Published in final edited form as:

Acta Physiol (Oxf). 2011 September ; 203(1): 37–45. doi:10.1111/j.1748-1716.2010.02242.x.

Neuronal and Non-Neuronal Modulation of Sympathetic Neurovascular Transmission

Heather Macarthur, Gerald H. Wilken, Thomas C. Westfall, and Lacy L. Kolo

Dept. Pharmacological and Physiological Science, Saint Louis University School of Medicine, 1402 South Grand Blvd., St. Louis, MO 63104, USA

Abstract

Norepinephrine, neuropeptide Y and adenosine triphosphate are co-stored in, and co-released from, sympathetic nerves. Each transmitter modulates its own release as well as the release of one another; thus, anything affecting the release of one of these transmitters has consequences for all. Neurotransmission at the sympathetic neurovascular junction is also modulated by non-sympathetic mediators such as angiotensin II, serotonin, histamine, endothelin and prostaglandins through activation of specific pre-junctional receptors. In addition, nitric oxide (NO) has been identified as a modulator of sympathetic neuronal activity, both as a physiological antagonist against the vasoconstrictor actions of the sympathetic neurotransmitters, and also by directly affecting transmitter release. Here we review the modulation of sympathetic neurovascular transmission by neuronal and non-neuronal mediators with an emphasis on the actions of NO. The consequences for co-transmission are also discussed, particularly in light of hypertensive states where NO availability is diminished.

Keywords

norepinephrine; NPY; ATP; nitric oxide; endothelium; hypertension

Introduction

Sympathetic neurovascular transmission was once thought to involve the single neurotransmitter norepinephrine. As evidence grew for the involvement of other neurotransmitters in this process, investigators, in conjunction with “Dale’s principle”, initially assigned a separate nerve to the transmitter in question (Burnstock, 1976, Stjarne, 1999). Hence, adrenergic, purinergic, peptidergic, and nitrergic nerves became accepted terms in describing the neural anatomy of the vascular system. However, we now understand that the simultaneous presence of different neurotransmitters at the vascular neuroeffector junction is elegantly explained by the concept of co-transmission of different neurotransmitters from the same nerves (Burnstock, 1976). As the concept of co-transmission became established, research revealed the regulation of co-transmission to be extremely fine-tuned and exerted by a wide variety of neuronal and non-neuronal mediators. Here we review the modulation of sympathetic neurovascular transmission by neuronal and non-neuronal mediators in a variety of *in vitro* and *in vivo* preparations. We also discuss the concept of differential modulation of sympathetic co-transmission. Finally, we focus on the

Reprint Correspondence: Heather Macarthur, Saint Louis University School of Medicine, 1402 South Grand Blvd., St. Louis, MO 63104, USA, Tel: 314-977-6456, Fax: 314-977-6411, macarthu@slu.edu.

Conflict of Interest

The authors declare no conflict of interest in the content of this manuscript.

cross-talk that exists between the endothelial lining of the blood vessel and the sympathetic nervous system via modulation of sympathetic neurovascular transmission by endothelial mediators and specifically nitric oxide (NO). Dysfunction of NO dependent modulation of sympathetic neurovascular transmission in the development of hypertension is also discussed.

Co-transmission at the Sympathetic Neurovascular Junction

It is well established that norepinephrine, neuropeptide Y (NPY), and adenosine triphosphate (ATP) are co-localized in, and co-released from sympathetic neurons (Ekblad *et al.*, 1984, Sneddon & Westfall, 1984, Vizi & Burnstock, 1988, De Deyn P.P., 1989).

The most well studied sympathetic neurotransmitter is norepinephrine. Upon release from the sympathetic nerve terminal, norepinephrine diffuses to the smooth muscle target cell where it activates α_1 receptors causing contraction of the smooth muscle cell and overall blood vessel constriction. Norepinephrine also activates α_2 receptors located on the sympathetic nerve terminal inhibiting its own release, as well as the release of the co-transmitters (Morris and Gibbins, 1992).

NPY is co-localized with norepinephrine in large dense core storage vesicles in the sympathetic nerve terminal (Lundberg *et al.*, 1982, Ekblad *et al.*, 1984, DiMaggio *et al.*, 1985, Uddman *et al.*, 1985, De Potter *et al.*, 1997, Westfall, 2004). Upon sympathetic nerve stimulation both NPY and norepinephrine are released from a variety of tissues including pig spleen, pig renal artery, guinea pig heart, rat mesenteric artery, rat portal vein and rat caudal artery (Lundberg *et al.*, 1986, Lundberg *et al.*, 1987, Pernow & Lundberg, 1989, Haass *et al.*, 1989b, Haass *et al.*, 1989a, Westfall, 2004). NPY activates post-junctional Y_1 receptors to directly contract vascular smooth muscle as well as potentiate the contractile effects of both norepinephrine and ATP in a variety of *in vitro* preparations including the rat mesenteric bed, rat portal vein, rat and rabbit cerebral vessels, rat, dog and guinea pig coronary vessels and also *in vivo* in the pithed rat (Westfall *et al.*, 1987b, Westfall *et al.*, 1988, Westfall *et al.*, 1990b, Wahlestedt & Reis, 1993, Grundemar & Hakanson, 1994, Zukowska-Grojec, 1995, Westfall, 2004). The development and use of specific NPY antagonists (Abounader *et al.*, 1995, Myers *et al.*, 1995, Leban *et al.*, 1995, Hegde *et al.*, 1995, Kirby *et al.*, 1995, Malmstrom *et al.*, 2002, Westfall, 2004) has shown that NPY is an endogenous neurotransmitter at the sympathetic neurovascular junction. NPY plays a physiological role in the regulation of vascular tone in the guinea pig vena cava and the rat mesenteric bed, and *in vivo* in whole pigs and the pithed rat (Malmstrom & Lundberg, 1995, Lundberg & Modin, 1995, Kennedy *et al.*, 1997, Han *et al.*, 1998b), as well as a pathophysiological role during stress and hypertension in both rats and humans (Erlinge *et al.*, 1992, Michel & Rascher, 1995, Zukowska-Grojec *et al.*, 1996, Han *et al.*, 1998a). NPY also acts pre-junctionally through Y_2 receptors inhibiting the release of all three neurotransmitters both *in vitro* and *in vivo* (Westfall *et al.*, 1987b, Westfall *et al.*, 1988, Westfall *et al.*, 1990b, Wahlestedt & Reis, 1993, Grundemar & Hakanson, 1994, Zukowska-Grojec, 1995).

