Modifications of Arterial Baroreflexes: Obligatory Roles in Cardiovascular Regulation in Stress and Poststress Recovery

Shoichiro NOSAKA

Department of Physiology, Mie University School of Medicine, Tsu, 514 Japan

Abstract: Despite the physiological importance of arterial baroreflexes as a powerful stabilizer of blood pressure, their functions themselves are not always stable and there are a variety of circumstances in which they are significantly modulated. During stressful conditions, including flight/flight, defense/attack, somatic nociception, visceral nociception, exercise, and mental stress, arterial baroreflexes are generally inhibited. The inhibition is purposeful for achieving dynamic readjustment of circulation needed for the animal's reaction to cope with these conditions. Central sites which are proposed to be involved in the inhibition include the motor cortex, amygdala, hypothalamus, dorso-lateral part of the periaqueductal gray matter, parabrachial nucleus, cerebellar vermis, etc. On the other hand, arterial baroreflexes are occasionally facilitated, during sleep, following endurance exercise, etc. The facilitation favors restoration of energy exhausted during a stressful phase in which the animal reacts actively to changing environment. The central sites proven to elicit the facilitation are the medial prefrontal cortex, the preoptic/anterior hypothalamus, the ventrolateral part of the periaqueductal gray matter, and the nucleus raphe magnus. The inhibition and facilitation of arterial baroreflexes, which probably occur alternatively, are essential mechanisms supporting reactions to stressful conditions and poststress recovery, respectively. This review describes when, how, and why the arterial baroreflexes are so modulated. [Japanese Journal of Physiology, 46, 271–288, 1996]

Key words: arterial baroreflexes, defense reaction, exercise, mental stress, pain.

Arterial Baroreflexes and Dynamic Control of Circulation

Arterial baroreflexes represent a most powerful negative feedback control mechanism first identified in biological systems. Thus, since the discovery of the aortic nerve by de Cyon and Ludwig in 1866, arterial baroreflexes have been occupying a central position in studies of cardiovascular regulation. In fact, the importance of blood pressure homeostasis due to these reflexes is unequivocally accepted. Those organs which are primarily essential for maintaining life, require a constant and substantially greater supply of blood than others. The heart, weighing 0.4% of body weight, receives 5% of cardiac output, while the brain, weighing 2% of body weight, receives as much as 14% of cardiac output [1]. Blood pressure, when maintained above a sufficiently high level, secures the transmural pressure difference to drive the filtration process across capillary walls. It secures a pressure head to drive capillary blood flow which allows small-molecule substances to be steadily transported by their flow-limited diffusion without attenuating the concentration gradient. Thus, baroreflex-mediated homeostasis of blood pressure contributes to constant transcapillary gas exchange and nutritional supplies, especially of immediate energy substrates, in vitally important organs.

Although the importance of baroreceptor-mediated stability of blood pressure is therefore widely recognized, cardiovascular functions are not always regulated for such stability and are modulated in a more dynamic fashion. Such a pattern of circulation control is typically observed during and even before the active
reactions of an animal against the environment. When viewed phylogenetically, a prototype of circulatory regulation can be found in close association with the animal's behavior or locomotion. For example, the heart of a bivalve does not beat at all when its valves are closed but starts beating when, and even before, it opens its valves to feed [2]. For another example, a motoneuron in *Aplysia*, referred to as a L.7 cell, which innervates the gill and siphon, sends an axon collateral to the heart and the abdominal aorta [3]. When it moves the gill and siphon for defensive withdrawal, the contraction of the auricle is also augmented, and the abdominal aorta constricted so as to shunt blood via the anterior aorta to the somatic muscles. Such examples show that the prototypic principle of cardiovascular regulation is not primarily to stabilize a cardiovascular parameter, but to meet the demand of the animal's behaviors.

Activation of major arterial baroreceptors (aortic and carotid sinus) causes general sympathetic inactivation and parasympathetic (especially cardiovagal) excitation. Since the blood vessels are more or less tonically constricted under ongoing sympathetic activities, the reflex withdrawal of the activities produces overall vasodilation. In this sense, the arterial baroreflexes are rather "stereotypic" in effect. In reality, however, circulation is controlled in a more "dynamic" way whereby some vessels are constricted while others are dilated. This brings about blood flow redistribution among organs, a wisdom of the body in requiring an increased blood supply to specific organs but having only a fixed amount of blood volume. This type of circulatory regulation occurs in animals which actively react to environmental changes [1]. Fight/flight or attack/defense behaviors of an animal are primarily expressed by somatic skeletal muscle activities. To support these activities, however, it is essential that blood flow is significantly increased in the skeletal muscles. For this purpose, capacitance vessels are constricted to mobilize the blood pooled inside [4], and the blood vessels in the viscera are constricted to supply blood preferentially to dilated ones in skeletal muscles. Such mobilization and bypass processes are of utmost importance since the skeletal muscle system is the largest organ in the body (50% of body weight) receiving 18% of cardiac output at rest and requiring a vast amount of blood, especially when it is set in motion [1]. Increased blood flow in skeletal muscles comes not only from the blood thus diverted but also from an increase in cardiac output.

Powerful vasoconstriction in the viscera and increased cardiac output inevitably produce an elevation in blood pressure, which again contributes to the blood supply to the skeletal muscles. As a consequence, however, this pressure rise must activate arterial baroreceptors. Without any countermeasure, the resulting arterial baroreflexes would interact with the blood flow supply to the skeletal muscles by offsetting visceral vasoconstriction and cardiac output. Furthermore, it is known that arterial baroreflexes include noncirculatory components as follows. When arterial baroreceptors are activated, gastrointestinal and urinary bladder motilities are increased [5], respiration (both tidal volume and frequency) decreased [5–10], pyramidal tract neurons inactivated [11], skeletal muscle tone and reflexes decreased [12], and level of consciousness lowered as evidenced by EEG synchronization [13–15]. All of them must directly or indirectly counteract the animal's behavioral performance in the face of an emergency. How does the animal cope with this dilemma, incompatibility of dynamic regulation and regulation for stability? The solution is simple and straightforward: the arterial baroreflexes are suppressed on such occasions.

