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## Baroreflex function in females: changes with the reproductive cycle and pregnancy

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### Abstract

This review briefly describes the changes in baroreflex function that occur during female reproductive life, specifically during the reproductive cycle and pregnancy. The sensitivity or gain of baroreflex control of heart rate and sympathetic activity fluctuates during the reproductive cycle, reaching a peak when gonadal hormones rise, during the follicular phase in women and proestrus in rats. The increase in baroreflex sensitivity (BRS) is likely mediated by estrogen, because ovariectomy in rats eliminates the BRS increase, the cyclic profile of changes in BRS mirror the changes in estrogen, and estrogen acts in the brainstem to increase BRS. Pregnancy, on the other hand, depresses both BRS and the maximal level of sympathetic activity and heart rate evoked by severe hypotension. The decrease in BRS may be mediated by a reduction in the actions of insulin in the arcuate nucleus to support the baroreflex. In addition, increased levels of the neurosteroid progesterone metabolite, 3 $\alpha$ -OH-DHP, act downstream in the rostral ventrolateral medulla to suppress maximal baroreflex increases in sympathetic activity. Consequently, these changes in baroreflex function impair blood pressure regulation in the face of hypotensive challenges like orthostasis and hemorrhage, a common event during delivery. As a result, peripartum hemorrhage is a major cause of human maternal mortality.

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The baroreceptor reflex is the major mechanism that maintains arterial pressure at set limits from moment to moment. Considerable data have documented that baroreflex function is not static, but changes under both physiologic and pathophysiological conditions. The purpose of this short review is to summarize the alterations in baroreflex function that occur in females during two physiological events: the reproductive cycle and pregnancy.

### Baroreflex function during the reproductive cycle

In women, the sensitivity or gain of baroreflex control of muscle sympathetic nerve activity (MSNA) increases during the mid-luteal phase of the menstrual cycle, when gonadal

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hormones (estrogen and progesterone) are elevated, compared to the early follicular phase, when these hormones are relatively low.<sup>1</sup> Basal MSNA and plasma levels of norepinephrine increase in parallel during the luteal phase.<sup>1;2</sup> Increases in cardiovagal baroreflex sensitivity (BRS) have also been observed in women at or near ovulation and the estrogen surge.<sup>3;4</sup> Rats exhibit similar baroreflex and gonadal hormone fluctuations during the estrous cycle. Baroreflex control of renal sympathetic nerve activity (RSNA) is enhanced during proestrus compared to diestrus; more specifically, both baroreflex gain and the maximal level of RSNA achieved during severe hypotension are elevated.<sup>5</sup> In addition, continuous measurements of spontaneous BRS (sBRS), which reflect largely cardiovagal reflex function, revealed increases in sBRS on the afternoon and evening of proestrus (Figure 1),<sup>5</sup> when estrogen levels peak and progesterone is increasing.

To test the role of gonadal hormones in these cyclical changes, sBRS was assessed in ovariectomized (OVX) rats.<sup>5</sup> OVX not only lowered sBRS and abolished diurnal variations (sBRS is normally lower during the light phase), it also eliminated daily fluctuations in sBRS (Figure 1).<sup>5</sup> These data indicate that gonadal steroids are required for both diurnal and for daily estrous cycle mediated changes in baroreflex function. Progesterone likely does not contribute to the increases in baroreflex function during the high gonadal hormone segment of the reproductive cycle, since a progesterone neurosteroid metabolite, 3 $\alpha$ -hydroxy-dihydroprogesterone (3 $\alpha$ -OH-DHP), decreases gain of baroreflex control of RSNA.<sup>6;7</sup> On the other hand, considerable evidence implicates estrogen. First, estrogen changes in parallel with BRS in both rats<sup>5;8</sup> and women.<sup>3</sup> Second, estrogen enhances BRS via an action in the brainstem.<sup>9-14</sup>

## Pregnancy impairs the baroreflex

During pregnancy, the cardiovascular system undergoes profound yet teleologically appropriate changes that serve to optimize fetal development and growth. Early in gestation, blood volume and cardiac output increase by 30-50%.<sup>6;15</sup> However, arterial pressure falls due to even greater decreases in systemic vascular resistance.<sup>6;15</sup> While most physiological changes induced by pregnancy are relatively benign to the mother, one deleterious consequence is a marked suppression of the function of the baroreceptor reflex.<sup>6;7;16;17</sup> Baroreflex dysfunction has been documented in several species besides humans, including rabbits, rats, goats, sheep, and dogs.<sup>6</sup> Because of an impaired ability to maintain arterial pressure, this change in autonomic regulation underlies frequent serious complications of pregnancy. Pregnant women are prone to orthostatic hypotension.<sup>18</sup> In addition, since hemorrhage accompanies every delivery, when blood loss is significant, severe hypotension can result.<sup>19</sup> Indeed, peripartum hemorrhage is a major cause of maternal mortality.<sup>6</sup>