The third sympathetic co-transmitter, ATP, is co-stored with norepinephrine in small synaptic vesicles and when released, activates P_{2X} receptors on the vascular smooth muscle to cause vasoconstriction in the guinea pig vas deferens, rabbit portal vein, rabbit aorta and rat caudal artery (Levitt & Westfall, 1982, Kirkpatrick & Burnstock, 1987, Lew & White, 1987, Westfall *et al.*, 1987a, Sedaa *et al.*, 1990). Responses to sympathetic nerve stimulation that are resistant to adrenergic antagonists, have been shown to be attenuated by purinergic receptor antagonists in many *in vitro* preparations including guinea pig and rat vas deferens, rabbit and guinea pig mesenteric arteries and rat tail artery (Fedan *et al.*, 1981, Kasakov &

Burnstock, 1982, Sneddon & Westfall, 1984, Sneddon & Burnstock, 1984, Ishikawa, 1985, von Kugelgen & Starke, 1985, Allcorn *et al.*, 1986, Bulloch & Starke, 1990, Hoyle, 1992, Kennedy *et al.*, 1996). In addition to contracting vascular smooth muscle, ATP also acts pre-junctionally via P_{2Y} receptors to inhibit the release of norepinephrine from many preparations including rat and rabbit portal vein, rabbit pulmonary artery, dog saphenous vein, and NPY from rat pheochromocytoma cells (Moyle & Westfall, 1979, Westfall *et al.*, 1990a, Chen *et al.*, 1997). Lower frequencies of nerve stimulation are required for the release of vesicles containing ATP and norepinephrine than for vesicles containing norepinephrine and NPY (Lundberg & Hokfelt, 1986, Morris & Gibbins, 1992). In addition, studies carried out both *in vitro* and *in vivo* demonstrate that transmission from sympathetic vasoconstrictor neurons to vascular smooth muscle involves at least three phases with distinct temporal and pharmacological properties. The mediator of the first or fast phase is ATP, the second or slow phase is norepinephrine and the very slow phase is NPY (Morris & Gibbins, 1992). Each phase of sympathetic neurotransmission can be blocked with P_{2X} , α_1 and Y_1 antagonists respectively (Ekblad *et al.*, 1984, Sneddon & Westfall, 1984, Vizi & Burnstock, 1988, De Deyn P.P., 1989, Chiba & Yang, 2002, Huidobro-Toro & Donoso, 2004).

It should be noted that other subtypes of P_2 receptors have been found both post and pre-junctionally in different tissues (Ralevic, 2009, Burnstock & Verkhatsky, 2010), and α_2 adrenoceptors reported post-junctionally (Docherty & McGrath, 1980, Francis, 1988, Ramagopal & Leighton, 1989), however for the sake of simplicity this review will not focus on the involvement of these receptors in sympathetic neurotransmission.

Schema 1 is a representation of co-transmission at the sympathetic neurovascular junction.

Differential Modulation of Sympathetic Neurotransmission

Differential modulation of sympathetic co-transmitter release is concluded to have occurred when a particular modulating factor (e.g. an α_2 receptor agonist) has more of an effect upon the release of one co-transmitter over another, despite the evidence that shows they are co-released together and therefore ought to be equally affected. There is good evidence for differential modulation of sympathetic co-transmitters. In several preparations, including the mouse vas deferens, rabbit ileocolic artery, the guinea pig vas deferens and guinea pig ileum, activation of pre-junctional α_2 -receptors depresses the release of norepinephrine more than the release of ATP (Hammond *et al.*, 1988, Starke *et al.*, 1989, Driessen *et al.*, 1993, von Kugelgen *et al.*, 1994). Additionally, when pre-junctional α_2 receptors are blocked by yohimbine, there is a greater increase in the overflow of norepinephrine than ATP or NPY, suggesting that endogenously released norepinephrine has a greater influence on its own release than that of its co-transmitters (Todorov *et al.*, 1996, Kolo *et al.*, 2004a).

ATP not only inhibits sympathetic neurotransmission through activation of pre-junctional P_{2Y} receptors, it can also facilitate transmission via P_{2X} receptor activation (Boehm, 1999, Boehm, 2003). Furthermore, adenosine, the final product of ATP metabolism, modulates sympathetic neurotransmission through pre-junctional inhibitory A_1 and facilitatory A_2 receptors (Cunha, 2001). The fact that nucleotidases that metabolize ATP to ADP, AMP and finally adenosine, are released from sympathetic neurons along with ATP, make the presence of A_1 and A_2 receptors particularly significant to the modulation of sympathetic neurotransmission (Westfall *et al.*, 2000a, Westfall *et al.*, 2000b). The difference in types and actions of receptors, as well as the activity of nucleotidases could explain some of the differential modulation that exists at the sympathetic neurovascular junction.

Blockade of pre-junctional NPY Y_2 receptors enhances α_1 receptor mediated contractile responses in the canine splenic artery indicating that endogenous NPY inhibits

norepinephrine release in this tissue. In contrast α -receptor sensitive contractions evoked by transmural stimulation in the guinea pig femoral artery are not modified in the presence of the Y_2 agonist, suggesting that control of sympathetic neurotransmission differs between tissue types.

Non-Sympathetic Modulation of Neurotransmission

Sympathetic neurotransmission is also modulated by a vast array of non-sympathetic mediators as evidenced by the pre-junctional location of inhibitory muscarinic (M_2 and M_4), serotonin, prostaglandin, histamine, enkephalin, endothelin, and dopamine receptors, as well as facilitatory adrenergic (β_2), angiotensin II (Ang II) and nicotinic receptors (Langer & Arbilla, 1990, Wiklund *et al.*, 1990). Like the modulation exerted by sympathetic neurotransmitters on their own release, activation of these non-sympathetic receptors also often exhibit differential properties. For example endothelin inhibits NPY but not norepinephrine overflow from the rat mesenteric bed whereas PGI_2 and PGE_2 decrease both transmitters equally (Hoang *et al.*, 2002, Hoang *et al.*, 2003). On the other hand endothelin inhibits ATP, but not catecholamine or NPY, release from the PC12 cell model of sympathetic neurons (Gardner *et al.*, 2005) and yet does inhibit norepinephrine release from the isolated rat stomach (Nakamura *et al.*, 2003). In addition although Ang II strongly increases norepinephrine overflow from sympathetic nerves via activation of pre-junctional AT_1 receptors, NPY overflow is only weakly enhanced (Nap *et al.*, 2003, Byku *et al.*, 2008). Interestingly the development of hypertension augments this AT_1 response on NPY overflow illustrating the fluidity of pre-junctional modulation and its contribution to pathophysiological conditions (Byku *et al.*, 2008).