Although less frequently studied, and apparently less evaluated, there are conditions in which arterial baroreflexes are augmented. The facilitation occurs when the animal is at rest after dynamic exercise [16, 17], and may contribute to energy recovery in the poststress phase and to the preparation of the physical condition for subsequent exposure to another stress. The situation resembles the relation of sleep to wakefulness in the daily cycle, and interestingly, the arterial baroreflexes are actually potentiated during sleep as stated later.

**Methodological Problems**

**Induction of arterial baroreflexes**

Arterial baroreflexes are induced by a variety of methods. Most commonly employed is baroreceptor activation due to i.v. injection of pressor agents like phenylephrine, etc. In some circumstances, baroreceptors are activated by balloon distension of the carotid sinus wall or by elevation of intraluminal pressure in the blind-sac, or perfused carotid sinus preparation isolated from systemic circulation [18]. In humans, transmural pressure of the carotid sinus is elevated by applying subatmospheric pressure to an airtight box enclosing the neck [19]. Conversely, baroreceptors are inactivated by occluding the common carotid arteries to examine the withdrawal effects of baroreceptor activities which are ongoing even in basal conditions [20]. All of these methods, however, have drawbacks in terms of specificity, reproducibility, or undesirable side effects. Pressor agents do not always stimulate baroreceptors in a pressure dependent manner but do
so more or less by direct action on the baroreceptors [21–23]. In isolated carotid sinus preparation, the blood flow to the forebrain is interrupted. Likewise, balloon distension of the carotid sinus or carotid occlusion transiently interrupts the forebrain blood flow, and activates chemoreceptors in a long-lasting challenge [20].

On the other hand, electrical stimulation of the baroreceptor afferents, if selectively conducted, appears to be the method of choice in all respects. It has been established in rabbits [24, 25] and rats [26, 27] that the aortic depressor nerve is composed of baroreceptor afferents and does not contain chemoreceptor afferents. If these species are used, electrical stimulation of this nerve produces arterial baroreflexes selectively and reproducibly.

Evaluation of arterial baroreflexes

Arterial baroreflexes comprise heart rate and blood pressure components. The major determinant of the heart rate component on baroreceptor activation is cardiovagal activity while that of the blood pressure component is sympathetic vasomotor activity especially after cessation of dramatic reflex bradycardia. In elaborate studies, the carotid sinuses are isolated and perfused to determine open loop gain by calculating the ratio of reflex changes in heart rate, blood pressure, or sympathetic nerve discharges to changes in the intrasinus perfusion pressure [28]. This method, however, interrupts blood flow to the forebrain, and requires repeated measurements with a variety of test stimuli. Thus, the following methods are often employed and are available with a fixed test stimulus.

The heart rate component of baroreflexes can be assessed either from changes in RR intervals or from changes in the number of heart beats reflexly reduced. The former method stems from the observation that RR interval is linearly related to frequency of vagal stimulation [29]. The latter can be obtained from the response area measurement in a heart rate tachogram recording after normalization [30], and is not influenced by a transient change of heart rate. In either case, percent inhibition or facilitation can be calculated by comparing changes during conditioning challenges vs. those in a controlled state.

Unlike relative stability of basal heart rate, basal blood pressure changes considerably from time to time. Thus, simple comparison of the magnitudes of the reflex fall is not valid since, as we always experience, the higher the basal level, the greater is the reflex fall. Ratio of fall to basal pressure is similarly unacceptable because the complete sympathetic inactivation does not lower blood pressure to zero. What we have taken for an alternative method is as follows. Within a short scale of time, variation of blood pressure is due to overall sympathetic nerve activities if the respiration is held constant. At a variety of spontaneously changing basal levels of blood pressure, the aortic depressor nerve is electrically stimulated to obtain the standard reflex fall from the respective basal levels of blood pressure. By plotting the magnitudes of falls against the varying basal levels, a regression line can be generated owing to the essentially linear relation of the two variables [30]. At a given basal blood pressure, an expected reflex fall in the absence of inhibition or facilitation can be obtained from this regression line. Comparison of a reflex fall during conditioning stimulation to the expected fall at the corresponding basal level yields percent inhibition or facilitation.

Skeletal Muscle Blood Flow in Arterial Baroreflexes

Skeletal muscles play a major role in the behavioral reaction to stressful conditions. Thus, it is important to know whether the activation of arterial baroreceptors increases or decreases blood flow in skeletal muscles, for instance, of the hindlimb. Both possibilities exist. Powerful reflex bradycardia causes reduction of cardiac output, inevitably leading to a decrease of blood flow in the whole body including the hindlimb; however, reflex withdrawal of vasoconstrictor tone in the skeletal muscles themselves favors an increase in their blood flow. Considering the effect on the whole body, however, blood flow in the skeletal muscles is expected to either increase or decrease depending on the baroreceptor-sensitive component of resting vasoconstrictor tone of blood vessels of the hindlimb muscle relative to those of the other organs. When the baroreceptor responsiveness of the resting vasoconstrictor tone is relatively high, the hindlimb blood flow should be increased when responding to baroreceptor activation. This idea was adopted by Djojosugito et al. in their study on hypothalamic defence reaction [31]. Their view may be correct because at rest, muscle blood flow is under a strong adrenergic constrictor tone which is highly baroreceptor-sensitive [32]. Coote et al. [33], however, claim that there is no need for the baroreceptor-dependent inactivation of sympathetic vasoconstriction to occur because maximal vasodilation, either neurogenic or metabolic, is elicited to increase muscle blood flow in such a situation.

