

## Bradykinin in the Treatment of Arterial Hypertension: Friend or Foe?

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**T**he renin-angiotensin-aldosterone (RAA) axis and the sympathetic nervous system are the basic mechanisms of hypertension. Angiotensin II has a vasoconstrictive action, causes target organ lesions, promotes atheromatosis and arteriole remodelling, and increases catecholamine release and sympathetic nervous system activity.<sup>1,2</sup> Similarly, aldosterone mimics the action of angiotensin II and catecholamines. For these reasons, the RAA system is the main target of our therapeutic interventions for hypertension. Angiotensin-converting enzyme (ACE) inhibitors were the first group of medications with this action. However, apart from blocking the production of angiotensin II, they also cause changes in the production of other vasoactive substances, such as bradykinin, which is considered responsible for the main side effects of these drugs. Bradykinin is a small vasodilatory peptide, with autocrine and paracrine properties, which stimulates the release of endothelial vasodilatory agents and prostaglandins.<sup>3</sup> It is liberated together with lys-bradykinin from kininogen, with the assistance of proteases called kallikreins. Apart from its vasodilatory action and the relaxation of vascular smooth muscle fibres, it also plays an important part in the pathological mechanisms of inflammation, in the production of other vasoactive substances, and in the insulin-dependent transportation and metabolism of glu-

cose. Its half-life is very short, about 15 seconds. Bradykinin is catabolised mainly via ACE. Other degradation pathways are carboxypeptidase-related ACE, aminopeptidase P, carboxypeptidase, dipeptidyl peptidase IV, endothelin converting enzyme, neprilysin, propyl oligopeptidase, and the neutral endopeptidase that is connected to the membrane.

Bradykinin acts mainly via two membrane receptors, B1 and B2. B2 is the receptor via which the action of bradykinin is mainly expressed in the cardiovascular system, whereas the B1 receptor is expressed mainly under pathological conditions that are related to inflammation and tissue damage. The antihypertensive action of bradykinin is exerted mainly via the B2 receptor and only in special circumstances via B1.<sup>4,5</sup> There is also a B3 receptor, which causes bronchospasm,<sup>6</sup> and a B4, which is mainly expressed in the oesophagus.<sup>7</sup>

Although bradykinin's contribution to arterial hypertension appears to be significant and its action is involved in the RAA-axis pathways, in clinical practice drug therapies act on it only indirectly and no interventions have been developed that are deliberately aimed at the kinins and their receptors.

### The role of bradykinin in blood pressure regulation

Bradykinin is a basic vasoactive peptide

of the kinin-kallikrein system that is involved in the regulation of blood pressure as well as of blood flow to the body's vital organs.<sup>8</sup> It has been shown in previous studies that bradykinin administration not only causes vasodilation, but also affects blood pressure in other ways, i.e. by increasing the elimination of water and sodium from the organism.<sup>9</sup> More specifically, infusion of bradykinin in the renal artery causes diuresis and natriuresis via an increase in blood flow to the kidney, mainly through the release of prostaglandins and nitric oxide (NO).<sup>10,11</sup> In contrast, continuous administration of bradykinin to animals prevents the increase in systemic and renal vascular resistances that follows the administration of angiotensin II.<sup>12</sup>

### Study of the effect of bradykinin on arterial hypertension

Bradykinin is difficult to study, because it is mainly a tissue hormone that has low plasma concentrations and an extremely short half-life. However, there appear to be changes in its rate of production or metabolism that are involved in the pathophysiology of hypertension. In experimental models, it appears that the degradation of bradykinin to Bk-(1-5) and Bk-(1-7) in the aorta of hypertensive animals is elevated, perhaps because of the increased action of ACE. Thus, various types of hypertension are considered to be associated with changes in the kinin profile.<sup>13</sup> It has been reported that bradykinin production in arterial hypertension – at least at the level of the kidneys – is reduced, leading to sodium retention.<sup>14</sup> In addition, bradykinin antagonism causes an increase in blood pressure in both normotensive and hypertensive rats.<sup>15,16</sup>

Transgenic mice that overexpress the bradykinin B2 receptor show a significant reduction in blood pressure.<sup>17</sup> In contrast, B2 receptor knock-out mice initially show a small increase in blood pressure, which becomes very high when they are given a high-salt diet.<sup>18,19</sup> In addition, mice who have undergone genetic disruption of the B2 receptors (Bk2r -/-) have higher than normal blood pressure, while this can protect against the development of mineralocorticoid hypertension in experimental animals.<sup>20</sup>