NO and Sympathetic Neurotransmission

The ability of the vascular endothelium to directly regulate vascular smooth muscle in an autocrine/paracrine fashion through the release of vasoactive substances is well established but, as discussed above, endothelial mediators, such as endothelin and prostaglandins, can also indirectly regulate vascular function by modulating sympathetic neurotransmission. The endothelial mediator Nitric Oxide (NO) has also been shown to possess such modulating effects. Studies have shown that upon sympathetic nerve stimulation, inhibition of NO synthesis with N^G -nitro-L-arginine results in an increase in vasoconstriction in the rat tail artery (Vo *et al.*, 1991), in the large coronary artery of anesthetized dogs (Woodman & Pannangpetch, 1994) and in the vessels of the isolated adrenal medulla of the dog (Breslow *et al.*, 1992). It has been proposed that the inhibitory effect of NO on the action of norepinephrine is due to post-junctional physiological antagonism (Cederqvist *et al.*, 1991, Cederqvist & Gustafsson, 1994). While the enhancement of vasoconstriction may be partly due to the removal of the relaxation normally caused by NO, there is also evidence that in the absence of NO there is an increase in the amount of norepinephrine released from sympathetic nerves. Endogenous NO has been shown to have an inhibitory effect on the stimulated release of catecholamines from sympathetic nerves and the adrenal medulla since blocking NO synthase (NOS) with either N^G -monomethyl-L-arginine or N^G -nitro-L-arginine facilitates the release of catecholamines into the plasma (Vo *et al.*, 1991, Navarro *et al.*, 1994, Ward *et al.*, 1996). In addition NOS inhibition facilitates the release of norepinephrine from adrenergic nerves in canine and guinea pig pulmonary blood vessels (Greenberg *et al.*, 1989, Cederqvist *et al.*, 1991), and increases adrenal catecholamine release in pithed rats (McLean *et al.*, 1999). In contrast NO has also been shown to increase norepinephrine overflow from renal sympathetic nerves (Tanioka *et al.*, 2002, Stegbauer *et al.*, 2008).

One explanation for the effect of NO on catecholamine release involves a pre-junctional activation of the cGMP second messenger pathway by NO within the nerve terminal, leading to either an inhibition (Greenberg *et al.*, 1989) or potentiation (Yamamoto *et al.*, 1993, Yamamoto *et al.*, 1994) of norepinephrine release. An alternative explanation is that NO directly reacts with catecholamines resulting in a decrease in biologically active neurotransmitter (Macarthur *et al.*, 1995). Indeed it has been shown that the biological activity of catecholamines decreases after incubation with either authentic NO, or the NO donors sodium nitroprusside or diethylamine NONOate, whereas NPY and ATP remain unaltered (Macarthur *et al.*, 1995, Kolo *et al.*, 2004b). Other investigators have demonstrated that in a test tube incubation, authentic NO almost completely converted dopamine, epinephrine and norepinephrine to their 6-nitro-derivatives (De la Breteche M., 1994, Daveu *et al.*, 1997). These findings suggest that NO can modulate sympathetic neurotransmission by deactivating norepinephrine after it has been released from the sympathetic neuron.

Endogenous NO diminishes norepinephrine activity at the Sympathetic Neurovascular Junction

Inhibiting endogenous NOS with L-NAME in the perfused mesenteric bed of the rat increases nerve stimulated perfusion pressure responses and norepinephrine overflow (Kolo *et al.*, 2004b). This finding is not mimicked by inhibiting soluble guanylate cyclase with ODQ (1H-[1,2,4]oxadiazolo[4,3,-a]quinoxalin-1-one) suggesting a direct interaction of NO with the norepinephrine portion of sympathetic neurotransmission, rather than a pre-junctional inhibition of release *per se* (Kolo *et al.*, 2004b). Furthermore the increase in norepinephrine overflow in the presence of a NOS inhibitor is accompanied by an α_2 -receptor dependent decrease in NPY (Kolo *et al.*, 2004b). Therefore, it appears that NO is a physiological modulator of sympathetic neurotransmission, by deactivating norepinephrine in the neurovascular junction, and placing a "brake" on both the post- and pre-junctional activity of the transmitter.

Loss of NO modulation of Sympathetic Neurotransmission in Hypertension

The enhanced overflow of norepinephrine, as well as increased perfusion pressure responses, in mesenteric preparations taken from spontaneously hypertensive rats are, at least in part, due to the loss of NO modulation of norepinephrine (Kolo *et al.*, 2004a). The events that lead to the development of hypertension are still unclear, but increased activity of the SNS and endothelial dysfunction have both been implicated (Goldstein, 1983, Westfall *et al.*, 1987c, Anderson *et al.*, 1989, Esler *et al.*, 1990, Esler *et al.*, 1991, Grisk *et al.*, 2002), although the precise causal mechanisms leading to increased sympathetic activity are still poorly understood.

Increased oxidative stress, evident in hypertension (Griendling *et al.*, 1994, Zalba *et al.*, 2000, Berry *et al.*, 2001, Cifuentes & Pagano, 2006), could well be a factor in the hyperactivity of the SNS since it will lead to loss of the bioavailability of NO as a result of a reaction with superoxide anion (O_2^-) (Nava *et al.*, 1998, Vaziri *et al.*, 1998, Maffei *et al.*, 2002). This loss of NO would lead to an increase in the amount of norepinephrine within the neurovascular junction and may explain the observations of compromised NO modulation of sympathetic neurotransmission in mesenteric preparations taken from hypertensive rats (Kolo *et al.*, 2004a). Indeed, perfusing mesenteric preparations taken from hypertensive rats with the antioxidant *N*-acetylcysteine reduces the overflow of norepinephrine in a NOS-dependent manner signifying a restoration of NO activity (Macarthur *et al.*, 2008). These observations appear to confirm that the hyperactivity of the sympathetic nervous system in hypertension may be driven, in part, by oxidative stress reducing the bioavailability of NO.

Schema 2 summarizes the NO modulation of sympathetic neurovascular transmission under normotensive and hypertensive conditions.

The role of NO in Differential Modulation of Sympathetic Neurotransmission

The modulation by NO of sympathetic neurotransmission is a possible explanation for some of the observed differential modulation discussed earlier. Some mediators that have apparent opposite effects on co-transmitter release may in fact be indirectly affecting neurotransmission through actions on NO and other endothelial mediators. For example Ang II greatly enhances norepinephrine overflow while only moderately affecting NPY in mesenteric preparations from normotensive rats (Byku *et al.*, 2008). This may be due to the fact that, in addition to directly enhancing norepinephrine and NPY release through AT₁ receptors on nerve terminals, Ang II also stimulates O₂⁻ production in vascular smooth muscle. This increase in O₂⁻ will decrease NO availability and further augment norepinephrine levels in the neurovascular junction that will then blunt NPY release via negative feedback mechanisms. A further example is the observation that, in addition to direct pre-junctional inhibitory effects on norepinephrine and NPY overflow, the angiotensin metabolite, Ang 1–7 decreases norepinephrine overflow from the mesenteric bed in a NOS dependent manner (Byku *et al.*, 2010).