Blood flow in a given organ \(F_r\) is determined by a product of the pressure head \(P_r\) and the vascular conductance \(C_r\), that is, \(F_r = P_r \times C_r\). Arterial baroreceptor activation affects both variables but in opposite direc-
tions. It reduces the former variable but increases the latter one. Thus, the net result can be either an increase or decrease. Cooe et al.'s idea appears to state that in the case when the blood vessels of hindlimb skeletal muscles are already dilated maximally, there will be no further reflex increase of $C_p$; and so inhibition of arterial baroreflexes is favorable for maintaining the increased blood flow in the skeletal muscles by minimizing reflex decrease in $P_e$.

It was reported that the femoral arterial conductance is indeed increased in response to baroreceptor afferent stimulation in anesthetized rats [34]. Using a laser Doppler method, however, we have found that reflex changes in muscle blood flow are variable in effect when arterial baroreflexes are provoked by electrical stimulation of the aortic depressor nerve (following bilateral section or paralysis of the vagus nerves, unpublished observation). In the former formula, $P_e$ is approximated to the product of cardiac output and total peripheral resistance (TPR). By defining the reciprocal of TPR as total peripheral conductance ($C_p$), the flow in question can increase or decrease depending on the ratio of $C_p$ to $C_T$, that is, on how baroreceptor-sensitive the conductance is, relative to that of the whole body. In contrast, cardiac output is critical for determining blood flow in any organ. For working muscles, the important parameter is blood flow, not vascular conductance.

Arterial Baroreflexes in the Defense Reaction

Hypothalamic defense reaction

Stimulation of a distinct area in the hypothalamus has been known to elicit a well coordinated complex of responses known as the defense reaction (for review see [35, 36]). The circulatory component of the reaction represents a typical example of dynamic circulatory control, including hypertension, tachycardia, and blood flow redistribution directed from the abdominal viscera to the skeletal muscles in the hindlimb. Additionally, mydriasis, augmented respiration (increases both in frequency and tidal volume), and decreases in gastrointestinal and urogenital functions occur. Furthermore, in the unanesthetized condition, the animal expresses rage and behavioral reactions as observed in a fight/flight situation.

The hypothalamic area thought to be responsible for the reaction, known as the defense area, differs among investigators, including the perifornical area in the anterorhidian hypothalamus [37–42], the posterior hypothalamus [43–49], Forel field/lateral hypothala- mus [28, 50, 51], ventromedial nucleus [52–54], and anterior hypothalamic area [53, 55]. As far as electrical tracking studies are concerned, however, the posterior hypothalamus may not be separable from, and therefore, may be considered to constitute a rostral extension of, the midbrain periaqueductal gray matter in terms of the defense reaction.

The increase in skeletal muscle blood flow in the hindlimb is the most remarkable feature characterizing the defense reaction [36]. However, the underlying mechanism was different among species. At first, a cholinergic vasodilator mechanism was proposed in cats and dogs [56], and this is now attributed to endothelium-derived relaxing factor, nitric oxide [46]. In other species, like rats, rabbits, and monkeys, administration of cholinergic antagonists like atropine fails to block the increase in hindlimb muscle blood flow during the defense reaction [36, 56]. Alternatively, β receptor-mediated relaxation likely contributes to the blood flow increase because a β-blocking agent abolishes it [34, 57]. In humans [58, 59] and also in rats [60], a nitrodergic mechanism is also reported to contribute somehow to stress-induced vasodilation of skeletal muscles.

In spite of these inconsistencies, the hypothalami- cally-induced defense reaction always accompanies hypertension. The magnitude of the defense reaction is so intense that it strongly activates arterial baroreceptors. If the arterial baroreflexes occur formularily as a consequence, all the components of the defense reaction would be attenuated as described earlier. It was Hilton's brief report that first addressed the question as to how this controversial issue is solved in the body [37]. He showed that the hypothalamic defense area, when stimulated, suppresses arterial baroreflexes during expression of the defense reaction. The validity of this observation has been repeatedly confirmed, in principle, by later investigations [31, 33, 34, 37–39, 43, 44, 50, 51, 55].

Inhibition of the heart rate component of baroreflexes (baroreflex bradycardia especially of vagal origin, BVB) during stimulation is unequivocally accepted (Fig. 1A) [31, 33, 34, 37, 38, 43, 50, 51, 55]. On the other hand, responses of the vascular component (blood pressure response after vagotomy or cholinergic blockade) have remained controversial. Some papers have shown that the vascular component is also suppressed [33, 34, 37], while others claim absence of change or rather an increase in sensitivity [31, 38, 43, 50, 51, 55]. This controversy may have partly resulted from the inconsistency of the methods employed for evaluating the effects of baroreceptor activation at altered levels of blood pressure during conditioning of defense area stimulation. Cooe et al. [33] showed that a baroreflex decrease in the renal
nerve activity responding to carotid sinus distension is completely abolished by the hypothalamic defense area stimulation in cats. In support of this, we showed that the blood pressure component was significantly, albeit less markedly, suppressed during stimulation of the hypothalamic defense area in rats [34].

Whatever effects of baroreceptor activation on the blood pressure component may be, it should be stressed that the defense reaction always accompanies elevated blood pressure. This implies that hypertension is not offset but is still preserved even during baroreceptor activation. As mentioned previously, the elevated pressure serves as a major driving energy for blood flow into the dilated blood vessels of working skeletal muscles.

