Adenosine Receptors

A Tantalizing Target for the Treatment of Salt-Sensitive Hypertension

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See related article, pp 511–521

Adenosine is an important extracellular signaling molecule that regulates cellular responses to hypoxia, energy depletion, and tissue injury via activation of G-protein–coupled receptors.[1,2] There are 4 adenosine receptor subtypes, A_1 A_{2A}, A_{2B}, and A_3; these are ubiquitously expressed on almost all cell types.[2] Both under- and overactivation of adenosine receptors have been implicated in cardiovascular diseases, such as diabetes mellitus, heart failure, and hypertension.[3] Thus, for several decades, adenosine receptors have appeared as a tantalizing target for the treatment of cardiovascular disease.

Despite significant research over the past 25 years seeking to understand the roles of adenosine receptors in the cardiovascular system, it has been difficult to unmask their therapeutic potential. This is likely because of the widespread expression of adenosine receptors and the fact that adenosine is a potent agonist at all subtypes.[1,3] This has led to the realization that intervention may need to be directed against local paracrine adenosine systems, as global adenosine receptor targeting may not only block pathological processes but also prevent beneficial roles of adenosine.[1] The lack of specific tools to examine the roles of the different adenosine receptor subtypes has hampered progress.

In this month's *Hypertension*, Jackson et al[4] have taken the bit between their teeth and knocked out A_1 A_{2A}, and A_{2B} receptor subtypes in the Dahl salt-sensitive rat strain. This mammoth effort has resulted in a hypertensive model in which the role of each adenosine receptor subtype can be examined separately. The A_3 receptor subtype was not included in these investigations as it was suggested that there was little evidence pointing to a role for this subtype in the cardiovascular system. This may not be correct, as the A3 receptor has been shown to attenuate salt-sensitive hypertension.[5] The movement of genetic technology to rat strains is to be applauded, as findings in knockout mice can be confirmed in another species, and the impact of larger body size in terms of the reproducibility of findings is also advantageous. In the present study, Jackson et al[4] investigated the effect of salt intake (0.3%–8% NaCl) on arterial pressure, using radiotelemetry (gold standard). Baseline blood pressure was unaffected by A_1 or A_{2B} receptor deletion, but A_{2A} deletion increased basal arterial pressure in this model. It was found that each receptor subtype modulated arterial pressure salt sensitivity.

Importantly, these studies examined both males and females and identified marked sex differences in the contribution of each adenosine receptor subtype to salt-sensitive hypertension. The deletion of A_1 and A_{2B} receptors attenuated the salt-induced increase in arterial pressure in females, but not males, and this was associated with a reduced risk of stroke. In contrast, A_{2A} receptor deletion augmented the arterial pressure response to increased salt intake in both sexes, but more so in males than females. The magnitude of the difference in arterial pressure response being in the order of ≈10 to 30 mm Hg. These studies, for the first time, establish an important role for adenosine receptors in salt-sensitive hypertension, which may contribute to known sex differences in the regulation of arterial pressure.[6] However, sex differences in adenosine receptor expression were not observed for any receptor subtype in wild-type Dahl salt-sensitive rats and thus could not explain the differential responses to adenosine receptor subtype knockout. Other possible explanations, for the disparate responses to adenosine receptor knockout, may reflect unequal local adenosine generation or adenosine transporter expression between the sexes and these possibilities warrant further study.

There are many limitations associated with these studies. It could be suggested that a global knockout was not ideal. In that, it is possible that the responses were because of compensatory upregulation of remaining adenosine receptor subtypes, and some evidence for this was provided, which needs to be followed up in future studies. However, as with all good studies, this work has resulted in more questions than answers. Having demonstrated a robust phenotype for the different adenosine subtypes in the regulation of salt-sensitive hypertension, future studies could focus on the generation of conditional and tissue-specific knockouts to delineate the mechanisms via which adenosine and its receptors contribute to salt-sensitive hypertension. Efforts to develop compounds that modulate adenosine receptor function have been hindered by safety issues, resulting in inhibition or activation of unwanted adenosine-mediated effects.[7] These effects will need to be overcome if therapies to treat hypertension and cardiovascular disease are to make it to the market. Finally, it should be acknowledged that these finding may be specific to Dahl salt-sensitive rats, and role of adenosine receptor subtypes in other salt-sensitive and salt-independent models awaits examination (Figure).

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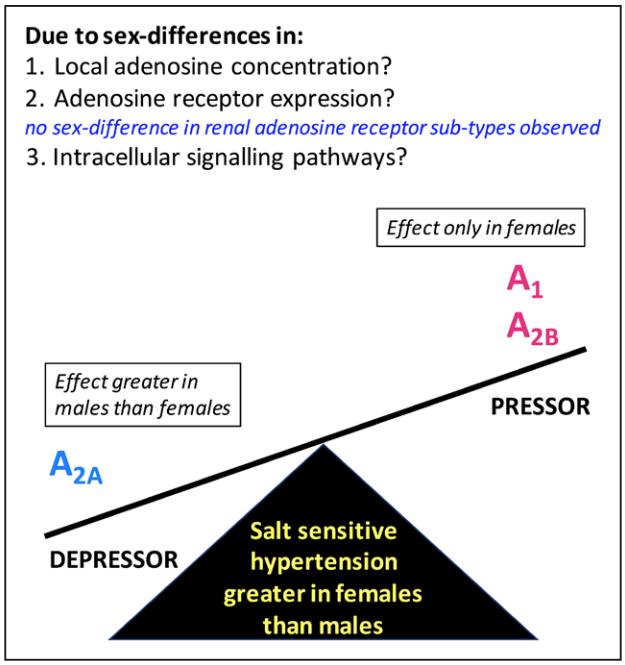

Figure. Schematic representation of the relative contribution of adenosine receptor subtypes to salt-induced increases in arterial pressure in male and female Dahl salt-sensitive rats. Illustrating the potential mechanisms by which adenosine signaling may contribute to the greater salt-sensitive hypertension observed in the females.

The clinical impact of this work has the potential to be far reaching in terms of understanding the causes of cardiovascular disease, identifying mechanisms underpinning sex differences in arterial pressure regulation and for the development of pharmacological treatments for cardiovascular disease. It is possible that only a subset of hypertensive patients, those that are salt sensitive, may be sensitive to adenosine-related effects. It is therefore significant that a recent study in humans demonstrated that the pressor response to high salt intake was greater in women than men.[8] Therefore, understanding sex differences in the role of adenosine in hypertension is of potential clinical relevance.

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Disclosures

None.

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