Conclusion

The results reviewed here demonstrate that sympathetic neurotransmission at the neurovascular junction is modulated by a variety of neuronal and non-neuronal mediators. Moreover, the modulation by endothelial mediators underlines the existence of extensive cross-talk between two major centers of vascular control, namely the endothelium of the blood vessel and the sympathetic nervous system. It may be that this cross-talk is of more significance in some organ systems than others especially when considering the effects on overall control of arterial pressure. For example, renal sympathetic nerves are of major importance given that activation of these nerves stimulates the Renin-Angiotensin-Aldosterone system (Karagiannis *et al.*, 1994, Taddei *et al.*, 1994, Esler *et al.*, 2010). Endothelial mediators are also known to be of vital importance to kidney function both for salt and water handling and also in the role played by the kidney in controlling arterial pressure (Ponnuchamy & Khalil, 2009). Therefore it is fair to speculate that the modulation of sympathetic neurovascular transmission in the kidney by endothelial mediators including NO may have major consequences for overall control of arterial pressure, and that dysfunction in this system may ultimately play an important role in the development of hypertension. Finally, it is of special interest to note that many direct modulators of sympathetic neurotransmission can also release NO and prostaglandins from the endothelium. This adds another dimension to the interpretation of overall modulation of sympathetic neurovascular transmission.

Acknowledgments

The authors would like to acknowledge support from the United States National Institutes of Health Grants HL61836 (HM), HL60260 (TCW), and NIGMS-GM083036 (TCW), as well as from The American Heart Association (LLK).

References

- Abounader R, Villemure JG, Hamel E. Characterization of neuropeptide Y (NPY) receptors in human cerebral arteries with selective agonists and the new Y1 antagonist BIBP 3226. *Br J Pharmacol.* 1995; 116:2245–2250. [PubMed: 8564255]

- Allcorn RJ, Cunnane TC, Kirkpatrick K. Actions of alpha, beta-methylene ATP and 6-hydroxydopamine on sympathetic neurotransmission in the vas deferens of the guinea-pig, rat and mouse: support for cotransmission. *Br J Pharmacol.* 1986; 89:647–659. [PubMed: 3028548]
- Anderson EA, Sinkey CA, Lawton WJ, Mark AL. Elevated sympathetic nerve activity in borderline hypertensive humans. Evidence from direct intraneural recordings. *Hypertension.* 1989; 14:177–183. [PubMed: 2759678]
- Berry C, Brosnan MJ, Fennell J, Hamilton CA, Dominiczak AF. Oxidative stress and vascular damage in hypertension. *Curr Opin Nephrol Hypertens.* 2001; 10:247–255. [PubMed: 11224701]
- Boehm S. ATP stimulates sympathetic transmitter release via presynaptic P2X purinoceptors. *J Neurosci.* 1999; 19:737–746. [PubMed: 9880594]
- Boehm S. P2Ys go neuronal: modulation of Ca²⁺ and K⁺ channels by recombinant receptors. *Br J Pharmacol.* 2003; 138:1–3. [PubMed: 12522065]
- Breslow MJ, Tobin JR, Bredt DS, Ferris CD, Snyder SH, Traystman RJ. Role of nitric oxide in adrenal medullary vasodilation during catecholamine secretion. *Eur J Pharmacol.* 1992; 210:105–106. [PubMed: 1376270]
- Bullock JM, Starke K. Presynaptic alpha 2-autoinhibition in a vascular neuroeffector junction where ATP and noradrenaline act as co-transmitters. *Br J Pharmacol.* 1990; 99:279–284. [PubMed: 1970268]
- Burnstock G. Do some nerve cells release more than one transmitter? *Neuroscience.* 1976; 1:239–248. [PubMed: 11370511]
- Burnstock G, Verkhatsky A. Vas deferens--a model used to establish sympathetic cotransmission. *Trends Pharmacol Sci.* 2010; 31:131–139. [PubMed: 20074819]
- Byku M, Macarthur H, Westfall TC. Nerve stimulation induced overflow of neuropeptide Y and modulation by angiotensin II in spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol.* 2008; 295:H2188–H2197. [PubMed: 18835922]
- Byku M, Macarthur H, Westfall TC. Inhibitory effects of angiotensin-(1–7) on the nerve stimulation-induced release of norepinephrine and neuropeptide Y from the mesenteric arterial bed. *Am J Physiol Heart Circ Physiol.* 2010; 298:H457–H465. [PubMed: 19933420]
- Cederqvist B, Gustafsson LE. Modulation of neuroeffector transmission in guinea-pig pulmonary artery and vas deferens by exogenous nitric oxide. *Acta Physiol Scand.* 1994; 150:75–81. [PubMed: 8135125]
- Cederqvist B, Wiklund NP, Persson MG, Gustafsson LE. Modulation of neuroeffector transmission in the guinea pig pulmonary artery by endogenous nitric oxide. *Neurosci Lett.* 1991; 127:67–69. [PubMed: 1652715]
- Chen X, DiMaggio DA, Han SP, Westfall TC. Autoreceptor-induced inhibition of neuropeptide Y release from PC-12 cells is mediated by Y2 receptors. *Am J Physiol.* 1997; 273:H1737–H1744. [PubMed: 9362238]
- Chiba S, Yang XP. Pharmacological analysis of functional neurovascular transmission in canine splenic arteries: role of neuropeptide Y. *Auton Autacoid Pharmacol.* 2002; 22:187–197. [PubMed: 12656944]
- Cifuentes ME, Pagano PJ. Targeting reactive oxygen species in hypertension. *Curr Opin Nephrol Hypertens.* 2006; 15:179–186. [PubMed: 16481886]
- Cunha RA. Adenosine as a neuromodulator and as a homeostatic regulator in the nervous system: different roles, different sources and different receptors. *Neurochem Int.* 2001; 38:107–125. [PubMed: 11137880]
- Daveu C, Servy C, Dendane M, Marin P, Ducrocq C. Oxidation and nitration of catecholamines by nitrogen oxides derived from nitric oxide. *Nitric Oxide.* 1997; 1:234–243. [PubMed: 9704585]
- De Deyn PP, B A P, Verzwijvelen A, D'Hooge R. Subcellular distribution and axonal transport of noradrenaline dopamine beta hydroxylase and neuropeptide Y in dog splenic nerve. *Neurochemistry International.* 1989; 15:3–5.
- De la Breteche M, C S, Lenfant M, Ducrocq C. Nitration of catecholamines with nitrogen oxides in mild conditions: a hypothesis for the reactivity of NO in physiological systems. *Tetrahedron Letters.* 1994; 35:7231–7232.

