

Baroreceptor Reflex

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Baroreflex Models

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Synonyms

[Baroreceptor reflex](#)

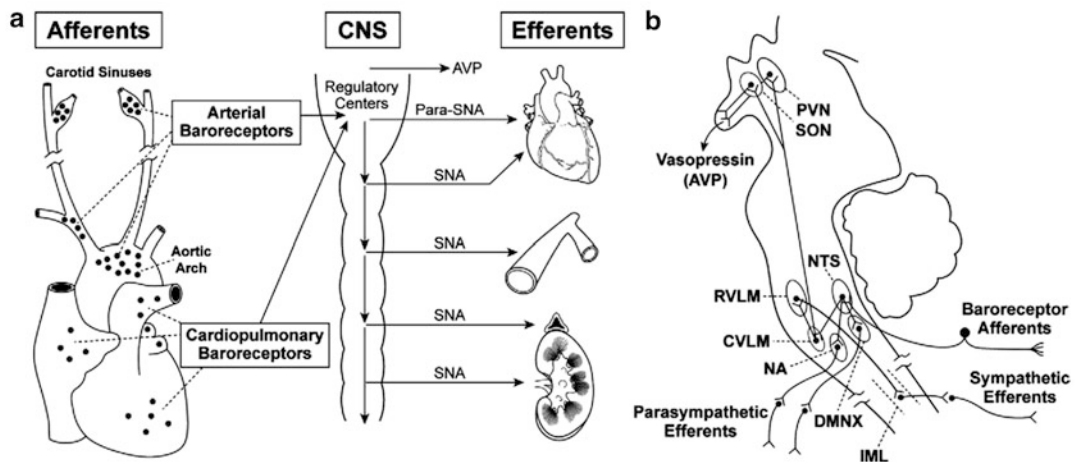
Definition

Blood pressure is controlled by several feedback mechanisms. The fastest one baroreceptor reflex (baroreflex) can be defined as the biological neural control system responsible for the **short-term** blood pressure regulation.

From modeling perspective the baroreflex feedback control system consists of three parts (Fig. 1):

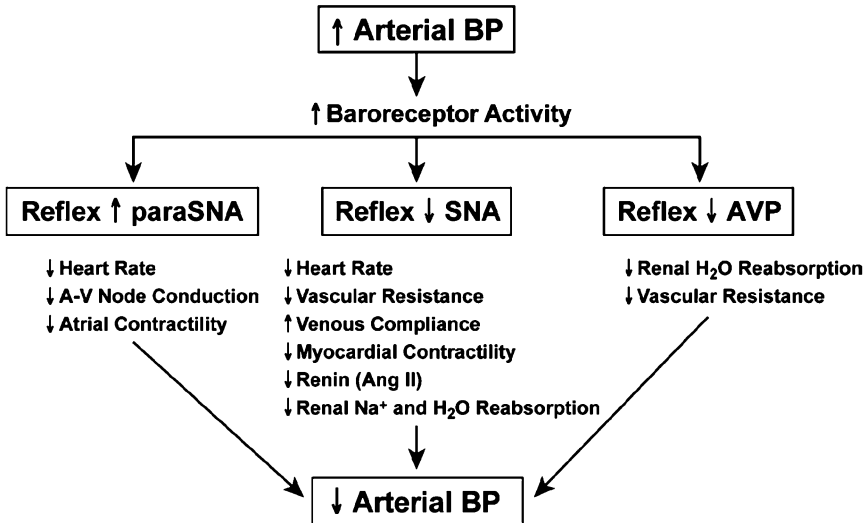
- The afferent part where the arterial pressure is being read out, transduced, and supplied
- The central nervous system (CNS) where this input is processed and converted to the sympathetic and parasympathetic nerve activities
- The effector organs that respond to sympathetic and parasympathetic tones by adjusting heart rate, contractility, vascular resistance, and a number of other physiological parameters