**Midbrain periaqueductal gray matter**

Following the introduction of the chemical stimulation technique which enables selective neuronal cell body activation without effect on passing axons, the classic concept regarding the central site integrating the defense area has been largely revised. This technique is based on the generally accepted view that the major excitatory transmitter in the central nervous system is excitatory amino acids (EAA), and all central neurons have receptors for EAA on the plasma membranes of their cell bodies [61]. Bandler’s group, which first developed this technique [62], found that the behavioral component of the defense reaction in cats is fully provoked by activation of cell bodies in the midbrain periaqueductal gray matter (PAG) but not in the hypothalamus [63, 64]. Later, it was found that the PAG forms a longitudinally-oriented columnar organization in functional [65–69] as well as cytological [70–75] aspects. The dorsal and/or lateral columns of the PAG have been shown to be involved in the behavioral expression of the defense reaction [65–67, 69], while the ventrolateral column produces an opposite effect, muscle immobility [65, 68]. The former columns are thus referred to as movement columns while the latter, are referred to as immobility columns [76]. Also noteworthy is that the PAG occasionally evokes a specific pattern of the defense reaction, “defensive freeze,” which is characterized by re-active immobility [69] and probably is related to the “vigilance” reaction elicited from the rabbit hypothalamus [47, 77]. It is interesting that both columns cause analgesia, although of different natures [78]. Furthermore, rostrocaudal differences in behavioral expression have been demonstrated [65, 66, 69, 76, 79].

Using the chemical stimulation technique, the cardiovascular component of the defense reaction was also shown to be elicited in a full pattern from the PAG [80], but only partially and incompletely from the hypothalamus, unlike the results of studies using electrical stimulation [81]. Prominent hypertension and tachycardia was associated with an increase in blood flow as well as with vascular conductance in the hindlimb [80–82]. Again, columnar organization has been depicted. These cardiovascular responses are elicited specifically from the dorsal/lateral columns, which produce behavioral defense reaction as mentioned above and are now referred to as “hypertensive” columns, while the ventrolateral column produces sympathoinhibition resulting in hypotension (“hypotensive” column). Regional blood flows are differentially changed among organs from rostral and caudal “hypertensive” columns [76, 77, 82, 83]. The typical cardiovascular responses accompanying vasodilation of the hindlimb and vasoconstriction of the kidney are elicited from the rostral portion of the “hy-
pertensive” columns [76, 79]. The caudal portion of the columns elicits just the opposite effect in respective vasculatures. Thus, the presence of cell bodies provoking both the behavioral and autonomic nervous components of the defense reaction inside the dPAG strongly suggests that the dPAG integrates the coordinated expression of the defense reaction. It seems that the premier position of the hypothalamus in the defense reaction has now been taken over by the dPAG.

Since the dPAG-induced defense reaction accompanies marked hypertension, it is of immediate concern how the arterial baroreflexes are operated during the reaction. This question has been challenged first by Hockman and Telesnik [84, 85]. They reported that the PAG provokes either inhibition or facilitation of baroreflex bradycardia provoked by electrical stimulation of the carotid sinus nerve [84]. Facilitation occurred either during or after the end of PAG stimulation. Inhibition was observed only when the test was made during PAG stimulation. In a later study, they demonstrated that PAG stimulation causes a poststimulatory, rebound bradycardia which is completely removed following sinoaortic denervation [85]. Thus their PAG responses appear to include two components, one, due to attenuation of ongoing baroreflexes, the other due to a rebound facilitation likely caused by poststimulus depression of the inhibitory mechanism. A drawback of this study, however, lies in the fact that electrical stimulation of the carotid sinus nerve provokes a mixture of not only baro- but also chemoreflex responses as mentioned earlier.

On the other hand, Jones et al. [86] demonstrated that chemical stimulation of the dPAG, using excitotoxin kainic acid, suppresses phenylephrine-induced baroreflex bradycardia. The slope of their curve relating RR intervals to blood pressure was blunted by the dPAG stimulation (decreased sensitivity). They also showed that the electrolytic lesioning of the dPAG attenuated the baroreflex inhibition due to hindlimb ischemia. Owing to the methods they used, the influence of the blood pressure component of baroreflexes was not addressed.

We confirmed that the dPAG, when electrically stimulated, inhibited baroreflex vagal bradycardia (BVB) produced by stimulation of the ADN in β receptor-blocked rats (Fig. 1B) [30]. The blood pressure component of the baroreflexes was also suppressed, though less markedly, before as well as after bilateral vagotomy. BVB inhibition persisted following spinal cord transection at the C1 level. It was found that cell body activation by DL homocysteic acid (DLH) suppresses baroreflex vagal bradycardia without an appreciable effect on the blood pressure component.

These results suggest that the inhibition of the blood pressure component of baroreflexes is of a high threshold or requires recruitment of a larger number of neurons than that of the heart rate component. The validity of this notion, however, has not been tested because excitatory amino acids cannot be injected in large doses owing to their depolarization-induced blocking action [87]. dPAG inhibition is mediated by the parabrachial nucleus because kinase lesions in the latter completely abolish it [30]. The PAG projection to the parabrachial nucleus has been demonstrated anatomically [88].

Contrary to these studies, it was reported that the lateral to ventrolateral part of the PAG, when electrically stimulated, increases the gain of the baroreflex sympatho-inhibition curve in addition to provoking a pressor response [89]. Electrical stimulation of such a boundary part, however, likely activates two distinct types of cells with opposite functions. Furthermore, electrical stimulation of the PAG is known to produce stimulus intensity-dependent reactions [90]. Low-intensity stimulation provokes defensive freeze, whereas high-intensity stimulation provokes flight reaction. During the freeze reaction, the baroreflex heart rate component is enhanced [90].