- De Potter WP, Partoens P, Schoups A, Llona I, Coen EP. Noradrenergic neurons release both noradrenaline and neuropeptide Y from a single pool: the large dense cored vesicles. *Synapse*. 1997; 25:44–55. [PubMed: 8987147]
- DiMaggio DA, Chronwall BM, Buchanan K, O'Donohue TL. Pancreatic polypeptide immunoreactivity in rat brain is actually neuropeptide Y. *Neuroscience*. 1985; 15:1149–1157. [PubMed: 3900804]
- Docherty JR, McGrath JC. A comparison of pre- and post-junctional potencies of several alpha-adrenoceptor agonists in the cardiovascular system and anococcygeus muscle of the rat. Evidence for two types of post-junctional alpha-adrenoceptor. *Naunyn Schmiedebergs Arch Pharmacol*. 1980; 312:107–116. [PubMed: 6105621]
- Diessen B, von Kugelgen I, Starke K. Neural ATP release and its alpha 2-adrenoceptor-mediated modulation in guinea-pig vas deferens. *Naunyn Schmiedebergs Arch Pharmacol*. 1993; 348:358–366. [PubMed: 7904050]
- Ekblad E, Edvinsson L, Wahlestedt C, Uddman R, Hakanson R, Sundler F. Neuropeptide Y co-exists and co-operates with noradrenaline in perivascular nerve fibers. *Regul Pept*. 1984; 8:225–235. [PubMed: 6379758]
- Erlinge D, Ekman R, Thulin T, Edvinsson L. Neuropeptide Y-like immunoreactivity and hypertension. *J Hypertens*. 1992; 10:1221–1225. [PubMed: 1335004]
- Esler M, Ferrier C, Lambert G, Eisenhofer G, Cox H, Jennings G. Biochemical evidence of sympathetic hyperactivity in human hypertension. *Hypertension*. 1991; 17:III29–III35. [PubMed: 2013490]
- Esler M, Jennings G, Lambert G, Meredith I, Horne M, Eisenhofer G. Overflow of catecholamine neurotransmitters to the circulation: source, fate, and functions. *Physiol Rev*. 1990; 70:963–985. [PubMed: 1977182]
- Esler MD, Lambert EA, Schlaich M, Navar LG. The Dominant Contributor to Systemic Hypertension: Chronic Activation of the Sympathetic Nervous System vs Activation of the Intrarenal Renin-Angiotensin System. *J Appl Physiol*. 2010
- Fedan JS, Hogaboom GK, O'Donnell JP, Colby J, Westfall DP. Contribution by purines to the neurogenic response of the vas deferens of the guinea pig. *Eur J Pharmacol*. 1981; 69:41–53. [PubMed: 7202512]
- Francis GS. Modulation of peripheral sympathetic nerve transmission. *J Am Coll Cardiol*. 1988; 12:250–254. [PubMed: 2837502]
- Gardner A, Westfall TC, Macarthur H. Endothelin (ET)-1-induced inhibition of ATP release from PC-12 cells is mediated by the ETB receptor: differential response to ET-1 on ATP, neuropeptide Y, and dopamine levels. *J Pharmacol Exp Ther*. 2005; 313:1109–1117. [PubMed: 15687374]
- Goldstein DS. Plasma catecholamines and essential hypertension. An analytical review. *Hypertension*. 1983; 5:86–99. [PubMed: 6336721]
- Greenberg S, Diecke FP, Peevy K, Tanaka TP. The endothelium modulates adrenergic neurotransmission to canine pulmonary arteries and veins. *Eur J Pharmacol*. 1989; 162:67–80. [PubMed: 2542057]
- Griendling KK, Minieri CA, Ollerenshaw JD, Alexander RW. Angiotensin II stimulates NADH and NADPH oxidase activity in cultured vascular smooth muscle cells. *Circ Res*. 1994; 74:1141–1148. [PubMed: 8187280]
- Grisk O, Kloting I, Exner J, Spiess S, Schmidt R, Junghans D, Lorenz G, Rettig R. Long-term arterial pressure in spontaneously hypertensive rats is set by the kidney. *J Hypertens*. 2002; 20:131–138. [PubMed: 11791036]
- Grundemar L, Hakanson R. Neuropeptide Y effector systems: perspectives for drug development. *Trends Pharmacol Sci*. 1994; 15:153–159. [PubMed: 7754533]
- Haass M, Cheng B, Richardt G, Lang RE, Schomig A. Characterization and presynaptic modulation of stimulation-evoked exocytotic co-release of noradrenaline and neuropeptide Y in guinea pig heart. *Naunyn Schmiedebergs Arch Pharmacol*. 1989a; 339:71–78. [PubMed: 2566928]
- Haass M, Hock M, Richardt G, Schomig A. Neuropeptide Y differentiates between exocytotic and nonexocytotic noradrenaline release in guinea-pig heart. *Naunyn Schmiedebergs Arch Pharmacol*. 1989b; 340:509–515. [PubMed: 2615846]

