Abstract

Blood pressure and pain are regulated by complex neuronal networks involving numerous areas in the central nervous system (CNS). The association between the cardiovascular and nociceptive central control systems has been shown, but the mechanisms underlying the functional link remain to be elucidated. The caudal ventrolateral medulla (CVLM) and the nucleus tractus solitarii (NTS) were evaluated as putative anatomical candidates in the blood pressure and pain interaction, as both medullary nuclei have important roles in the cardiovascular and pain control. The participation of the renin-angiotensin and the glutamatergic systems in cardiovascular and nociceptive control is well known. Therefore, angiotensin II and N-methyl-D-aspartate (NMDA) receptors were evaluated as mediators of the aforementioned association.

In the first part of this work, the nociceptive and cardiovascular effects of administrating angiotensin II in the CVLM were addressed. Blood pressure evaluation showed no differences comparing the effects of angiotensin II and saline. Inflammatory and acute thermal pain models showed hyperalgesia elicited by angiotensin II injection in the CVLM, which was prevented by prior administration of losartan, an AT₁ receptors antagonist. The second part of the present work showed that the pontine A5 noradrenergic cell group relays the descending transmission of the hyperalgesia reported in the first study, as partial destruction of the A5 noradrenergic neuronal population by the injection of the selective neurotoxin anti-dopamine B hydroxylase into the CVLM prevented that hyperalgesia. CVLM neurons expressing AT₁
receptors were shown to project to the A\textsubscript{5} group, evidencing the synaptic circuit that
mediates the nociceptive response to angiotensin II injection in the CVLM. The third
part aimed at modulating the expression of the NR1 subunit of NMDA receptors at the
NTS by lentiviral gene transfer and assessing nociceptive and cardiovascular responses.
Diminished expression of NR1 caused hypertension, hypoalgesia, and decreased
neuronal activation at the spinal cord. Administration of the specific agonist NMDA
reversed the reported effects in blood pressure, pain, and spinal neuronal activation.
The time-course of the two responses was distinct, suggesting different neuronal
circuits mediating blood pressure and pain from the NTS.

The present work brings new evidence on the importance of angiotensin II in
nociception, as this was the first study reporting hyperalgesia after administration of
angiotensin II in a discrete component of the supraspinal pain control system. The
pontine noradrenergic A\textsubscript{5} group relays descending modulation of nociceptive
transmission elicited by angiotensin II administration in the CVLM. The integrative role
of NMDA receptors located in the NTS in the association between blood pressure and
pain was also evidenced. Collectively, these studies contribute to unravel central
neurobiologic links that mediate the association between cardiovascular and pain
control.