Chronic hypertension enhances the presynaptic effect of baclofen in the nucleus of the solitary tract

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• The nucleus of the solitary tract (NTS) is the first central integration site of baroreceptor afferent inputs. GABAergic mechanisms in the NTS play a crucial role in baroreflexes.

• GABA$_B$ receptors are located at both pre- and post-synaptic sites in the NTS. Baclofen, a selective GABA$_B$ receptor agonist, acts at both sites and has inhibitory effects in the NTS (Brooks et al. 1992).
Baclofen-induced pressor response (BIPR)

- Microinjection of baclofen into the NTS results in an increase in arterial pressure, heart rate, and renal sympathetic nerve discharge (Sved & Sved, 1989), consistent with inhibition of baroreflex function.

- BIPR is enhanced in several animal models of chronic hypertension: spontaneously hypertensive rat (Catelli & Sved, 1988, Yin & Sved, 1998), deoxycorticosterone (DOCA)-salt hypertensive rats (Tsukamoto & Sved, 1993), and one-kidney, renal wrap models of hypertension (Zhang & Mifflin, 1998; Durgam et al. 1999; Vitela & Mifflin, 2001; Mei et al. 2003).
Hypertension enhances post-synaptic effect of baclofen in the NTS

30 µM baclofen

![Graph showing concentration of baclofen vs. outward current percentage.]

- Hypertensive (n=7): EC$_{50}$ = 3.0 ± 0.5 µM
- Normotensive (n=5): EC$_{50}$ = 9.1 ± 3.2 µM

(Zhang & Mifflin, 2007)
Methods

• Unilateral DiA labeling of aortic nerve was used to identify second-order neurons in caudal NTS receiving direct inputs from arterial baroreceptor.

• One kidney, renal wrap rat model of chronic hypertension. Experiments were performed at four weeks after surgery.

• Whole-cell recordings were performed on a horizontal NTS slice preparation. Evoked EPSCs (eEPSCs) were recorded by electrical stimulation on ipsilateral solitary tract (ST).

• Composition of pipette solutions (in mM): 125 CsCl, 1 MgCl₂, 10 HEPEs, 1.1 EGTA, 2 Mg₂ATP, 0.3 Na₂GTP, 5 QX-314.
Results

The mean arterial blood pressure is significantly higher in renal-wrap hypertensive (HT) rats than in normotenstive (NT) rats.
Left. Raw data showing the inhibitory effect of baclofen on the amplitude of eEPSCs, but not onset latency. Data is the average of 10 tracings collected from a normotensive rat. There was no discernable alteration of holding current, indicating that the cesium in the pipette solution abolished post-synaptic baclofen evoked increases in potassium conductance. Right. There is no significant difference in amplitudes of eEPSCs between NT and HT neurons.
Left: Baclofen at 1 µM caused significantly greater inhibition of eEPSCs in HT neurons than NT neurons. Right: There is significant difference in EC$_{50}$ of baclofen-evoked inhibition of eEPSCs between NT and HT neurons ($p<0.05$).
Compared with data of baclofen post-synaptic In normotensive (NT) rats (Zhang & Mifflin, 2007), the EC$_{50}$ of pre-synaptic baclofen effect was significantly lower than that of post-synaptic effect ($p<0.001$).
Raw data showing that in a NT NTS neuron, 1 μM baclofen reduced amplitude of eEPSCs and increased paired-pulse ratio (PPR=A2/A1).
A. Baclofen significantly attenuated paired-pulse depression by increasing paired-pulse ratio (PPR) at different intervals in NT cells. *: $p<0.05$. B. Compared to normal control cells, HT cells had greater PPR, and baclofen induced greater increase in PPR. *: $p<0.05$; **: $p<0.01$. 
Summary & Conclusions

Baclofen inhibits glutamate release from baroreceptor afferents in the NTS. In renal-wrap chronic hypertension, baclofen inhibition of pre-synaptic glutamate release is enhanced.

Chronic hypertension enhances GABA_B pre- and post-synaptic inhibition of NTS neurons receiving arterial baroreceptor afferent inputs. This could be an adaptive neural mechanism in response to increased glutamatergic baroreceptor afferent inputs during chronic hypertension.

Future research will focus on mechanisms underlying hypertension-induced alteration in the function of GABA_B receptors.
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