- Hammond JR, MacDonald WF, White TD. Evoked secretion of [3H]noradrenaline and ATP from nerve varicosities isolated from the myenteric plexus of the guinea pig ileum. *Can J Physiol Pharmacol.* 1988; 66:369–375. [PubMed: 3167671]
- Han S, Chen X, Cox B, Yang CL, Wu YM, Naes L, Westfall T. Role of neuropeptide Y in cold stress-induced hypertension. *Peptides.* 1998a; 19:351–358. [PubMed: 9493868]
- Han S, Yang CL, Chen X, Naes L, Cox BF, Westfall T. Direct evidence for the role of neuropeptide Y in sympathetic nerve stimulation-induced vasoconstriction. *Am J Physiol.* 1998b; 274:H290–H294. [PubMed: 9458879]
- Hegde SS, Bonhaus DW, Stanley W, Eglen RM, Moy TM, Loeb M, Shetty SG, DeSouza A, Krstenansky J. Pharmacological evaluation of 1229U91, a novel high-affinity and selective neuropeptide Y-Y1 receptor antagonist. *J Pharmacol Exp Ther.* 1995; 275:1261–1266. [PubMed: 8531090]
- Hoang D, Macarthur H, Gardner A, Westfall TC. Endothelin-induced modulation of neuropeptide Y and norepinephrine release from the rat mesenteric bed. *Am J Physiol Heart Circ Physiol.* 2002; 283:H1523–H1530. [PubMed: 12234805]
- Hoang D, Macarthur H, Gardner A, Yang CL, Westfall TC. Prostanoid-induced modulation of neuropeptide Y and noradrenaline release from the rat mesenteric bed. *Auton Autacoid Pharmacol.* 2003; 23:141–147. [PubMed: 14511074]
- Hoyle, CHV. Transmission: Purines. In: Burnstock, G.; Hoyle, CHV., editors. *Autonomic Neuroeffector Mechanisms*. Reading, U.K.: Harwood Academic Publishers; 1992.
- Huidobro-Toro JP, Veronica Donoso M. Sympathetic co-transmission: the coordinated action of ATP and noradrenaline and their modulation by neuropeptide Y in human vascular neuroeffector junctions. *Eur J Pharmacol.* 2004; 500:27–35. [PubMed: 15464018]
- Ishikawa S. Actions of ATP and alpha, beta-methylene ATP on neuromuscular transmission and smooth muscle membrane of the rabbit and guinea-pig mesenteric arteries. *Br J Pharmacol.* 1985; 86:777–787. [PubMed: 3000499]
- Karagiannis A, Douma S, Vogiatzis K, Petidis K, Doumas M, Vyzantiadis A, Efremidis S, Zamboulis C. The relationship between the sympathetic nervous system and the renin-angiotensin system in renovascular hypertension. *Acta Cardiol.* 1994; 49:425–434. [PubMed: 7839761]
- Kasakov L, Burnstock G. The use of the slowly degradable analog, alpha, beta-methylene ATP, to produce desensitisation of the P2-purinoceptor: effect on non-adrenergic, non-cholinergic responses of the guinea-pig urinary bladder. *Eur J Pharmacol.* 1982; 86:291–294. [PubMed: 6297936]
- Kennedy B, Shen GH, Ziegler MG. Neuropeptide Y-mediated pressor responses following high-frequency stimulation of the rat sympathetic nervous system. *J Pharmacol Exp Ther.* 1997; 281:291–296. [PubMed: 9103509]
- Kennedy C, McLaren GJ, Westfall TD, Sneddon P. ATP as a co-transmitter with noradrenaline in sympathetic nerves--function and fate. *Ciba Found Symp.* 1996; 198:223–235. discussion 235–238. [PubMed: 8879828]
- Kirby DA, Koerber SC, May JM, Hagaman C, Cullen MJ, Pelleymounter MA, Rivier JE. Y1 and Y2 receptor selective neuropeptide Y analogues: evidence for a Y1 receptor subclass. *J Med Chem.* 1995; 38:4579–4586. [PubMed: 7473586]
- Kirkpatrick K, Burnstock G. Sympathetic nerve-mediated release of ATP from the guinea-pig vas deferens is unaffected by reserpine. *Eur J Pharmacol.* 1987; 138:207–214. [PubMed: 3113984]
- Kolo LL, Westfall TC, Macarthur H. Modulation of neurotransmitter release by NO is altered in mesenteric arterial bed of spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol.* 2004a; 287:H1842–H1847. [PubMed: 15205164]
- Kolo LL, Westfall TC, Macarthur H. Nitric oxide decreases the biological activity of norepinephrine resulting in altered vascular tone in the rat mesenteric arterial bed. *Am J Physiol Heart Circ Physiol.* 2004b; 286:H296–H303. [PubMed: 14684362]
- Langer SZ, Arbilla S. Presynaptic receptors on peripheral noradrenergic neurons. *Ann N Y Acad Sci.* 1990; 604:7–16. [PubMed: 2171408]
- Leban JJ, Heyer D, Landavazo A, Matthews J, Aulabaugh A, Daniels AJ. Novel modified carboxy terminal fragments of neuropeptide Y with high affinity for Y2-type receptors and potent

- functional antagonism at a Y1-type receptor. *J Med Chem.* 1995; 38:1150–1157. [PubMed: 7707318]
- Levitt B, Westfall DP. Factors influencing the release of purines and norepinephrine in the rabbit portal vein. *Blood Vessels.* 1982; 19:30–40. [PubMed: 6800424]
- Lew MJ, White TD. Release of endogenous ATP during sympathetic nerve stimulation. *Br J Pharmacol.* 1987; 92:349–355. [PubMed: 2823948]
- Lundberg JM, Hokfelt T. Multiple co-existence of peptides and classical transmitters in peripheral autonomic and sensory neurons--functional and pharmacological implications. *Prog Brain Res.* 1986; 68:241–262. [PubMed: 2882554]
- Lundberg JM, Modin A. Inhibition of sympathetic vasoconstriction in pigs in vivo by the neuropeptide Y-Y1 receptor antagonist BIBP 3226. *Br J Pharmacol.* 1995; 116:2971–2982. [PubMed: 8680732]
- Lundberg JM, Pernow J, Franco-Cereceda A, Rudehill A. Effects of antihypertensive drugs on sympathetic vascular control in relation to neuropeptide Y. *J Cardiovasc Pharmacol.* 1987; 10 Suppl 12:S51–S68. [PubMed: 2455193]
- Lundberg JM, Rudehill A, Sollevi A, Theodorsson-Norheim E, Hamberger B. Frequency- and reserpine-dependent chemical coding of sympathetic transmission: differential release of noradrenaline and neuropeptide Y from pig spleen. *Neurosci Lett.* 1986; 63:96–100. [PubMed: 3005926]
- Lundberg JM, Terenius L, Hokfelt T, Martling CR, Tatemoto K, Mutt V, Polak J, Bloom S, Goldstein M. Neuropeptide Y (NPY)-like immunoreactivity in peripheral noradrenergic neurons and effects of NPY on sympathetic function. *Acta Physiol Scand.* 1982; 116:477–480. [PubMed: 6763452]
- Macarthur H, Mattammal MB, Westfall TC. A new perspective on the inhibitory role of nitric oxide in sympathetic neurotransmission. *Biochem Biophys Res Commun.* 1995; 216:686–692. [PubMed: 7488165]
- Macarthur H, Westfall TC, Wilken GH. Oxidative stress attenuates NO-induced modulation of sympathetic neurotransmission in the mesenteric arterial bed of spontaneously hypertensive rats. *Am J Physiol Heart Circ Physiol.* 2008; 294:H183–H189. [PubMed: 17965279]
- Maffei A, Poulet R, Vecchione C, Colella S, Fratta L, Frati G, Trimarco V, Trimarco B, Lembo G. Increased basal nitric oxide release despite enhanced free radical production in hypertension. *J Hypertens.* 2002; 20:1135–1142. [PubMed: 12023683]
- Malmstrom RE, Lundberg JM. Neuropeptide Y accounts for sympathetic vasoconstriction in guinea-pig vena cava: evidence using BIBP 3226 and 3435. *Eur J Pharmacol.* 1995; 294:661–668. [PubMed: 8750731]
- Malmstrom RE, Lundberg JN, Weitzberg E. Effects of the neuropeptide Y Y2 receptor antagonist BIIE0246 on sympathetic transmitter release in the pig in vivo. *Naunyn Schmiedeberg's Arch Pharmacol.* 2002; 365:106–111. [PubMed: 11819028]
- McLean KJ, Jarrott B, Lawrence AJ. Hypotension activates neuropeptide Y-containing neurons in the rat medulla oblongata. *Neuroscience.* 1999; 92:1377–1387. [PubMed: 10426492]
- Michel MC, Rascher W. Neuropeptide Y: a possible role in hypertension? *J Hypertens.* 1995; 13:385–395. [PubMed: 7629398]
- Morris, JL.; Gibbins, IL. Co-transmission and Neuromodulation. In: Burnstock, G.; Hoyle, CHV., editors. *Autonomic neuroeffector mechanisms*. Reading. UK: Harwood Academic Publisher; 1992.
- Moylan RD, Westfall TC. Effect of adenosine on adrenergic neurotransmission in the superfused rat portal vein. *Blood Vessels.* 1979; 16:302–310. [PubMed: 230871]
- Myers RD, Wooten MH, Ames CD, Nyce JW. Anorexic action of a new potential neuropeptide Y antagonist [D-Tyr27,36, D-Thr32]-NPY (27–36) infused into the hypothalamus of the rat. *Brain Res Bull.* 1995; 37:237–245. [PubMed: 7627566]
- Nakamura K, Okada S, Yokotani K. Endothelin ET A- and ET B-receptor-mediated inhibition of noradrenaline release from isolated rat stomach. *J Pharmacol Sci.* 2003; 91:34–40. [PubMed: 12686728]
- Nap A, Balt JC, Mathy MJ, Van Zwieten PA. AT(1)-receptor blockade and sympathetic neurotransmission in cardiovascular disease. *Auton Autacoid Pharmacol.* 2003; 23:285–296. [PubMed: 15255813]