**Hypothalamic defense reaction revisited**

As already stated, the role of the hypothalamus in the integration of the defense reaction has been considered to be limited since cell body activation does not provoke the full-pattern of the reaction, either behavioral or autonomic. However, recent studies using microinjection of excitatory or inhibitory amino acids, their antagonists, or neurotransmitter/modulator candidates, have repeatedly confirmed the existence of cell bodies yielding cardiovascular or behavioral components of the defense reaction within the hypothalamus [91–107]. Major pressor/tachycardiac sites appear to include the posterior hypothalamus [91, 93, 95], the dorsomedial hypothalamic nucleus [100, 103, 106, 107], the paraventricular nucleus [94, 98, 105], anterior hypothalamic area [96, 105], the ventromedial nucleus [97], and the perifornical region [101, 102]. Most significantly, microinjection of a GABA antagonist, such as picrotoxin or bicuculline, increases blood pressure and heart rate, and suppresses phenylephrine-induced baroreflex bradycardia [91]. Thus the classic concept is not entirely denied, only revised. The BVB inhibition of the hypothalamic and/or limbic origins is likely mediated by the dPAG since the dPAG lesion largely attenuates it [30].
Target sites of baroreflex inhibition

Baroreflex inhibition associated with the defense reaction has been studied by electrophysiological approaches. Target-site candidates include the nucleus tractus solitarius (NTS), the caudal and rostral ventrolateral medula (CVLM, RVL), and vagus cardio-inhibitory preganglionic cells (VCIN), etc. The first attempt was reported by Weiss and Crill [108]. They demonstrated that antidromic-compound spike potentials, evoked in the carotid sinus nerve by electrical stimulation of the NTS region, are facilitated by preceding stimulation of the hypothalamus. This study, an application of Wall's method [109], provided evidence that the hypothalamus, when excited, depolarizes the carotid sinus nerve terminals presynaptically in the NTS, thereby producing presynaptic inhibition of signal transmission in the nucleus. This attractive finding, however, was refuted by a systematic study by Jordan and Spyer [110]. Later, Spyer's group demonstrated in cats that the hypothalamic defense area, when electrically stimulated, inhibits all the baroreceptor-sensitive neurons in the NTS by producing IPSP [111]. The inhibition is GABA-mediated as it is abolished by bicuculline microinjection into the NTS [112]. Inhibition of baroreflexes at all once at their common gate station, the NTS, seems to be advantageous considering that all components of the baroreflexes, circulatory as well as noncirculatory, interact in the expression of the defense reaction.

Target sites of baroreflex inhibition caused by the hypothalamic defense area and the dPAG were readressed in rats at our laboratories. First, a possibility that either the hypothalamic defense area or the dPAG alters the excitability of the baroreceptor afferent terminals was negated [34, 113]. The antidromic-compound spike potentials evoked by stimulation of the NTS were not changed at all. Then the field potentials were evoked in the NTS and in the NA region by electrical stimulation of the ADN which, as aforementioned, contains baroreceptor but not chemoreceptor afferents in this species. It was found, however, that the field potentials evoked in the NTS were not affected during conditioning stimulation of either the hypothalamic defense area or the dPAG [34, 113]. In contrast, those field potentials obtained from the NA region were suppressed by both of these stimulations. These findings suggest that the major target site of BVB inhibition by the forebrain is not the NTS but the vagus cardioinhibitory preganglionic cells, a large portion of which reside around the NA [114, 115]. This notion was confirmed by recording unitary orthodromic responses of the NTS neurons to ADN stimulation as well as unitary antidromic responses to stimulation of the cardiac branch of the vagus nerve.

The conclusions from the two groups are inconsistent, and there are considerable differences in some respects. First, the animals used were different, cats vs. rats. Second, the recording methods of the two groups were different, i.e., unitary (occasionally intracellular recordings) vs. mainly field potential (occasionally unitary recordings). Third, the nerves used for test stimulation were different, i.e., the carotid sinus nerve (CSN) vs. the aortic depressor nerve (ADN). A recent paper has shown that the hypothalamic defense area, when electrically stimulated, yields a facilitatory response (EPSP) in chemoreceptor-sensitive cells in the NTS [116]. This finding suggests that the results of field potential analyses require caution in interpretation. If the defense area suppresses baroreceptor-sensitive neurons but excites chemoreceptor-sensitive neurons in the NTS, it is probable that on hypothalamic stimulation, an inhibitory effect on the baroreceptor-evoked field potentials is offset by field potentials due to excitation of chemoreceptor-sensitive cells. However, this possibility could be ruled out because in field potential recordings, field potentials evoked by conditioning stimulation alone were subtracted from those evoked by combined conditioning and test stimulations [34]. The finding that baroreceptor-sensitive neurons in the rat NTS did not respond to stimulation from either the hypothalamus or the dPAG [34, 113] supports the view that in this species there must be a major target site other than the NTS.

Role of the presynjucational mechanism in centrally-induced baroreflex inhibition

Recently, it has been established that reciprocal presynjucational mechanisms are involved in sympathetic/parasympathetic interactions. Most extensively studied among them has been the sympathetic presynjucational inhibition on acetylcholine release from terminals of the vagus cardiac branch. Vagus bradycardia induced by stimulation of a peripheral cut end of the cervical vagus nerve is remarkably suppressed by preceding stimulation of the cardiac sympathetic nerve [117, 118]; stimulation of the cardiac sympathetic nerves or application of their transmitters did not affect the bradycardia induced by cholinomimetic drugs [119, 120]. NE, NPY, and galanin have been proposed as the transmitters responsible for the inhibition [121–127]. Although it is established that BVB inhibition during the defense reaction is largely mediated by a central mechanism, there is a possibility that such a presynjucational mechanism contributes to the BVB inhibition because the defense reaction always accompa-
nies powerful sympathoexcitation. The results of our study addressing this issue are as follows [128].