A series of experiments in conscious rabbits, studied in both the nonpregnant and pregnant state, investigated the hemodynamic mechanisms by which pregnancy impairs blood pressure control during hemorrhage. Normally during blood loss, reflex-mediated increases in sympathetic activity help to maintain arterial pressure both by vasoconstriction, to increase systemic vascular resistance, and by venoconstriction, to maintain preload and cardiac output.<sup>20-22</sup> During pregnancy, the more rapid development of hypotension during blood loss was largely attributed to a failure to maintain cardiac output.<sup>19</sup> Therefore, pregnancy appears to attenuate reflex venoconstriction, due either to a blunted increase in sympathetic activity to veins or to reduced venous reactivity. In addition, in pregnant animals, insufficient increases in systemic vascular resistance also contribute to inadequate arterial pressure maintenance during hemorrhage.<sup>19</sup> Studies of regional conductance changes revealed that the mesenteric and renal circulations are regulated normally.<sup>19;23</sup> However, suboptimal reflex vasoconstriction of the terminal aortic or the femoral vascular bed was observed when pregnant rabbits were bled.<sup>19;23</sup> Hindquarter vascular reactivity is preserved

during pregnancy;<sup>24</sup> therefore, it appears that reflex increases in sympathetic activity to the skin and muscle of the leg are also impaired. On the other hand, although the sympathetic innervation of the uterine circulation markedly regresses during pregnancy,<sup>25;26</sup> it is unlikely that a failure to constrict this bed is a significant factor, since in many species uterine blood flow accounts for only a small fraction of the total cardiac output.<sup>23</sup> Collectively, therefore, pregnant individuals may be more prone to hemorrhagic hypotension, because of impaired reflex sympathetically-mediated vasoconstriction and femoral vascular vasoconstriction.

The decrease in baroreflex control of the autonomic nervous system has been detected using several methodological approaches, including non-invasive techniques in women employing the analysis of heart rate and arterial pressure in the frequency domain.<sup>6;17</sup> Similar conclusions have been derived from assessments of sBRS and infusion of vasoactive drugs to construct complete sigmoidal baroreflex relationships between arterial pressure and heart rate or sympathetic nerve activity (Figure 2).<sup>6;17</sup> Three features of these curves are commonly attenuated: the maximum gain or slope of the most linear segment of the curves, the maximal level of sympathetic activity or heart rate achieved during severe hypotension, and the “setpoint” or the arterial pressure level associated with the midpoint of the curve. This latter change is likely mediated by resetting of baroreceptor afferents, which causes the baroreflex function curve to shift toward the lower arterial pressure level during pregnancy.<sup>6</sup> However, the mechanisms that underlie the decreases in the baroreflex maximum and in baroreflex gain are complex and may involve distinct brain sites and hormonal mechanisms.<sup>6</sup>

Within the brain, the core baroreflex pathway resides in the brainstem.<sup>27</sup> Baroreceptor afferents terminate in the nucleus tractus solitarius (NTS) and in response to increases in pressure excite NTS second order neurons via a glutamatergic synapse. NTS neurons project to and excite (also via glutamate) interneurons in the caudal ventrolateral medulla that project to and release GABA to inhibit sympathetic premotor neurons in the rostral ventrolateral medulla (RVLM). Thus, pregnancy-induced modulation of baroreflex function could occur at any or all of these central sites, although the RVLM appears pivotal.