Previous studies suggest that a reduction of the transcription of the bradykinin B2 receptor via the B2R 258C allele can lead to a reduction in baroreceptor sensitivity through a reduction in bradykinin activity.<sup>21</sup> In addition, the B1 receptor polymorphism BE1 +9/+9 is associated with increased vascular resistances<sup>22</sup> and affects the vasodilation caused by ACE in-

hibitors via the B2 receptor.<sup>23</sup> Some other polymorphisms of the same receptor (e.g. -58C) appear to increase the cardiovascular risk in hypertensive patients.<sup>24</sup>

However, it appears that bradykinin not only exerts a protective effect against hypertension *per se*, but also confers protection on the target organs afflicted by it. More specifically, it increases myocardial blood flow, improves cardiac metabolism, and probably promotes the development of the myocardial capillary net. Kinins are believed to exert a protective effect on the myocardium, mainly through activation of the B2 receptor.<sup>25,26</sup> In addition, bradykinin protects against oxidative stress and consequent endothelial cell senescence.<sup>27</sup> An increase in age and, by extension, vascular senescence is associated with a reduction in the number of bradykinin receptors and a reduced response of NO to bradykinin.<sup>28,29</sup>

More generally, the protective action of bradykinin is not only related to hypertension, but is also involved in other clinical conditions, such as acute myocardial infarction,<sup>30</sup> via activation of the B2 receptor, and it is to this that the beneficial effects of bradykinin on the cardiovascular system are mainly attributed.

### Bradykinin and drugs for the RAA axis

We know that part of the antihypertensive and cardioprotective action of ACE inhibitors is the result of the reduced bradykinin degradation those drugs cause, leading to an increase in bradykinin levels.<sup>31,32</sup> However, bradykinin's part in the therapeutic effect of ACE inhibitors has been overlooked in favour of its contribution to side effects, namely coughing and angioedema in response to the decrease in bradykinin degradation.<sup>33</sup>

The therapeutic effects of ACE inhibitors are due in part to the action of bradykinin, mainly on the B2 receptors. However, it is difficult to interpret them solely in terms of bradykinin's vasodilatory action. The antihypertensive action of ACE inhibitors has been found to decrease dramatically following the administration of B2 antagonists.<sup>34</sup> There also appears to be a direct interaction between the catalytic action of ACE and the B2 receptor.<sup>35</sup>

As mentioned above, ACE inhibitors also cause inhibition of bradykinin degradation to inert substances. Blocking the B2 receptors (e.g. with Hoe 140 or icatibant) cancels the antihypertensive and antifibrotic action of ACE inhibitors in experimental models, as well as their protective effect against left ven-

tricular hypertrophy. Administration of ramipril to hypertensive rats protects against the development of left ventricular hypertrophy, in both doses that have an antihypertensive effect and in lower doses, but the protection is lost when a selective B2 receptor blocker, Hoe 140, is coadministered.<sup>36,37</sup> This demonstrates that the action of bradykinin plays an important role in the prevention of left ventricular hypertrophy in hypertension, probably via the action of NO and PGI<sub>2</sub> on cell proliferation and increase. On the other hand, angiotensin-(1-7), whose production is increased by ACE inhibitors, also reinforces the vasodilatory action of bradykinin in hypertensive rats.<sup>38</sup>

Similarly, the renin inhibitor aliskiren appears to increase the tissue deposition of bradykinin, although it has not been determined so far whether part of the therapeutic effect of aliskiren is due to bradykinin.<sup>39</sup>

### Future prospects

Disturbances of the action and the metabolism of bradykinin play an important role in arterial hypertension. Furthermore, it is responsible for part of the beneficial properties of therapeutic modalities such as ACE inhibitors. However, the increase in bradykinin levels that they cause may lead to adverse effects—mainly via the B1 receptors that activate the inflammation cascade—that warrant the interruption of treatment. Possible selective activation of only the B2 receptors could provide the beneficial effects of bradykinin while avoiding the side effects. Recently, a bradykinin analogue has been created—NG 291 (Hyp3, Thi5 NChg7, Thi8-bradykinin)—that has the properties of a B2-selective agonist. It is more stable than bradykinin, with a longer half-life and much greater resistance to proteolytic enzymes,<sup>40</sup> and has been used successfully in animal models.<sup>30</sup> It is likely that the future will open the way to the use of such substances in clinical practice.

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