The cervical vagus nerves of both sides were cut, and the distal cut ends stimulated to produce vagus bradycardia (VIB) in anesthetized, β-blocked rats. In addition, bradycardia of an identical magnitude was induced by i.v. acetylcholine (AIB). It was found that electrical stimulation of the dPAG inhibits VIB, but not AIB. Likewise, NE infusion was shown to suppress VIB, but not AIB. Both dPAG and NE inhibition was abolished by i.v. prazosin, an α₁-receptor blocker. Thus there is indeed a peripheral, prejunctional mechanism whereby acetylcholine release from the cardiac branch of the vagus is inhibited via α₁-receptors by NE released from the cardiac sympathetic nerve. Paradoxically, however, i.v. prazosin attenuated dPAG inhibition of BVB only slightly, although significantly. This apparent discrepancy was accounted for by the difference of latencies of onset for central and prejunctional inhibitions. BVB was suppressed immediately following the onset of dPAG stimulation, whereas VIB inhibition required a lengthy preceding stimulation of the dPAG. Long latency onset of dPAG inhibition of VIB reflects the time required for NE to be accumulated in the target tissue. In fact, there is an electrochemical demonstration which shows that the intracellular NE concentration increases with time in intense sympathethic stimulation [129]. In conclusion, the dPAG has a potential ability to suppress BVB by a prejunctional mechanism. This mechanism, however, is set in motion only when dPAG stimulation is sustained. Therefore, dPAG stimulation inhibits BVB promptly, and mainly by a central mechanism, leaving only a limited fraction of vagal outflow for the prejunctional inhibition of slow onset.

Other central sites inhibiting arterial baroreflexes

In addition to the hypothalamic defense area and the dPAG as mentioned above, other central nervous system structures have been proposed to have potential inhibitory actions on arterial baroreflexes. These include: the cerebral motor cortex [130], amygdala [131, 132], cerebellar cortex [133–136], parabrachial nucleus [137, 138], cerebellar fastigial nucleus [139–141], inferior olive [142], and locus ceruleus [143]. Subsequent chemical stimulation studies, however, do not support the presence of cell bodies having such functions in the fastigial nucleus [144], or the inferior olive [145–148]. Even among studies using the chemical stimulation method, controversy still exists regarding baroreflex modification by the locus ceruleus [149, 150]. It is conceivable that those structures shown to inhibit arterial baroreflexes somehow contribute to either the initiation, integration, or mediation of the defense reaction, and are functionally interrelated with each other. As mentioned earlier, the hypothalamic defense area, the dPAG, and the parabrachial nucleus are considered to constitute a functional complex in terms of BVB inhibition [30]. The hypothalamic defense area may at least represent a relay station of the defense reaction initiated in the amygdala complex [151, 152]. Besides, the parabrachial nucleus is found to be a relay station of cardiovascular responses initiated from the posterior cerebellar vermis, lobule IXb [134].

Arousal and mental stress

In connection with the defense reaction, arousal or mental stress is also known to produce inhibition of baroreflexes [131, 132]. Cardiac baroreflex sensitivity in a conscious cat is reduced during confrontation with another aggressive cat [131]. Similar results are obtained in conscious rats confronted with a mouse [132]. Sympathetic nerve activities in human volunteers recorded from the peroneal nerve are markedly reduced in response to an phenylephrine-induced increase in blood pressure. However, an arithmetic task, the serial subtraction of a two-digit number from a four-digit number, increases sympathetic nerve activities, which is, in this case, resistant to i.v. phenylephrine [153]. A verbal arithmetic task is also found to suppress the heart rate component of the baroreflexes [16]. Among the central sites mentioned, the amygdala may play a potential role for initiation of the baroreflex inhibition in conscious humans exposed to mental stress, since the amygdala are recognized as the site of fear and anxiety [154].

Mental stress has been shown to accompany redistribution of regional blood flow. In conscious humans, mental stress increases blood flow as well as vascular conductance of the forearm [155].

Modulation of Arterial Baroreflexes by Noxious Sensory Inputs

Noxious somatosensory inputs

When a noxious somatosensory stimulus is given to an animal, it shows a flight reflex known as the noxious flexion reflex. Besides this behavioral response, blood pressure and heart rate are increased ("sciotic pressor reflex" in case of sciatic nerve stimulation). The stimulus may additionally provoke the defense reaction if the animal is not anesthetized. Even in an anesthetized, cuffed rat, vascular conductance of the hindlimb muscle is increased when the sciatic
nerve of the contralateral side is stimulated with high intensity electric current [34, 156]. The redistribution of blood flow allows us to consider that the circulation is dynamically regulated in this situation. Thus it is also beneficial if arterial baroreflexes are then suppressed to make full use of blood pressure elevation for needed blood supply to the skeletal muscles. In fact, it has been long known that this is the case [34, 157–161].

In chloralose-urethane anesthetized rats, for example, electrical stimulation of a central cut end of the sciatic nerve almost completely suppresses the vagal heart rate component (BVB) of arterial baroreflexes (Fig. 2A) [34]. The blood pressure component of the baroreflexes during sciatic nerve stimulation is variably affected, either inhibited or unchanged. Figure 2A, however, shows that the component is definitely inhibited.

Muscle polymodal receptors have been proposed as the sensory receptors connected with the sensory afferent fibers producing the baroreflex inhibition. In this regard, intramuscular injection of bradykinin was shown to produce BVB inhibition [160]. Most interesting is the finding that hindlimb muscle contraction due to repetitive stimulations of the distal cut end of the ventral roots from the lumbar cord progressively suppresses BVB with time [160, 162], although the suppression is abolished following muscle paralysis [160]. These findings suggest that metabolites released from exercising skeletal muscles are responsible for BVB inhibition.