One hormonal mechanism that underlies decreases in the baroreflex maximum is the action of 3 $\alpha$ -OH-DHP to enhance GABAergic suppression of RVLM premotor neurons<sup>6</sup> (Figure 3). 3 $\alpha$ -OH-DHP levels, as well as the enzymes responsible for the synthesis of 3 $\alpha$ -OH-DHP from progesterone, are increased in the brain at end-gestation, the time at which baroreflex function reaches its nadir. In addition, acute systemic or RVLM administration of 3 $\alpha$ -OH-DHP in virgin rats reduces the maximal reflex levels of RSNA similarly to pregnancy. The link between 3 $\alpha$ -OH-DHP and increased GABAergic tone in the RVLM is supported by the well-documented ability of this neurosteroid, by binding to the GABA<sub>A</sub> receptor, to enhance its function. More importantly, evidence indicates that RVLM premotor neurons receive greater tonic GABAergic suppression during pregnancy.<sup>6</sup>

Another hormone that is involved in the pregnancy-induced baroreflex impairment is insulin. Insulin resistance is a normal adaptation of pregnancy that, by increasing circulating glucose levels, serves to enhance placental glucose transfer to the fetus. However, several lines of evidence support the hypothesis that insulin resistance also contributes to the decrease in baroreflex gain, by decreasing brain insulin levels.<sup>6</sup> First, decreases in insulin sensitivity and baroreflex gain are temporally correlated in pregnant rabbits, rats and humans.<sup>6;28;29</sup> Second, treatment of pregnant rabbits with the insulin sensitizing drug, rosiglitazone, improves baroreflex function.<sup>29</sup> Third, insulin enters the brain via transport from plasma across the blood brain barrier, and insulin resistant states are associated with decreases in insulin transport.<sup>30</sup> Indeed, during pregnancy, brain insulin levels fall.<sup>29;31</sup>

Fourth, in conscious pregnant rats, intracerebroventricular (icv) infusion of insulin normalizes baroreflex gain, while in virgin rats insulin infusion is ineffective.<sup>31</sup> Thus, during pregnancy, it appears that a factor that contributes to insulin resistance may also reduce transport of insulin into the brain. Since insulin acts centrally to enhance baroreflex function,<sup>32,33</sup> the consequent fall in brain insulin results in a parallel decrease in BRS.

Additional recent data suggest that low brain insulin may underlie in part impaired baroreflex function in other insulin resistant states. Like pregnancy, obesity impairs cardiac baroreflex gain<sup>34-37</sup> and decreases brain insulin.<sup>38-40</sup> Also like pregnancy, rosiglitazone treatment of obese animals improves cardiac baroreflex gain,<sup>41</sup> and icv insulin infusion normalizes baroreflex function, both by increasing baroreflex gain and by increasing the baroreflex maximum.<sup>42</sup> Thus, normal brain insulin levels may be required for maintenance of optimal baroreflex control of heart rate. Furthermore, low brain insulin may contribute to the baroreflex impairment noted in other insulin resistant states, such as aging, congestive heart failure, hypertension and Alzheimer's Disease. However, future study is required to test this hypothesis.

The brain sites and circuitry by which insulin supports baroreflex function have recently been identified (Figure 3). Unlike 3 $\alpha$ -OH-DHP, which acts in the RVLM, initial studies revealed that insulin initiates its effects in the forebrain, since lateral icv, but not fourth ventricular, insulin infusion increased baroreflex gain.<sup>32</sup> Further work identified the arcuate nucleus as the site at which insulin acts to activate the sympathetic nervous system and increase baroreflex gain, via a neural pathway that includes the paraventricular nucleus of the hypothalamus (PVN).<sup>43</sup> Two major sets of neurons in the arcuate nucleus project to the PVN: pro-opiomelanocortin (POMC) neurons, which release alpha-melanocyte-stimulating hormone, and neuropeptide Y neurons.<sup>44</sup> Recently, PVN melanocortin receptors were shown to contribute to the sympathoexcitatory response to insulin, suggesting that POMC neurons convey, at least in part, the signal from the arcuate nucleus to PVN.<sup>45</sup> The role of neuropeptide Y neurons has not been investigated. From the PVN, the neuronal pathway appears to converge with brainstem baroreflex circuitry in the RVLM, since the sympathoexcitatory effect of insulin is reversed by blockade of RVLM ionotropic glutamate receptors.<sup>45</sup>

This circuitry, specifically the potential for integration of insulin and 3 $\alpha$ -OH-DHP signaling in the RVLM, provides a mechanistic explanation for the findings that in pregnant animals, rosiglitazone treatment to increase insulin sensitivity<sup>29</sup> and icv insulin infusion<sup>31</sup> each normalized baroreflex gain, yet failed to improve the attenuated baroreflex maximum levels of heart rate normally observed. Because GABAergic inhibition of RVLM premotor neurons is increased during pregnancy due to increases in 3 $\alpha$ -OH-DHP, this suppression could prevent insulin's usual effect to increase baroreflex maximum levels<sup>32</sup> as well (Figure 3).