The afferent part is represented by baroreceptors, mechanoreceptors located in the great arteries, heart, and pulmonary vasculature, that transduce arterial pressure into action potential trains. Baroreceptors provide input to second-order neurons in nucleus tractus solitarius (NTS) located in the lower brainstem. Via a network of interneurons, the second-order barosensitive neurons provide an excitatory input to cardiac vagal motoneurons (CVM) in nucleus ambiguus (NA) and dorsal motor nucleus of vagus (DMNX) and inhibit the pre-sympathetic neurons in rostral ventrolateral medulla (RVLM). CVMs and pre-sympathetic RVLM neurons define



Baroreflex Models, Fig. 1 Location of baroreceptors and neural pathways of baroreflex responses. Abbreviations: CNS central nervous system, *para-SNA* parasympathetic nerve activity, *SNA* sympathetic nerve activity, *NTS* nucleus tractus solitarius, *NA* nucleus ambiguus, *DMNX*

dorsal motor nucleus of vagus, *CVLM* caudal ventrolateral medulla, *RVLM* rostral ventrolateral medulla, *IML* intermediolateral column, *PVN SON* supraoptic nucleus of hypothalamus (From Chapleau 2011 with permission)



Baroreflex Models, Fig. 2 Baroreflex negative feedback control of arterial blood pressure (BP) (From Chapleau 2011 with permission)

parasympathetic (para-SNA) and sympathetic (SNA) nerve activities, respectively. **Baroreflex models** are aimed to quantify para-SNA and SNA reflex responses to sharp changes in arterial BP and, thus, attempt to describe the neural part of the system.

Closed-loop models of cardiovascular system usually include a baroreflex compartment, and a number of effector organs controlled by sympathetic and parasympathetic activities (Fig. 2).

Detailed Description

Deviations in blood pressure (BP) and blood volume are sensed in cardiovascular system by **baroreceptors**, mechanosensitive nerve endings activated by vascular or cardiac distension (Fig. 2). **Arterial baroreceptors** (located in the aortic arch and the carotid sinuses, see Fig. 1) increase their activity when BP rises, and reduce it if BP lowers. **Cardiopulmonary baroreceptors** in the heart, vena cava and pulmonary vasculature are aimed to sense central blood volume, and are sometimes called *volume receptors* or *low-pressure receptors*.

The afferent activity from arterial baroreceptors is sent to the medullary brainstem area

called nucleus tractus solitarius (NTS) through glossopharyngeal nerve (from carotid sinus baroreceptors) and vagus nerve (from aortic arch) that together are known as the **buffer nerves**. In the NTS this information is processed by an intricate network of interneurons that control efferent parasympathetic (para-SNA) and sympathetic (SNA) nerve activities and release of antidiuretic peptide vasopressin (AVP) (see Fig. 1). All these mechanisms in response to changes in the arterial BP cause reflexes (Fig. 2) that ultimately push BP in the opposite direction providing a negative feedback control of arterial BP called **arterial baroreflex**. The CNS pathways of cardiopulmonary baroreceptors are similar to that of arterial ones except their activation has little effect on heart rate (HR) which is the fastest mechanism of BP control.

Due to complexity of the system, modeling studies usually focus on a particular aspect depending on phenomena considered while using simplified description of other compartments. Several integrative mathematical models were used to elucidate the role of baroreflex in cardiovascular instabilities, such as heart rate variability and spontaneous fluctuations of the arterial pressure (e.g., Mayer waves).

Pressure-Electrical Transduction

As a result of a change in arterial pressure, the cross-sectional area of the arteries changes leading to mechanical deformation of artery walls. Changes in the membrane strain resulting from the artery wall deformation lead to changes in the conductance of a variety of mechanosensitive ion channels in the sensory terminals of arterial baroreceptors. The cumulative effect of the opening of those channels in response to rise in pressure is an increased inward (depolarizing) current. If the resulting depolarization exceeds certain threshold, baroreceptors start firing action potentials with a rate defined by the magnitude of this current.