In close relation to this, exercise is known to produce a reflex increase in blood pressure (exercise pressor reflex) [163] and to suppress phenylephrine-induced bradycardia in animals and humans [164–170]. It is well known that blood flow in the skeletal muscles is increased during exercise, and even before onset of exercise [1]. Therefore, it is possible that both the exercise pressor reflex and the associated BVB inhibition are, at least, partly accounted for as a consequence of the defense reaction triggered by sensory stimuli or by anticipation of them. In fact, simultaneous stimulations of the hypothalamic defense area and the sciatic nerve caused a remarkable facilitation of respective BVB inhibitions [34]. In agreement with this view, Jones et al. [87] claimed that the dPAG mediates BVB inhibition produced by somatic pain because inhibition is reduced following a dPAG lesion. Largely, however, BVB inhibition due to painful stimuli is of reflex origin, and not so dependent on forebrain structures, because it still occurs following decerebration [167, 169]. Furthermore, it is likely that the facilitated respiratory effort during exercise contributes, at least partly, to BVB inhibition. This suggestion is based on the finding that the BVB is inhibited in the inspiratory phase during the respiratory cycle due to a central mechanism [171].

Types of afferent fibers conveying BVB inhibition are considered to belong to A-delta and C fiber groups (groups III and IV) [34, 161], although contribution of group III fibers to blood pressure responses remains controversial, producing pressor or depressor responses probably depending on the fiber subtypes [172, 173]. This issue will be discussed later. Further, spinal ascending pathways conveying the sensory inputs have been delineated. These pathways are not confined to the dorsolateral funiculi which mediate pressor and depressor responses to somatic input [174], but are strikingly multifold, taking all of the possible courses to reach the brainstem where the target neuronal baroreflex components are located [160].

The target site of BVB inhibition by noxious somatic stimuli is delineated by electrophysiological methods similar to those for target sites of inhibition.
by stimulations of the hypothalamic defense area and the dPAG. It was shown that as in hypothalamic and dPAG inhibitions, BVB inhibition due to somatic noxious inputs occurs at the level of the vagus cardioinhibitory preganglionic cells in the nucleus ambiguus region [160] or in the dorsal motor nuclei [175].

How the blood pressure component of the baroreflexes is modulated during painful-stimulus application, has not been studied frequently. Available data suggest that it is inhibited in vagus intact rats [34] and vagotomized rabbits [158]. The inhibition, however, is variable and not marked when compared with BVB inhibition.

**Noxious visceral input**

Noxious stimuli applied on the viscera, such as luminal distension or application of algic agents on the serosa, are known to elicit increases in blood pressure and heart rate [176]. Recently, it was found that such stimuli also inhibit arterial baroreflexes, especially the vagal bradycardiac component (BVB). In anesthetized rats, hydrostatic distension of the stomach suppresses BVB elicited by ADN stimulation (Fig. 2B) [177]. This inhibitory effect is abolished by transection of the splanchnic nerves of both sides, and mimicked by electrical stimulation of the central cut end of the nerve of a given side, indicating that the effect is mediated by the splanchnic nerve [177]. Powerful contraction of the stomach wall due to the application of a cholinomimetic agent to the serosal surface has the same effect (unpublished observations). BVB inhibition is similarly observed by distension of the ileum, esophagus [177], urinary bladder [177, 178] and colon/rectum (unpublished observations). Distension of the estrus uterus also inhibits BVB in rats [179]. This inhibition, however, is mediated not only by the hypogastric nerve alone but also by the pelvic nerve. According to Hussain et al. [180], occlusion of a branch of the coronary artery also inhibits the arterial baroreflex probably through excitation of ventricular chemosensitive endings. Thus, baroreflex inhibition is rather a general phenomenon occurring in animals which suffer from visceral pain of any origin.

At present, the physiological significance of baroreflex inhibition associated with visceral pain is unknown. BVB inhibition due to uterine distension and colorectal distension may be beneficial for hemodynamic readjustment during labor and defecation, respectively. In contrast to blood flow redistribution in the defense reaction, however, it is interesting to note that painful stimulation of the stomach (acid challenge of the mucosa) evokes vasodilation in the kidneys and vasoconstriction in the skeletal muscles [181]. This may assist animals to remove a painful stimulus in the viscera or to recuperate the resultant tissue damage.

**Baroreflex Facilitation**

**Situations facilitating arterial baroreflexes**

Arterial baroreflexes are known to vary in sensitivity during the daily cycle in humans. During sleep, baroreflex gain, as measured by changes in heart rate vs. changes in blood pressure, is largest whereas it is lowest during exercise [16, 166] or the arousal state [16] as stated previously. Following exercise, either of severe [17] or moderate degrees [182], the baroreflex gain is augmented. This change is not due to so called resetting whereby baroreceptor sensitivity is reduced. Face immersion into cold water augments baroreflex bradycardia due to neck suction [183]. Furthermore, it is reported that baroreflex facilitation is observed in late pregnancy [184].

In experimental animals, low intensity afferent stimulation of the sciatic nerve produces a depressor response accompanied by BVB facilitation [157]. The fiber types involved may be of a low threshold subtype in group III. This notion is drawn from the finding that BVB facilitation due to low threshold stimulation is accompanied by a depressor response, which, according to Coote et al. [171], is provoked by a low threshold subtype of group III fibers. In this connection, afferent stimulation of group II and III fibers was found to suppress the cardiovascular defense reaction produced by the dPAG [185]. In contrast, high intensity stimulation suppresses BVB inhibition accompanying a pressor response [157] as stated earlier.