## Summary

Normal reproductive events in females evoke significant changes in baroreflex function. During the reproductive cycle, the sensitivity or gain of baroreflex control of sympathetic nerve activity and heart rate increases with the surge of gonadal hormonal levels, in particular of estrogen. In contrast, pregnancy depresses both baroreflex gain and the maximal level of sympathetic activity and heart rate induced by severe hypotension. The decrease in baroreflex gain may be mediated by a reduction in the actions of insulin in the arcuate nucleus to support the baroreflex. In addition, increased levels of the neurosteroid 3 $\alpha$ -OH-DHP act downstream in the RVLM to suppress maximal reflex-induced increases in sympathetic activity.

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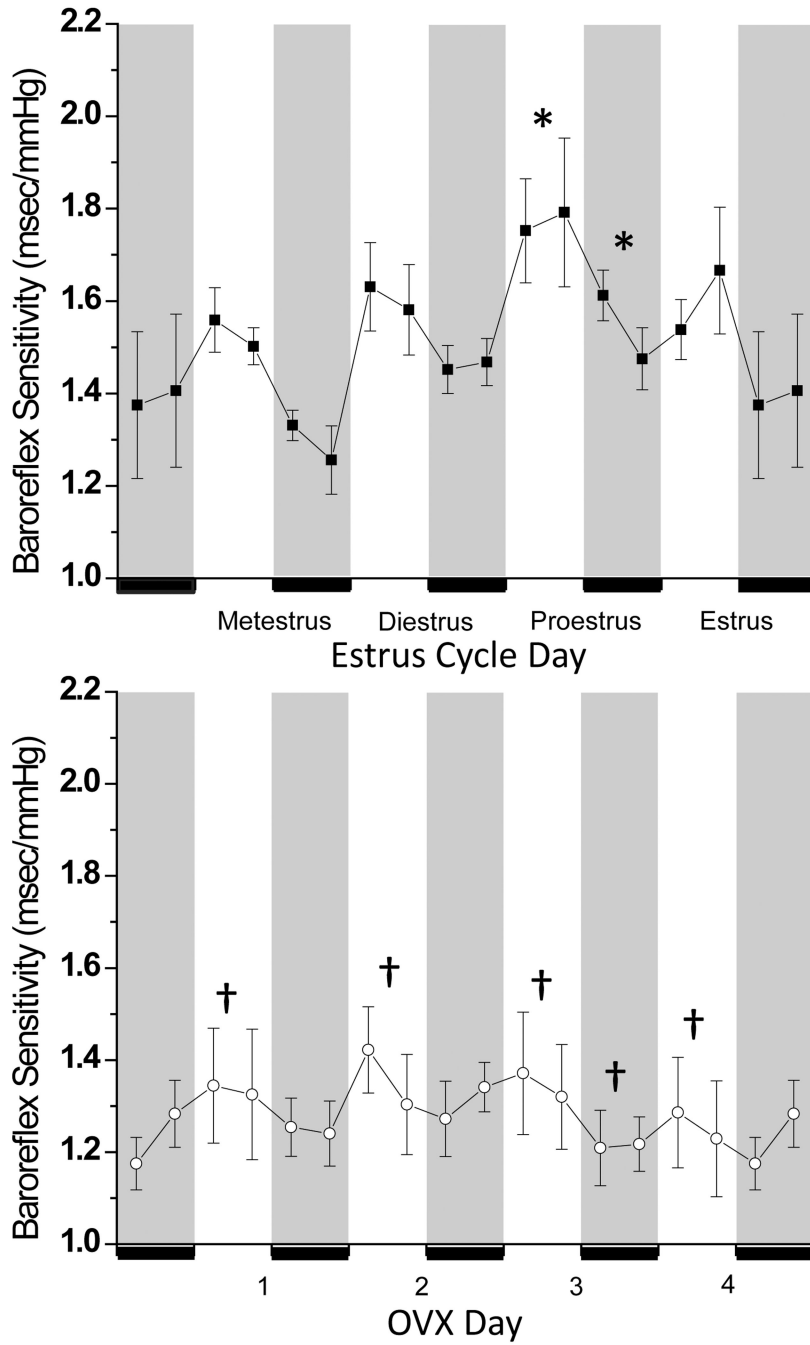
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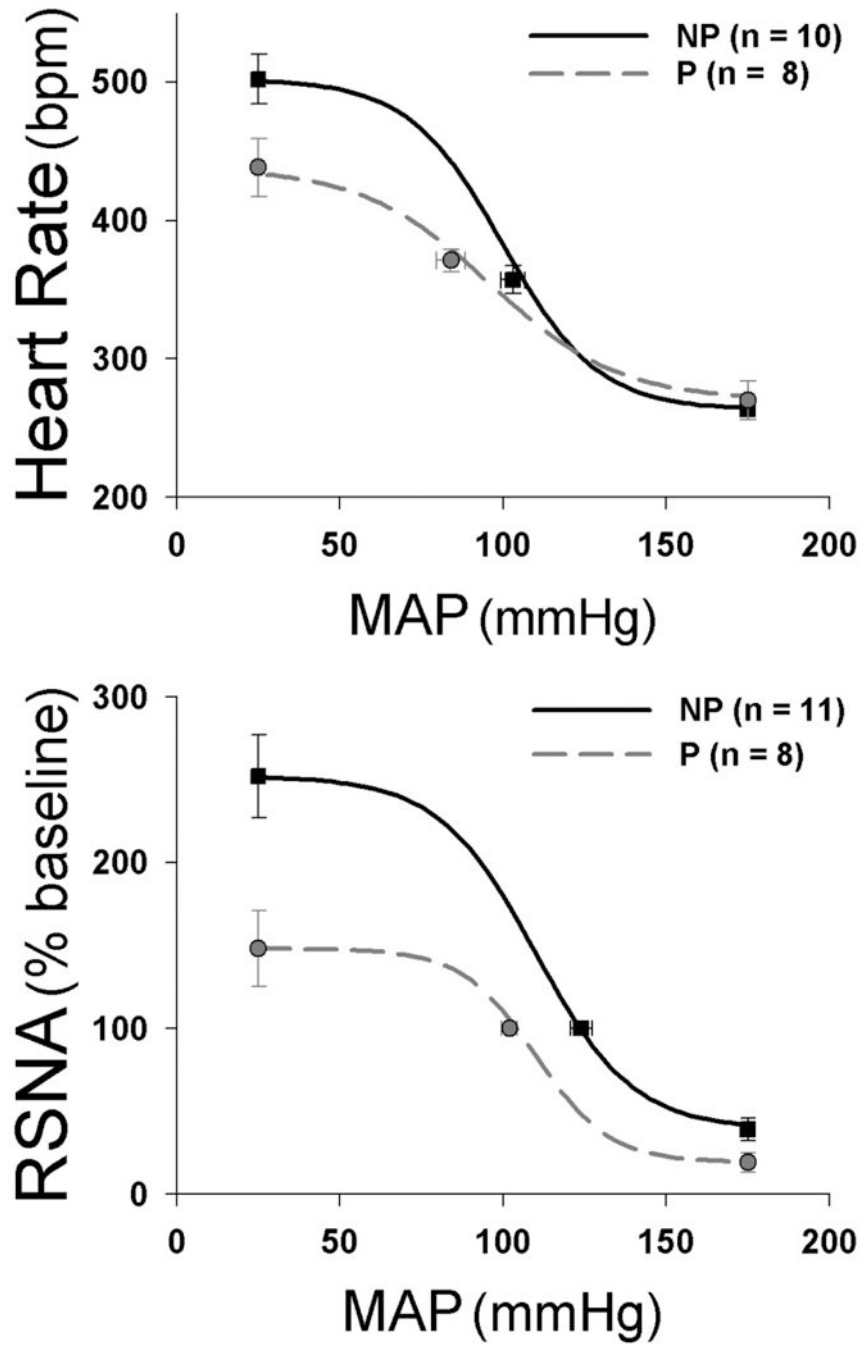
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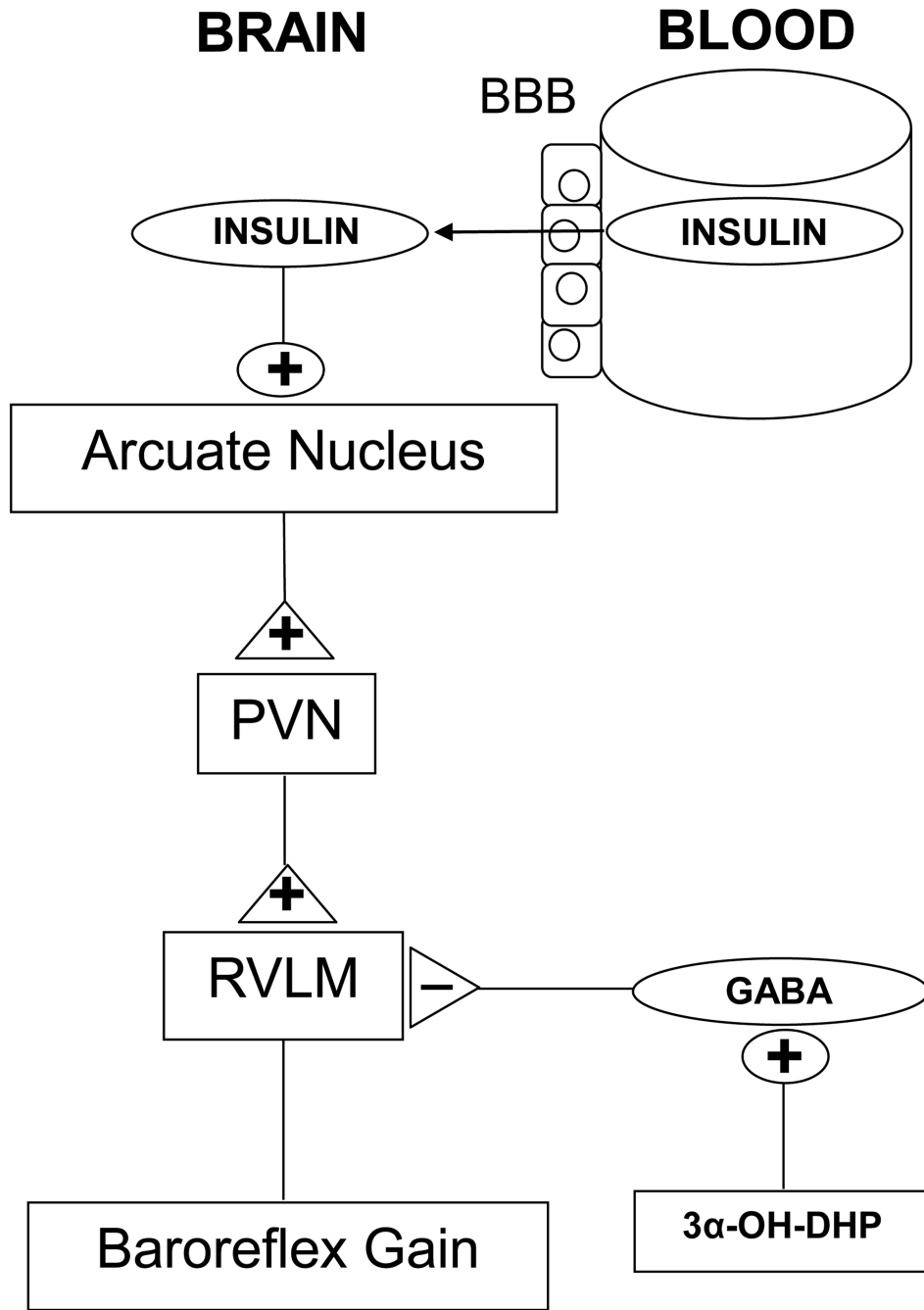