In mechanoreceptors variations in membrane strain affect protein conformations and, hence, cause changes in the probabilities for mechanosensitive membrane channels to be in open and close states (Morris 1990). Accordingly, a net inward current flow through mechanosensitive ion channels is often modeled as a nonspecific current with zero reversal potential and Boltzmann-like dependence of the conductance on arterial pressure P :

$$I_{\text{baro}} = \frac{g_{\text{max}}}{1 + \exp(-K(P - P_{1/2}))} (V - E_m)$$

where g_{max} is a maximal conductance of this current, $P_{1/2}$ is half-activation pressure, K defines the sensitivity and E_m is a reversal potential usually accepted 0.

Rose et al. (1995) used a little different approach. Their baroreceptors had a pressure-dependent depolarizing current which was linear above a threshold pressure: $I_{\text{baro}} = K(P - P_{\text{thr}})$ if $P > P_{\text{thr}}$ and $I_{\text{baro}} = 0$ otherwise.

Baroreceptors

Baroreceptor response to changes in arterial BP is very complex, nonlinear, and has multiple time-scales. Rapid jumps in BP lead to much stronger changes of baroreceptor activity than gradual excursions of the same magnitude. Acute hypertension results in a sharp rise in the baroreceptor activity which, however, declines in time if hypertension is maintained. After acute

withdrawal from the increased BP, baroreceptors first exhibit reduced activity (post-excitatory depression) which then adapts back to baseline.

In short, the properties of the firing rate of the baroreceptors in response to changing arterial pressure modeling-wise important can be formulated as follows (Ottesen et al. 2004):

- Firing rate increases with BP.
- The response exhibits threshold and saturation.
- Sufficiently fast decreases in pressure cause firing rate to fall below the threshold.
- A step change in pressure causes a step change in firing rate followed by a decay in firing rate (called adaptation or resetting depending on the timescale).
- Response curves are sigmoidal and show asymmetric hysteresis-like behavior.

Conductance-Based Baroreceptor Model

Baroreceptor fibers are divided into two different types, A-type and C-type, depending on whether they are myelinated or not. Schild et al. (1994) performed a thorough study of their electrophysiological properties and developed a conductance-based model of A- and C-type cells based on voltage-clamp recordings in rat nodose sensory neurons (carotid sinus baroreceptors). Their model included two Na^+ currents exhibiting fast and slow tetrodotoxin (TTX)-insensitive kinetics; low- and high-threshold Ca^{2+} currents exhibiting transient and long-lasting dynamics, respectively; and outward K^+ currents consisting of a delayed-rectifier K^+ current and Ca^{2+} -activated K^+ current. The model also includes extra- and intracellular C^{2+} dynamics.

Firing Rate-Based Baroreceptor Model

In Ottesen et al. (2004) a very elegant model is suggested that accounts for major properties of baroreceptor response. His model describes nonlinear responses of a baroreceptor to changes in carotid pressure in terms of a single nonlinear ordinary differential equation:

$$\frac{dn}{dt} = k \cdot \frac{dP_c}{dt} \cdot \frac{n(M-n)}{(M/2)^2} - \frac{n-N}{\tau}$$

where n is the firing rate of the baroreceptor, P_c is the carotid pressure, M is the maximal firing rate, τ is the adaptation time constant, k is a weighting constant, and N denotes the threshold. Instantaneous rate of change of the firing rate is proportional to the time derivative of carotid pressure and to the firing rate itself. Accordingly, the change in firing rate is most sensitive to change in carotid pressure when the value of the firing rate is in the middle of its physiological range $[0, M]$ and almost insensitive near the boundary. This defines the sigmoidal form of the response curve.

