Council's Corner: Hypertension Issues - a personal View

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Protective Arm of Renin-Angiotensin System: Possible New Drug Target - from Inhibition to Regulation of Renin-Angiotensin System

The renin-angiotensin system (RAS) plays a role not only in blood pressure regulation, but also in the cardiovascular system. The development of drugs for hypertension and other cardiovascular diseases has been largely dominated by inhibitors of the angiotensin-converting enzyme (ACE)/angiotensin II/angiotensin type 1 (AT1) receptor axis as the classical RAS. Angiotensin II binds two major receptors, the AT1 receptor and type 2 (AT2) receptor. It has been recognized that AT2 receptor activation not only opposes AT1 receptor actions, but also has unique effects beyond inhibitory crosstalk with AT1 receptor signaling. From this point of view, AT2 receptor agonists such as compound 21 have been developed and are expected to be useful agents for improving various pathological disorders. Recent experimental studies have also demonstrated the existence of novel pathways beyond the classical actions of RAS. Angiotensin-(1-7) is produced from angiotensin I or angiotensin II by the catalytic activity of angiotensin-converting enzyme 2 (ACE2), and the Mas receptor has been identified as the binding protein mediating the inhibitory actions of angiotensin-(1-7) on angiotensin II-mediated AT1 receptor actions. A new axis of RAS, the ACE2/angiotensin-(1-7)/Mas axis, has been highlighted as the counteracting partner of the ACE/angiotensin II/AT1 receptor. Moreover, it is reported that angiotensin-(1-7) can act as an endogenous ligand with AT2 receptor selectivity over the AT1 receptor. These results support the concept that interruption of crosstalk of various angiotensin receptors could determine and orient pathological states, resulting in the onset of cardiovascular diseases. Moreover, angiotensin II mediates various effects through complex signaling pathways on binding to its G-protein-coupled receptors (GPCRs), the AT1 receptor and AT2 receptor. These receptors are regulated by GPCR-interacting proteins such as AT1 receptor-associated protein (ATRAP), ARAP1 (AT1 receptor-associated protein) and AT2 receptor-interacting protein (ATIP). The newly discovered angiotensin-(1-12), which is cleaved from angiotensinogen by a yet-to-be-defined non-renin enzyme, is converted to angiotensin II largely by chymase, and numerous studies have suggested that there exist other proteases capable of cleaving angiotensin substrate. Other angiotensin peptides such as angiotensin A and alamandine are attributable to substitution of aspartic acid with alanine in position 1. The new peptide alamandine differs from angiotensin-(1-7) only by the presence of an alanine residue. Another intriguing finding of the present investigation is the connection of alamandine to the family of Mas-related G-protein-coupled receptors (MrgD).

Further elucidation of the regulatory mechanisms of the functions of RAS beyond the classical ACE/angiotensin II/AT1 receptor axis could provide possibilities for the development of novel drugs that regulate RAS in a more sophisticated manner rather than inhibiting RAS, thereby treating hypertensive patients and achieving cardiovascular risk reduction more efficiently.

REFERENCES:

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