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DOI: 10.30824/1906-14

My views on Hypertension

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Not surprisingly, my daily work as a pharmacologist and basic scientist has a major impact on my view on hypertension. As a pharmacologist, my interest is primarily the treatment of hypertension: the major advances in anti-hypertensive treatment over the last ~ 5 decades, the still insufficient treatment options for certain patient groups such as patients with resistant hypertension or women with preeclampsia and, consequently, the identification of novel drug targets. The focus of my own research is the angiotensin AT_2-receptor (AT_2R), which mediates tissue protective actions and which in many instances is a counter player of the AT_1-receptor [1].

Working with this receptor, which is stimulating endogenous protective mechanisms (including lowering of blood pressure), made me aware that the common approach for identifying new drug targets for the treatment of hypertension and other diseases is usually following a certain concept: In most cases, the starting point in drug discovery is the investigation of a pathomechanism, which the new drug is supposed to inhibit or interrupt. All currently approved drugs interfering with the renin-angiotensin-system (RAS) work according to this principle.

However, pharmacological interference in disease can also consist in strengthening endogenous mechanisms, which naturally counteract the disease mechanisms. For example, a new area in cancer therapy, immuno-oncology, is following this principle and has become one of the most promising and fruitful sources of new treatments – a fact that was recognised by the 2018 Nobel Prize in Medicine/Physiology [2].

In the treatment of systemic hypertension, the principle of reinforcing natural mechanisms is only rarely used. In contrast, in pulmonary hypertension, increasing the levels of the endogenous vasodilator nitric oxide (NO) is a common treatment approach, which is achieved by drugs such as phosphodiesterase-5 inhibitors (e.g. sildenafil), soluble guanylate cyclase stimulators or by direct application of NO [3].

Another example of a drug that stimulates an endogenous mechanism for therapeutic use are neprilysin-inhibitors, which are used in fixed combination with the ARB valsartan to prevent degradation and thereby increase levels of the protective natriuretic peptides [4]. These so-called ARNIs are approved for the treatment of chronic heart failure with reduced ejection fraction, but may also have potential for the treatment of hypertension [4]. Drugs for therapeutic use of what is now called "the protective arm of the RAS" are currently in preclinical and clinical development.

Such drugs comprise recombinant human ACE2, the enzyme which is responsible for synthesis of the protective angiotensin fragment angiotensin[1-7], as well as agonists for the AT_2-receptor and the receptor for angiotensin[1-7], MAS[5].

The potential of these drugs for the treatment of systemic hypertension is not clear yet. Preclinical experiments point to the fact that they may only be efficient in certain patient groups such as obese patients or women with preeclampsia, or that only their central effects may be strong enough for a clinically relevant anti-hypertensive effect [6–8]. But the fact that these drugs generally stimulate mechanisms of regeneration and repair seems – according to preclinical evidence - to translate into a significant attenuation of end-organ damage related to hypertension and also diabetes, which may be a significant advantage of these drugs [9].

Therefore, my personal, "pharmacology-flavoured" view on hypertension is that in order to overcome the remaining unmet medical needs such as resistant hypertension, hypertension in preeclampsia or hypertension-related end-organ damage, the approach for finding novel treatments may have to be widened and in addition to inhibition of pathomechanisms also include the search for endogenous systems, which can be used therapeutically by pharmacological reinforcement.

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