Experimental data shows that the adaptation has many different timescales from seconds to hours or even days. As mentioned, baroreceptor fibers are divided into different types, fast A and slow C fibers, in accordance to whether they are myelinated or not. The fast A fibers are further divided into subtypes. It was suggested that different types of baroreceptors can be characterized by significantly different adaptation time constants (Ottesen and Olufsen 2011). In this case their integrated activity n is calculated as

$$n = N + \sum_{i=1}^K \Delta n_i$$

where Δn_i is a deviation of the firing rate of the type i baroreceptor from the threshold value N , driven by a nonlinear differential equation similar to the above:

$$\frac{d}{dt} \Delta n_i = k_i \cdot \frac{dP_c}{dt} \cdot \frac{n(M-n)}{(M/2)^2} - \frac{1}{\tau_i} \Delta n_i$$

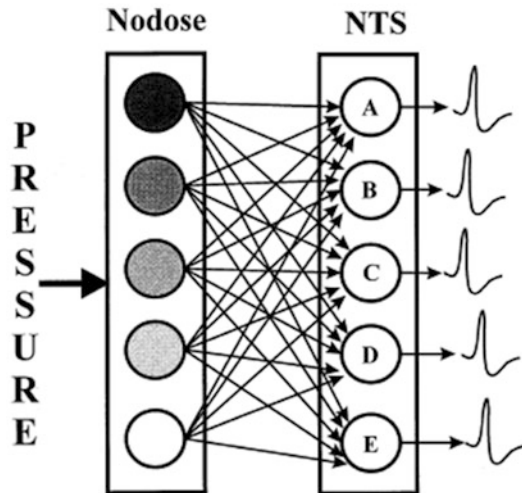
and K is a number of different baroreceptor types. Ottesen and Olufsen (2011) show the example where a satisfactory fit of the experimentally observed responses of the firing rate to a step input pressure requires $K = 3$ types of baroreceptors with time constants $\tau_1 \approx 0.5$, $\tau_2 \approx 10$, and $\tau_3 \approx 3000$ s.

Nucleus Tractus Solitarius (NTS)

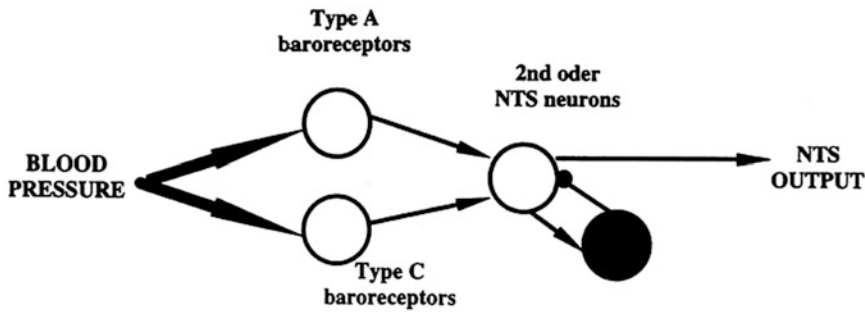
Baroreceptors map the spatial pressure distribution onto the inputs to the second-order neurons

in the NTS. One of the puzzles of the identified baroreflex-related neurons in NTS is that in spite of receiving direct inputs from the first-order neurons, their activity does not have any frequency component corresponding to cardiac frequency. Somehow they do not respond to each heartbeat by performing a “low-pass filtration” of their inputs.

Rogers et al. (2000) suggested that this property can be concerned either with specific biophysical properties of NTS baroreceptors (Fig. 3) or with specific interactions in the NTS network of second-order interneurons (Fig. 4). By analyzing the responses of the second-order NTS neurons to induced blood pressure pulses, they have noticed that barosensitive second-order NTS neurons respond to blood pressure changes with a burst of activity whose frequency is much lower than the frequency of cardiac cycle, and the activity of these neurons is inhibited just



Baroreflex Models, Fig. 3 Schematic used by Rogers et al. (2000) for NTS model based on specific electrophysiological properties. Arterial pressure is transduced by baroreceptors (nodose) according to their pressure thresholds, indicated by shading (*top cell*: highest pressure threshold). All NTS neurons receive input from all baroreceptors. Each input to any given NTS cell is equally weighted. The only difference between the NTS neurons is the total synaptic weight provided by the baroreceptors, which is varied systematically with the top neuron (A) receiving the highest total drive and the bottom neuron (E) receiving the lowest total drive



Baroreflex Models, Fig. 4 Architecture of the model proposed to explain variability of NTS neuronal responses to buffer nerve shock and arterial pressure increases. This model consists of two populations of baroreceptors, type A and type C, that have different pressure thresholds and sensitivities. The two baroreceptor populations provide

before and after the bursts. Using these observations they developed a series of mathematical models of early stages of baroreflex based on the intrinsic cell properties and network mechanisms.