- Nava E, Farre AL, Moreno C, Casado S, Moreau P, Cosentino F, Luscher TF. Alterations to the nitric oxide pathway in the spontaneously hypertensive rat. *J Hypertens*. 1998; 16:609–615. [PubMed: 9797172]
- Navarro J, Sanchez A, Saiz J, Ruilope LM, Garcia-Estan J, Romero JC, Moncada S, Lahera V. Hormonal, renal, and metabolic alterations during hypertension induced by chronic inhibition of NO in rats. *Am J Physiol*. 1994; 267:R1516–R1521. [PubMed: 7529003]
- Pernow J, Lundberg JM. Release and vasoconstrictor effects of neuropeptide Y in relation to non-adrenergic sympathetic control of renal blood flow in the pig. *Acta Physiol Scand*. 1989; 136:507–517. [PubMed: 2571235]
- Ponnuchamy B, Khalil RA. Cellular mediators of renal vascular dysfunction in hypertension. *Am J Physiol Regul Integr Comp Physiol*. 2009; 296:R1001–R1018. [PubMed: 19225145]
- Ralevic V. Purines as neurotransmitters and neuromodulators in blood vessels. *Curr Vasc Pharmacol*. 2009; 7:3–14. [PubMed: 19149635]
- Ramagopal MV, Leighton HJ. Analysis of the presence of postjunctional alpha-2 adrenoceptors in the rat anococcygeus muscle. *J Pharmacol Exp Ther*. 1989; 250:492–499. [PubMed: 2547934]
- Sedaa KO, Bjur RA, Shinozuka K, Westfall DP. Nerve and drug-induced release of adenine nucleosides and nucleotides from rabbit aorta. *J Pharmacol Exp Ther*. 1990; 252:1060–1067. [PubMed: 2319458]
- Sneddon P, Burnstock G. ATP as a co-transmitter in rat tail artery. *Eur J Pharmacol*. 1984; 106:149–152. [PubMed: 6152212]
- Sneddon P, Westfall DP. Pharmacological evidence that adenosine triphosphate and noradrenaline are co-transmitters in the guinea-pig vas deferens. *J Physiol*. 1984; 347:561–580. [PubMed: 6142947]
- Starke K, Gothert M, Kilbinger H. Modulation of neurotransmitter release by presynaptic autoreceptors. *Physiol Rev*. 1989; 69:864–989. [PubMed: 2568648]
- Stegbauer J, Kuczka Y, Vonend O, Quack I, Sellin L, Patzak A, Steege A, Langnaese K, Rump LC. Endothelial nitric oxide synthase is predominantly involved in angiotensin II modulation of renal vascular resistance and norepinephrine release. *Am J Physiol Regul Integr Comp Physiol*. 2008; 294:R421–R428. [PubMed: 18046021]
- Stjarne L. Catecholaminergic neurotransmission: flagship of all neurobiology. *Acta Physiol Scand*. 1999; 166:251–259. [PubMed: 10610611]
- Taddei S, Virdis A, Mattei P, Duranti P, Favilla S, Salvetti A. Vascular renin-angiotensin system and sympathetic nervous system activity in human hypertension. *J Cardiovasc Pharmacol*. 1994; 23 Suppl 1:S9–S14. [PubMed: 7519697]
- Tanioka H, Nakamura K, Fujimura S, Yoshida M, Suzuki-Kusaba M, Hisa H, Satoh S. Facilitatory role of NO in neural norepinephrine release in the rat kidney. *Am J Physiol Regul Integr Comp Physiol*. 2002; 282:R1436–R1442. [PubMed: 11959687]
- Todorov LD, Mihaylova-Todorova S, Craviso GL, Bjur RA, Westfall DP. Evidence for the differential release of the cotransmitters ATP and noradrenaline from sympathetic nerves of the guinea-pig vas deferens. *J Physiol*. 1996; 496 (Pt 3):731–748. [PubMed: 8930840]
- Uddman R, Ekblad E, Edvinsson L, Hakanson R, Sundler F. Neuropeptide Y-like immunoreactivity in perivascular nerve fibres of the guinea-pig. *Regul Pept*. 1985; 10:243–257. [PubMed: 3887502]
- Vaziri ND, Ni Z, Oveisi F. Upregulation of renal and vascular nitric oxide synthase in young spontaneously hypertensive rats. *Hypertension*. 1998; 31:1248–1254. [PubMed: 9622137]
- Vizi ES, Burnstock G. Origin of ATP release in the rat vas deferens: concomitant measurement of [3H]noradrenaline and [14C]ATP. *Eur J Pharmacol*. 1988; 158:69–77. [PubMed: 2851460]
- Vo PA, Reid JJ, Rand MJ. Endothelial nitric oxide attenuates vasoconstrictor responses to nerve stimulation and noradrenaline in the rat tail artery. *Eur J Pharmacol*. 1991; 199:123–125. [PubMed: 1893923]
- von Kugelgen I, Kurz K, Bultmann R, Driessen B, Starke K. Presynaptic modulation of the release of the co-transmitters noradrenaline and ATP. *Fundam Clin Pharmacol*. 1994; 8:207–213. [PubMed: 7927116]
- von Kugelgen I, Starke K. Noradrenaline and adenosine triphosphate as co-transmitters of neurogenic vasoconstriction in rabbit mesenteric artery. *J Physiol*. 1985; 367:435–455. [PubMed: 2865364]

