Brain-stem microRNAs implicated in hypertension

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BRAIN-STEM NUCLEI PLAY A CRUCIAL role in the regulation of blood pressure (BP) and other cardiovascular functions (2, 4). Defect(s) in central neural mechanisms that control sympathetic outflow have been suggested to be involved, in part, in the onset and maintenance of the elevated BP in hypertension. It is well known that hypertension involves a genetic predisposition. Since the genetic “defects” responsible may reside in the regulatory DNA of genes encoding proteins that control BP, differences in gene expression in relevant tissues between hypertensive and control strains of genetically hypertensive rats (13) and mice (10, 11), as well as between essential hypertensive patients and normotensive humans (12), have been determined at the transcriptome-wide level. These studies have implicated various intracellular pathways in the etiology of hypertension onset, maintenance, or response to the elevated BP (10–13).

Gene expression is controlled not only at the transcriptional level, but also posttranscriptionally. A major class of mediators of posttranscriptional regulation are microRNAs (miRNAs). These reduce the stability and repress the translation of messenger RNAs (mRNAs) (17). In recent years studies have been undertaken to determine the transcriptome-wide differences in expression of miRNAs in hypertension (8, 9, 12). This has led to the identification of differentially expressed miRNAs and their target mRNAs in kidneys (12) and lymphocytes (8, 9) of patients with essential hypertension. The actions of the proteins encoded by these mRNAs suggest roles in hypertension onset, maintenance and/or target-organ damage.

DeCicco and coworkers (3) have, for the first time, compared miRNA expression in two brain-stem regions, the nucleus of the solitary tract (NTS) and rostral ventrolateral medulla (RVLM), of spontaneously hypertensive rats (SHR) and normotensive Wistar Kyoto (WKY) rats (3). Changes in angiotensin (ANG) II signaling and neuroinflammatory pathways within these regions are believed to contribute to neurogenic hypertension. Of 419 miRNAs 24 miRNAs exhibited differential expression in at least one of these brain-stem regions. By searches of bioinformatic databases the miRNAs containing target sequences for these miRNAs were identified, together with specific miRNA-mRNA interaction data. Levels of various predicted target mRNAs were then estimated by semiquantitative PCR. Correlations were found between expression levels of specific miRNAs with various putative target mRNAs identified. The outcome was the discovery of multiple pathways potentially involved in the miRNA-mediated processes that could lead to hypertension. These included ANG II signaling, catecholaminergic processes, neuroinflammation, and neuromodulation.

Some of the miRNAs were postulated to have a “double-negative” effect in that when upregulated they would downregulate the mRNA of an inhibitor of a prohypertensive factor, so leading to hypertension. Conversely, downregulation of a particular miRNA capable of suppressing the mRNA for a prohypertensive factor would increase the prohypertensive factor, thus enhancing its capacity to raise BP. Mechanisms by which increases in other miRNAs would lower levels of proteins normally able to oppose rises in BP could also be envisaged.

Of particular interest were differences found in expression of specific miRNAs across different stages, namely prehypertension, hypertension onset, and established hypertension. The prehypertensive phase is highly relevant because abnormalities during this stage are responsible for causation of hypertension. They found the RVLM showed numerous miRNA expression differences during the prehypertensive phase, whereas in the NTS most miRNA expression differences were seen in the onset phase of hypertension. Previous work has shown that the RVLM regulates arterial pressure by angiotensinergic activation and GABAergic inhibition (1, 4). Inhibition of ANG II type 1 receptors in the RVLM greatly reduces BP in SHRs (5).

One of the miRNAs differentially expressed in the prehypertensive phase was miR-181a. Renal downregulation of this miRNA has been implicated in hypertension etiology in the Schlager BPH/2J genetically hypertensive mouse strain (7), a model of neurogenic hypertension, and in essential hypertension (12). The mechanism involves sympathetically mediated suppression of renal miR-181a (6, 14), so alleviating the destabilizing effect this miRNA has on renin mRNA, thus leading to activation of an intrarenal renin-angiotensin system and thence BP elevation (15). Although angiotensinergic mechanisms were implicated by DeCicco et al. (3), it is not clear how miR-181a might be involved in brain-stem mechanisms.

Most of the new findings will require a multitude of different experiments before the actions of each of the differentially expressed miRNAs in the RVLM and NTS of the SHR and WKY are elucidated. In the meantime, a plausible scheme was proposed for two of the miRNAs found to be differentially expressed. One, miR-135a (enriched in astrocytes and upregulated in the SHR), may lower interleukin 1 receptor antagonist (Il1rn) mRNA, prostaglandin reductase 1 (Ptgr1) mRNA, and ANG II receptor type 1-associating protein (Agtrap) mRNA, so leading to increased interleukin-1 signaling and the levels of leukotriene B4 and ANG II type 1 receptor. The outcome would be increased inflammation, activation of ANG II signaling pathways, and elevation in BP. High leukotriene B4 in the NTS and elevated proinflammatory cytokines in the RVLM have been implicated in SHR and other forms of hypertension. DeCicco et al. (3) predicted that another microRNA, miR-376a (enriched in neurons and upregulated in the NTS of SHRs), would suppress Agtrap mRNA and thus increase ANG II type...
1 receptor signaling. Thus the study found that miRNAs capable of downregulating prohypertensive processes such as ANG II-mediated signaling pathways (in neurons) and leukotriene-mediated inflammation (in astrocytes) were lower in the SHR, consistent with a role for those miRNAs in BP elevation.

Apart from their role in ANG II signaling and inflammation, miR-135a and miR-376a also potentially have actions on genes that transcribe other proteins, such as those related to channels, membranes, G proteins, hormones, neurotransmitters, metabolism, and immediate early genes, as the authors point out. Therefore, there are numerous possible mechanisms by which miR-135a and miR-376a could trigger processes that lead to hypertension. Nevertheless, DeCicco et al. (3) have provided a wealth of new data suggesting pathways by which aberrant expression of multiple miRNAs might affect cardiovascular control mechanisms in the NTS and RVLM and thereby play a role in the etiology of hypertension in the SHR.

Like genes, rodent miRNAs have human homologs. This and the value of the SHR as an animal model of essential hypertension mean the findings could provide potential insights into possible brain-stem mechanisms responsible for high BP in humans (16). The findings therefore have the potential to be used for development of novel antihypertensive therapies.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

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