Intrinsic Properties-Based Model

Individual NTS neurons were modeled using a single-compartment description in the Hodgkin–Huxley formalism. The most important feature of their individual neuron model was that in addition to ionic channels responsible for spiking behavior (like fast sodium and potassium delayed rectifier channels), they incorporated mechanisms for the response adaptation (A-type potassium, calcium-dependent potassium, and low threshold calcium currents). This mechanism together with intracellular calcium dynamics allowed them to reproduce several important properties of the second-order baroreceptors previously identified experimentally: (1) frequency adaptation in the cell’s response to a step stimulus; (2) sensitivity to the rate of change of input; and (3) the lack of response to each pulse of a pulsatile stimulus; however, if these pulses were imposed on a ramp stimulus, the cell could respond to each pulse.

Inhibition-Based Model

Barosensitive NTS neurons show a variety of responses to both buffer nerve shock and arterial pressure increases. These neurons may respond to

input to the excitatory population of second-order NTS neurons. This population sends excitatory inputs to the population of inhibitory neurons (represented by the shaded circle), which in turn inhibits the former (Adapted from Rogers et al. 2000 with permission)

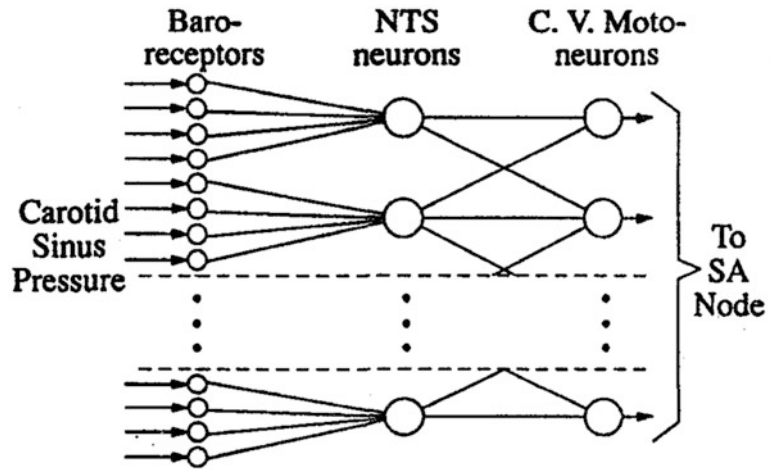
buffer nerve shock with excitation (EPSPs), inhibition (IPSP), or an EPSP/IPSP combination. Accordingly, they may be excited, inhibited, or responded with an extinction response to increases in arterial pressure. To account for a variety of responses, Rogers et al. (2000) proposed a populational model of barosensitive NTS neurons based on specific neural circuitry. In this case they also used Hodgkin–Huxley-based description but without Ca^{2+} and $\text{K}(\text{Ca}^{2+})$ conductances. So this model solely relies on the network architecture, rather than on the neurons’ biophysical properties.

Barotopic Hypothesis

Because of the different pressure thresholds, baroreceptors have a distributed sensitivity to BP and its rate of change. “Barotopic” organization hypothesis suggests that individual baroreceptors’ pressure thresholds (below which they are silent) are topically distributed in an interval of the pressures and that each second-order barosensitive neuron receives inputs from the first-order ones, whose thresholds lie in a definite small interval of pressure values.

Rose et al. (1995) used this architecture in their model of baroreflex control of heart rate. The neural portion of their model included baroreceptors, neurons of the nucleus tractus solitarius (NTS), and cardiac vagal motoneurons (CVM) (Fig. 5) all described in Hodgkin–Huxley style.