- Wahlestedt C, Reis DJ. Neuropeptide Y-related peptides and their receptors--are the receptors potential therapeutic drug targets? *Annu Rev Pharmacol Toxicol.* 1993; 33:309–352. [PubMed: 8494343]
- Ward LE, Hunter LW, Grabau CE, Tyce GM, Rorie DK. Nitric oxide reduces basal efflux of catecholamines from perfused dog adrenal glands. *J Auton Nerv Syst.* 1996; 61:235–242. [PubMed: 8988480]
- Westfall DP, Sedaa K, Bjur RA. Release of endogenous ATP from rat caudal artery. *Blood Vessels.* 1987a; 24:125–127. [PubMed: 3593975]
- Westfall DP, Shinozuka K, Forsyth KM, Bjur RA. Presynaptic purine receptors. *Ann N Y Acad Sci.* 1990a; 604:130–135. [PubMed: 2221704]
- Westfall TC. Prejunctional Effects of neuropeptide Y and its role as a Cotransmitter. In: Michel, M., editor. *Neuropeptide Y and Related Peptides.* Berlin/Heidelberg: Springer-Verlag; 2004.
- Westfall TC, Carpentier S, Chen X, Beinfeld MC, Naes L, Meldrum MJ. Prejunctional and postjunctional effects of neuropeptide Y at the noradrenergic neuroeffector junction of the perfused mesenteric arterial bed of the rat. *J Cardiovasc Pharmacol.* 1987b; 10:716–722. [PubMed: 2450243]
- Westfall TC, Chen XL, Ciarleglio A, Henderson K, Del Valle K, Curfman-Falvey M, Naes L. In vitro effects of neuropeptide Y at the vascular neuroeffector junction. *Ann N Y Acad Sci.* 1990b; 611:145–155. [PubMed: 2248475]
- Westfall TC, Martin J, Chen XL, Ciarleglio A, Carpentier S, Henderson K, Knuepfer M, Beinfeld M, Naes L. Cardiovascular effects and modulation of noradrenergic neurotransmission following central and peripheral administration of neuropeptide Y. *Synapse.* 1988; 2:299–307. [PubMed: 2850631]
- Westfall TC, Meldrum MJ, Carpentier S, Naes L, Zhang SQ. Alterations in the release of norepinephrine at the vascular neuroeffector junction in hypertension. *Blood Vessels.* 1987c; 24:94–99. [PubMed: 3593978]
- Westfall TD, Menzies JR, Liberman R, Waterston S, Ramphir N, Westfall DP, Sneddon P, Kennedy C. Release of a soluble ATPase from the rabbit isolated vas deferens during nerve stimulation. *Br J Pharmacol.* 2000a; 131:909–914. [PubMed: 11053210]
- Westfall TD, Sarkar S, Ramphir N, Westfall DP, Sneddon P, Kennedy C. Characterization of the ATPase released during sympathetic nerve stimulation of the guinea-pig isolated vas deferens. *Br J Pharmacol.* 2000b; 129:1684–1688. [PubMed: 10780974]
- Wiklund NP, Ohlen A, Wiklund CU, Hedqvist P, Gustafsson LE. Endothelin modulation of neuroeffector transmission in rat and guinea pig vas deferens. *Eur J Pharmacol.* 1990; 185:25–33. [PubMed: 2171959]
- Woodman OL, Pannangpetch P. Enhancement of noradrenergic constriction of large coronary arteries by inhibition of nitric oxide synthesis in anaesthetized dogs. *Br J Pharmacol.* 1994; 112:443–448. [PubMed: 7915608]
- Yamamoto R, Wada A, Asada Y, Niina H, Sumiyoshi A. N omega-nitro-L-arginine, an inhibitor of nitric oxide synthesis, decreases noradrenaline outflow in rat isolated perfused mesenteric vasculature. *Naunyn Schmiedeberg's Arch Pharmacol.* 1993; 347:238–240. [PubMed: 8474540]
- Yamamoto R, Wada A, Asada Y, Yuh T, Yanagita T, Niina H, Sumiyoshi A. Functional relation between nitric oxide and noradrenaline for the modulation of vascular tone in rat mesenteric vasculature. *Naunyn Schmiedeberg's Arch Pharmacol.* 1994; 349:362–366. [PubMed: 8058108]
- Zalba G, Beaumont FJ, San Jose G, Fortuno A, Fortuno MA, Etayo JC, Diez J. Vascular NADH/NADPH oxidase is involved in enhanced superoxide production in spontaneously hypertensive rats. *Hypertension.* 2000; 35:1055–1061. [PubMed: 10818064]
- Zukowska-Grojec Z. Neuropeptide Y. A novel sympathetic stress hormone and more. *Ann N Y Acad Sci.* 1995; 771:219–233. [PubMed: 8597401]
- Zukowska-Grojec Z, Dayao EK, Karwowska-Prokopczuk E, Hauser GJ, Doods HN. Stress-induced mesenteric vasoconstriction in rats is mediated by neuropeptide Y Y1 receptors. *Am J Physiol.* 1996; 270:H796–H800. [PubMed: 8779858]

Co-Transmission at the Sympathetic Neurovascular Junction

Schema 1.

Schema depicts co-transmission of norepinephrine (NE), neuropeptide Y (NPY) and adenosine triphosphate (ATP) at the sympathetic neurovascular junction.

A) NO induced modulation of NE and NPY neurotransmission **B) NO induced modulation of NE and NPY neurotransmission in developing hypertension** **Schema 2.**

A) Schema depicts the modulation exerted by nitric oxide (NO) on the norepinephrine (NE) portion of sympathetic neurotransmission under normal conditions. NO, produced in the endothelial cell from L-Arginine, diffuses to the vascular smooth muscle where it activates soluble guanylate cyclase (sGC) leading to an increase in cGMP and vasorelaxation. NO further diffuses into the neurovascular junction where it reacts with, and deactivates, NE, thus placing a “brake” on the post and pre-junctional activity of NE. As a consequence neuropeptide Y (NPY) release is enhanced. The effect on adenosine triphosphate (ATP) is unknown. **B)** Schema depicts how NO-induced modulation of NE alters during developing hypertension. Increased superoxide (O_2^-) production within the vascular smooth muscle limits the activity of NO and thus limits the amount of NO that diffuses to the sympathetic neurovascular junction. The presence of less NO effectively removes the “brake” on the activity of NE resulting in enhanced NE-induced post-junctional vasoconstriction and pre-junctional inhibition of NPY release. The effect on ATP is unknown.