**Central mechanisms facilitating baroreflexes**

Several sites in the central nervous system have been known to exert a facilitatory influence on arterial baroreflexes. These include the preoptic/anterior hypothalamic area [186–189], the lateral hypothalamic area [187], the ventrolateral part of the PAG (vPAG) [190], the nucleus raphe magnus [190], and the medial prefrontal cortex [191]. Stimulation of all these structures provoke a depressor response in conjunction with bradycardia. Thus, it is possible that other hypotension/bradycardia provoking sites such as the insular cortex [192], and the trigeminal nucleus [193], have similar baroreflex-augmenting capacities, although they have not been tested yet.

Inui et al. conducted systematic studies showing that BVB facilitation due to POA stimulation is abolished by vPAG lesions [187] while BVB facilitation by vPAG stimulation is removed by lesioning the nucleus raphe magnus [190]. It is concluded that these three nuclei constitute a functional complex
in series in terms of BVB facilitation. This complex probably functions as a rostral neuronal network not only facilitating in demand, but also tonically potentiating the baroreflex mechanism in the medulla. The latter notion comes from the finding that a lesion in the PO/AHA region, attenuates baroreflexes [188, 189] and that some neurons in these areas receive excitatory input of baroreceptor origin [194]. There is histological evidence supporting the connection from the POA to the vPAG [195], and from both of these sites to the nucleus raphe magnus [196].

**Baroreflex facilitation vs. inhibition**

Considering the overall influences of baroreflexes, baroreflex facilitation is definitely beneficial for animals needing rest, energy restoration, and recuperation from exhaustion or from injury. This effect contrasts with that of baroreflex inhibition which gives preference to an immediate, emergent reaction against stressful environmental changes. Do not the two opposing mechanisms interfere with each other? An important clue for answering this question has been provided, though indirectly, by Lovick and her group. First, it was shown that the cardiovascular component (hypertension, tachycardia, and increased blood flow in the hindlimb) of the defense reaction due to electrical stimulation of the dPAG is largely attenuated by chemical stimulation of cell bodies in the vPAG [83]. More recently, they reported that the nuclei raphe magnus and obscurus, when chemically stimulated, inhibit the cardiovascular defense reaction evoked by the dPAG [197]. The majority of the PAG neurons are inhibited responding to activation of cells in the nucleus raphe obscurus via serotonergic receptors [198]. These findings suggest that the vPAG neurons exert an inhibitory influence on the dPAG neurons, at least partly, via a long loop involving the pontomedullary raphe nuclei. Whether this notion can be applied for activities of the respective sectors of the PAG in terms of their inhibitory or excitatory effects on baroreflexes, remains to be tested. Lovick et al.'s reports have put a focus on the influence of the “re recuperative” system dominating over the “defense” system. Interaction in a converse way, however, must be present for the full-fledged defense reaction to occur as it actually does in stressful conditions.

**Conclusion**

The physiological importance of arterial baroreflexes cannot be overemphasized. Homeostatic maintenance of blood pressure is especially important for the brain, a vital essential organ, which requires uninterrupted blood supply at any moment in an animal's daily life. Arterial baroreflexes, however, have a variety of consequences not only affecting circulation but also gastrointestinal motility and secretion, respiration, muscle tone, behavior, and emotion. Besides acting as a powerful stabilizer of blood pressure, they assist the animals' energy recovery from exhaustion in the resting condition. In fact, these functions are potentiated during sleep, in the postexercise phase, and under certain sensory stimuli presumably comfortable to the organisms. At rest, a central facilitatory mechanism in the forebrain is likely operating because decerebration attenuates arterial baroreflexes.

In stressful situations, however, all components of arterial baroreflexes should interact in the animals' expression of the reaction which then becomes of prime importance. They include fight/flight, attack/defense, exposure to, or anticipation of noxious somatic stimuli, visceral nociception, exercise, arousal, and mental stress. Cardiovascular responses to support the animal's behavioral reaction to these situations include blood pressure elevation, and increases in heart rate and skeletal muscle blood flow; the former must provoke

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**Fig. 3. Schematic diagram showing central and prejunctional sites involved in inhibition and facilitation of baroreflex vagal bradycardia (BVB) in rats.** Open ovals show the sites inhibiting BVB; stippled ovals, those facilitating BVB. Open squares, neuronal elements responsible for BVB generation. + and − indicate excitatory and inhibitory influences, respectively. ADN, aortic depressor nerve; a, R, α1 receptors; AMG, amygdala; β, R, β receptors; dPAG, dorsolateral part of midbrain periaqueductal gray matter; HDA, hypothalamic defense area; mR, LIXb, posterior cerebellar vermis lobules IX; muscarinic receptors; MPFC, medial prefrontal cortex; NRM, nucleus raphe magnus; NTS, nucleus tractus solitarius; PBN, parabrachial nucleus; POA, preoptic nucleus; RVLM, rostral ventrolateral medulla; Symp., cardiac sympathetic nerve terminals; VCIN, vagus cardioinhibitory preganglionic cells; vPAG, ventrolateral part of midbrain periaqueductal gray matter.
arterial baroreflexes, which would in turn hinder the expression of all the responses. In nearly all of these situations, the arterial baroreflexes are proven to be suppressed. Besides, presence of the baroreflex inhibiting mechanism would provide an answer to the mysterious question why in certain conditions, hypertension can occur in combination with tachycardia, and not with bradycardia.

It is appropriate to consider that in the daily cycle, arterial baroreflexes are operating with changing sensitivities under control of the facilitatory and inhibitory mechanisms. Central substrates responsible for the two mechanisms have been proposed and each conceivably constitutes a respective, functional integrity (Fig 3). The presence of mutually inhibitory interactions of the two mechanisms is thought to be a prerequisite for either one to alternatively develop to the full extent. The validity of this view depends on experimental confirmation in future studies.

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