Baroreflex Models,
Fig. 5 Architecture of
 a neural portion of the
 model by Rose et al. (1995)
 (Reproduced with
 permission)



In addition to basic spiking currents baroreceptors in their model included A-type potassium current responsible for rapid adaptation and a pressure-dependent depolarizing current which was linear above a threshold pressure (see section “Pressure-Electrical Transduction”). Each baroreceptor had its own threshold pressure P_{thr} , and the thresholds had a sigmoidal distribution. Each NTS neuron received excitatory inputs from several baroreceptors with close thresholds and projected to several CVMs. The NTS neurons and CVMs had six conductances: sodium, delayed-rectifier potassium, A-type potassium, AHP-type potassium, L-type calcium, leakage conductances, and intracellular calcium dynamics including pumping and buffering. The CVMs projected to the sinoatrial (SA) node where their action potentials activated an acetylcholine (ACh)-activated inward rectifier K^+ hyperpolarizing current which slowed the depolarization of the node and hence decreased the heart rate. The effect of vagal impulses on the hyperpolarizing current was greater for those arriving later in the cardiac cycle.

Sympathetic and Parasympathetic Activities

Second-order baroreceptors in the NTS through a network of interneurons modulate parasympathetic and sympathetic efferent outputs by exciting cardiac vagal motoneurons (CVM) in NA and DMNX and inhibiting pre-sympathetic neurons of RVLM, respectively. The details of this

network are unknown. For the sake of simplicity, NTS is often considered as a source of single excitatory drive that directly activates CVMs. The effect on SNA is mediated by GABAergic interneurons in CVLM that in turn inhibit pre-sympathetic neurons in RVLM. In firing rate-based approach, the parasympathetic and sympathetic activities are usually calculated as ascending and descending sigmoid functions of aggregate NTS output, respectively. Ottesen et al. (2004), for example, suggest the following sigmoids:

$$n_{sym}(n) = \frac{1}{1 + (n/n_0)^v}, \quad n_{par}(n) = 1 - n_{sym}(n)$$

$$= \frac{1}{1 + (n/n_0)^{-v}}$$

where $n_{sym}(n)$ and $n_{par}(n)$ are SNA and para-SNA, respectively, n is NTS output, n_0 is the baseline NTS output with fully adapted baroreceptor activity, and v defines the steepness of the curves.

The parasympathetic output is provided directly by vagal motoneurons, while sympathetic activity is formed by a longer chain of neural structures and involves several neurotransmitter systems. This difference is often taken into account by introducing a time delay in sympathetic response which can constitute up to several seconds. Ottesen and Olufsen (2011), for example, model parasympathetic activity as

proportional to the baroreceptor firing rate $n(t)$ and SNA is defined by the delayed version of $n(t)$:

$$n_{\text{par}}(t) = \frac{n(t)}{M}, \quad n_{\text{sym}}(t) = 1 - \frac{n(t - t_d)}{M}$$

where M is the maximal baroreceptor firing rate, and t_d is the time delay.

Respiratory Baroreflex

As mentioned, the classical baroreflex control of sympathetic nerve activity (SNA) operates via the second-order baroreceptor neurons that project to the caudal ventrolateral medulla region (CVLM). Through this path, the baroreceptor activation provides activation of CVLM neurons which in turn inhibit the pre-sympathetic rostral ventrolateral medulla (RVLM) neurons hence lowering both the RVLM activity and SNA. This pathway provides a direct negative SNA reflex response.

Sympathetic activity contains the respiratory modulation, which suggests that sympathetic and respiratory networks interact. Respiratory activity is also known to be modulated by the baroreceptor input. Together these facts imply that there may be another baroreflex pathway mediated by the respiratory neurons.

