rated at the beginning of the two year period), a surprisingly high variance could be accounted for, as predicted by the theory of learned hypertension. For those 34 subjects reporting high daily stress, baroreceptor dependent pain inhibition and blood pressure changes were highly correlated ($r = .56$; $P < 0.001$). In subjects reporting only medium or low daily stress, however, no significant correlation between these two variables was observed. In sum, these results lend strong support for the theory of learned hypertension.

This theory has a number of direct clinical implications. The lack of compliance in hypertensive subjects is well known to every clinician. The theory of learned hypertension would expect that removing a potent coping strategy without offering an alternative would not be well tolerated by the patient. According to this theory, it is important for the successful treatment and prophylaxis of hypertension to teach the patient alternative coping strategies. Therefore, psychological stress and pain coping programs should accompany pharmacological or mechanical attempts to decrease blood pressure. Only then can we expect that the patient will achieve a lowering of blood pressure or a blocking of phasic blood pressure hyperactivity, without either failing to be compliant or developing other stress-related diseases.

Phasic blood pressure hyperactivity has been discussed as an important risk factor associated with hypertensive development (Pickering and Gerin, 1990; Manuck et al., 1990; Turner, 1994). Thus, subjects showing the response specificity of blood pressure hyperactivity may be at risk for developing hypertension at a later point in time. It has been previously shown that hypertension develops in stages: in the first stage, the blood pressure becomes labile, meaning that the variance of blood pressure fluctuation increases. In terms of our theory of learned hypertension, these fluctuations serve as operants; subjects would begin to apply their 'blood pressure increase' coping strategies during the first stage of hyperten-

sion. Successful pharmacological interventions at this stage are primarily based on the prescription of betaadrenergic blockers, medications that block the hyperactivity of the sympathetically driven increases of cardiac activity, thus preventing vehement rises in phasic blood pressure. After the stage of labile hypertension, however, hypertension may continue to manifest itself, despite previous pharmacological intervention.

Whether or not baroreceptor dependent reinforcement resulting from blood pressure increases also acts on the transition to this stage and to what extent it might do so on further blood pressure modifications remains an open question.

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