**Figure 1.** sBRS increases during proestrus in rats (n=5), and this daily estrous cycle variation is abolished following ovariectomy (OVX; n=6). \* P<0.05 compared to at least one other day within group (comparisons made among either light or dark periods only); †: P<0.05 OVX compared to cycling at the same time. The dark phase of the day-night cycle is indicated by gray shading. This figure was reprinted from Reference 5 with kind permission of the American Physiological Society.





**Figure 2.** In conscious rats, pregnancy (P) impairs baroreflex control of heart rate (top) and renal sympathetic nerve activity (RSNA; bottom) compared to the nonpregnant (NP) state. This figure was reprinted from Reference 6 with kind permission of the American Physiological Society.



**Figure 3.** Mechanisms that contribute to impaired baroreflex function during pregnancy. Insulin in blood is transported across the blood-brain barrier (BBB) into brain, where, via actions in the hypothalamic arcuate nucleus, it enhances baroreflex function. The excitation initiated by insulin in the arcuate nucleus is conveyed via the paraventricular nucleus (PVN) to a brainstem baroreflex relay, the rostral ventrolateral medulla (RVLM). During pregnancy, falls in brain insulin (which supports baroreflex function) decreases baroreflex gain. In addition, GABAergic suppression of RVLM premotor neurons mediated by the neurosteroid 3α-OH-DHP decreases maximum levels of sympathetic activity elicited by severe hypotension.