Baekey et al. (2010) have demonstrated that transient pressure pulses perturb the respiratory pattern in a phase-dependent manner, and those perturbations strongly depend on the integrity of the pons. The stimuli were delivered during inspiration, post-inspiration, or late expiration. With pons intact, the applied barostimulation had almost no effect on the amplitude and duration (i.e., inspiratory period) of the phrenic bursts even when stimuli were delivered during inspiration. At the same time, these stimuli suppressed or abolished inspiratory modulation of SNA. In contrast, the same stimuli delivered during post-inspiration or late expiration produced an increase in the expiration period and decreased SNA. The barostimulation-evoked prolongation of expiration was greater if stimulation was applied later during the expiratory phase. After pontine transection the barostimulation shortened

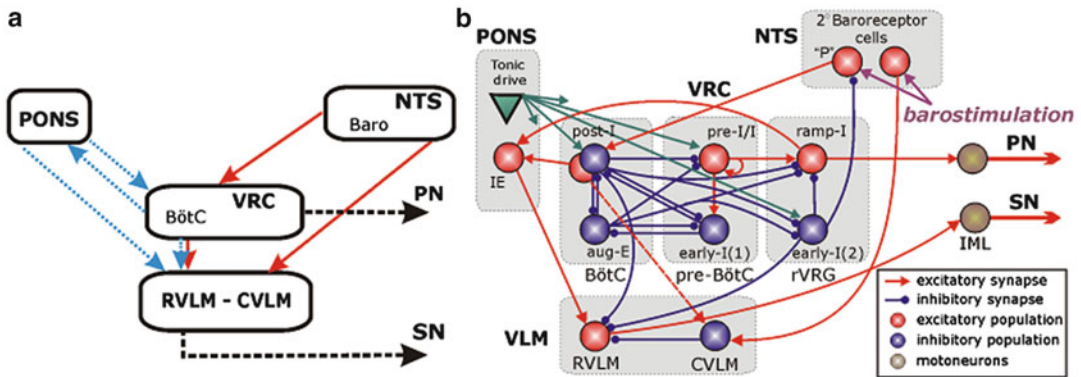
the apneustic inspiratory burst. In all cases the sympathetic baroreflex-induced lowering of SNA persisted confirming the presence of a direct baroreflex pathway which bypasses the respiratory network.

Based on their experimental findings, Baekey et al. (2010) developed a mathematical model of baroreceptor-respiratory-sympathetic interactions that explained phase-dependent respiratory response to transient barostimulation. One of the implications of their model was that there is indeed a second pathway from baroreceptors to pre-sympathetic neurons in RVLM. This second pathway is mediated by respiratory circuits, specifically by the post-I neurons of BötC. This baroreflex pathway is strongly dependent on the respiratory-sympathetic interactions and needs pons to be intact.

Another interesting implication of their model is that the sympathetic baroreflex gain depends on the respiratory phase, because a subpopulation of NTS second-order baroreceptors is inhibited during inspiration (Fig. 6).

The Role of Cardiopulmonary Baroreceptors

A majority of modeling studies only take into account arterial baroreceptors. However, under certain conditions blood volume regulation provided by cardiopulmonary baroreceptors plays a major role in blood pressure control. To understand the interplay between different mechanisms, Ursino (2000) developed a closed-loop mathematical model which included both arterial and cardiopulmonary baroreceptors and four effector components: heart period, systemic peripheral resistance, systemic venous unstressed volume, and heart contractility. He simulated the model to mimic the baroreflex response to mild and severe acute hemorrhages and found that the cardiopulmonary baroreceptors play a significant role in the control of systemic arterial pressure during mild hemorrhages (lower than 3–4 % of the overall blood volume). Under these conditions arterial pressure could be maintained at its normal level solely by cardiopulmonary feedback loop without the intervention of the arterial baroreceptors. During more severe hemorrhages the latter take over the responsibility for pressure



Baroreflex Models, Fig. 6 (a) Conceptual model of interaction between respiratory-related activity of the ventral respiratory column (VRC), pontine circuits (PONS), sensory network in the nucleus tractus solitarius (NTS), and rostral and caudal ventrolateral medulla (RVLM/CVLM). The sympathetic baroreceptor reflex operates via two pathways (red solid arrows): one direct pathway includes baroreceptors, 2nd-order barosensitive cells (Baro) in the NTS and CVLM, which inhibits RVLM and SNA; the other pathway routes via the Böttinger complex (BötC) in the VRC, whose post-inspiratory neurons inhibit

RVLM and SNA. Blue dotted arrows represent the effects of VRC and PONS on RVLM providing respiratory modulation of SN activity. (b) The schematic of the computational model by Baekey et al. (2010) showing interactions between different populations of respiratory neurons within major brainstem compartments involved in the control of breathing and sympathetic motor activity (pons, BötC, pre-BötC, rVRG, VLM, and NTS). Each population (shown as a sphere) consists of 20–50 single-compartment neurons described in the Hodgkin–Huxley style (Adapted from Baekey et al. 2010 with permission)

control, and the contribution of cardiopulmonary baroreceptors becomes negligible.

Ursino (2000) noticed that according to their model the stability region in the parameter space of the closed-loop system is quite narrow. For example, an increase in the static gain of the baroreceptors or a decrease in the rate-dependent component may lead to self-sustained oscillations similar to Mayer waves.

Baroreflex and Mayer Waves

Mayer waves are synchronous oscillations in SNA and arterial BP slower than respiratory rhythm. The origin and physiological mechanisms of these oscillations are currently unknown. The fact that Mayer waves are abolished by sinoaortic baroreceptor denervation strongly suggests the involvement of arterial baroreflex in this phenomenon. The baroreflex theory of Mayer waves explains the emergence of self-sustained oscillations in arterial pressure by the instability caused by fixed time delays in the baroreflex (presumably sympathetic) feedback loop (see the review by Julien (2006) and the literature therein cited). Since virtually any

system with the delayed feedback is unstable for sufficiently large time delay values, many different models of dynamic arterial pressure control have succeeded in predicting Mayer waves (Julien 2006). The magnitude of the time delay is the determinant factor of the emerging oscillation frequency. Mayer wave frequency varies significantly between species which suggests that different species should have significantly different time delays in baroreflex feedback loop. In spite of numerous hypotheses suggested, no consistent explanation of this species-to-species variability was yet provided. Another challenge for the baroreceptor theory is the dependence of Mayer wave amplitude on the mean SNA level which the existing models fail to explain.

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Basal Ganglia System as an Engine for Exploration

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Definition

The basal ganglia (BG) system is a deep brain circuit with wide-ranging brain functions. Exploration refers to the sampling of a variety of behaviors not firmly established within a learned repertoire. While the neural source of variability driving exploration within the subcortex has not

been identified, the hypothesis that the indirect pathway of the BG is the subcortical substrate for exploration leads to explanations for how a range of putative BG functions might be performed.

Detailed Description

Reinforcement Learning and the Basal Ganglia

For nearly a century, a certain “mysteriousness” has been attributed to the function of the basal ganglia (BG) system – a deep brain circuit of multiple interconnected nuclei, with rich connections to large parts of the cortex (Kinnier Wilson in his Croonian lectures in 1925, Marsden 1982). The mystique surrounding BG has its roots perhaps in the multifarious functions of this circuit. Action selection, action gating, sequence generation, motor preparation, reinforcement learning, timing, working memory, goal-directed behavior, and exploratory behavior – the list of putative BG functions is long and perhaps, by the current state of knowledge, is also incomplete. Lesions of this circuit can show manifestations in many forms – from simple reaching movements to handwriting, balancing and gait, speech and language function, eye movements, and force generation, in addition to cognitive and affective manifestations. A long line of neurological (Parkinson’s disease, Huntington’s disease, athetosis, chronic fatigue syndrome) (DeLong 1990) and neuropsychiatric disorders (schizophrenia, obsessive-compulsive disorder, ADHD, apathy, abulia, insomnia) (Ring and Serra-Mestres 2002) are associated with BG impairment.

In one of the earliest forays into the mystery of the BG, Albin et al. (1989) interpreted BG anatomy to consist of two pathways (Albin et al. 1989) with complementary roles in motor manifestations (Fig. 1). BG consist of several nuclei – striatum (caudate and putamen), globus pallidus externa/interna, subthalamic nucleus, and substantia nigra pars compacta (SNc)/reticulata. The BG circuit as a whole receives extensive inputs from the cortex and projects back to cortex via thalamus. Cortical signals to