Journal of the American Society of Hypertension ■(■) (2018) 1–8

Research Article

A proposed mechanism for the Berecek phenomenon with implications for cardiovascular reprogramming

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Manuscript received March 12, 2018 and accepted June 15, 2018

Abstract

Berecek et al reported in the 1990s that when spontaneously hypertensive rat (SHR) mating pairs were treated with captopril and the resulting pups were continued on the drug for 2 months followed by drug discontinuation, the pups did not develop full blown hypertension, and the cardiovascular structural changes associated with hypertension in SHR were mitigated. The offspring of the pups also displayed diminished hypertension and structural changes, suggesting that the drug therapy produced a heritable amelioration of the SHR phenotype. This observation is reviewed. The link between cellular renin angiotensin systems and epigenetic histone modification is explored, and a mechanism responsible for the observation is proposed. In any case, the observations of Berecek are sufficiently intriguing and biologically important to merit re-exploration and definitive explanation. Equally important is determining the role of renin angiotensin systems in epigenetic modification. J Am Soc Hypertens 2018;■(■):1–8.

Keywords: Angiotensin II; epigenetic; intracrine; reprogramming.

Introduction

Beginning in 1993, Berecek et al reported a series of observations on spontaneously hypertensive rats (SHRs) treated *in utero* with the angiotensin converting enzyme inhibitor (ACEI) captopril.[1–7] When SHR mating pairs were treated with captopril and the resulting pups were continued on the drug for 1 or 2 months followed by drug discontinuation, the pups did not develop full blown hypertension and SHR cardiovascular structural changes were mitigated.[1–5] In these animals, off-captopril blood pressure was generally higher than on-captopril pressures and Wistar Kyoto rat (WKY) blood pressure, but lower than SHR pressure.[5] The sensitivity of these offspring to centrally administered (intracerebroventricular [ICV]) angiotensin II, as assessed by enhanced drinking behavior, was also diminished.[1] Surprisingly, the offspring of the pups also displayed diminished hypertension and structural changes suggesting that the drug therapy produced a heritable amelioration of the SHR phenotype.[1,5] Because short-term administration of captopril had been shown in another model to lead to later downregulation of relevant cardiovascular genes, one of the initial explanations for the Berecek findings was that captopril therapy had affected gene expression in a heritable, likely epigenetic, fashion.[5,8] Downregulation of central nervous system and/or renal angiotensin II type I receptors (AT1Rs) and changes in vascular and/or neuronal structure were offered as possible explanations.[1–7] This ability of short-term captopril therapy to produce apparently heritable phenotypic changes will here be referred to as the Berecek phenomenon, and it will be argued that the phenomenon does not primarily result from epigenetic mechanisms or changes in the brain, cardiovascular, or renovascular structure, although these alterations participate in the responsible physiological mechanism.[1–11]

Before these reports from Berecek et al, others had shown that renin angiotensin system (RAS) interruption early in the life of the SHR, before fixed cardiovascular structural changes had occurred, could provide long lasting protection from hypertension and from cardiovascular structural alterations after drug discontinuation.[9–11] The Berecek experiments were different in that they involved *in utero* exposure to captopril, and they also examined effects on the F2 generation. Of note, another group subsequently produced transient RAS interruption in postnatal

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1933-1711/$ - see front matter
https://doi.org/10.1016/j.jash.2018.06.009

SHR (albeit on a somewhat different time table from Berecek) with A-81988, a high-affinity angiotensin AT1R blocker (ARB), and found that short-term drug administration mitigated blood pressure rise and cardiovascular structural changes even after drug discontinuation but did not prevent hypertension in the F1 generation; hypertension was actually worsened in male pups.[12] Moreover, sensitivity to ICV angiotensin II was not diminished once the ARB was stopped in the treated animals. However, this sensitivity was reduced during ARB administration indicating that the drug could access at least some relevant brain areas. Similarly, the ARB is well absorbed from the gut and actually worsened hypertension in male pups and so it likely could access some relevant sites affecting a future fetus.[12]

RAS Memory

The Berecek phenomenon is an early example of what might be called RAS memory (RASM). In 1963, Dickinson and Lawrence demonstrated that the administration of subpressor doses of angiotensin II to rabbits led to the development of hypertension over several days, the animals eventually responding to the peptide based on prior administration of the agent.[13] The tentative explanation proposed for this ''autopotentiation'' was induction of cerebral vasoconstriction by subpressor doses of angiotensin II leading to dysregulation of the medullary vasoconstriction center. This was likely the first of several examples of RASM such as the studies of Harrap et al and Morton et al, with the Berecek observations following later.[1–11] More recently, other examples consistent with RASM have been reported. For example, Siragy et al demonstrated that hyperglycemia upregulated renal aldosterone synthase, and this effect was prevented by the administration of an ARB.[14] One week of normoglycemia reduced renal aldosterone synthase, but the hyperglycemia-induced increase was only reduced by half, indicating a long-term memory effect of the original insult. Johnson et al treated rats with subpressor doses of angiotensin II either subcutaneously or ICV, some of the animals also being coadministered ARB ICV.[15] After a 1-week rest period, a pressor dose of angiotensin II was administered. The subsequent blood pressure response was augmented by prior pretreatment with subpressor doses of angiotensin, an effect which was prevented when an ARB had been administered ICV with the subpressor angiotensin II. Subpressor angiotensin II upregulated RAS components AT1R, AT2R, angiotensin converting enzyme (ACE), ACE 2, mineralocorticoid receptor, and aldosterone synthase in lamina terminalis (LT). Subsequent pressor doses of angiotensin II led to more robust augmentation of these RAS components, as well as a greater upregulation of LT renin and angiotensinogen in angiotensin II pretreated as compared to control animals.[15] Collectively, these observations suggest a feedforward RAS-mediated form of RASM. Johnson suggested that angiotensin II–induced potentiation was the result of brain Hebbian neuroplasticity possibly associated with epigenetic changes.[15,16] Finally, Harrison et al have described a complex immunological memory mechanism that involves an angiotensin II–induced dendritic cell accumulation of isoketal protein adducts that serve as neoantigens and are associated with dendritic cell cytokine secretion. Adoptive transfer of these dendritic cells into naïve animals render the animals susceptible to subpressor doses of angiotensin II. These angiotensin II–exposed dendritic cells also support the proliferation of T-cells derived from animals that had been previously infused with angiotensin II.[17,18]

Intracrine Memory

More than 30 years ago, this laboratory began investigating the intracellular actions of angiotensin II and then developed the concept of intracrine peptide action, meaning the intracellular actions of an extracellular signaling protein either in its cell of synthesis or in a target cell after internalization.[19–23] In specific cases, intracrine internalization by target cells can be mediated by receptor internalization, nonreceptor-mediated mechanisms, or by intercellular trafficking in exosomes. A surprisingly large number of peptides act in an intracrine fashion and included among these are hormones, growth factors, cytokines, enzymes, and DNA-binding proteins, among others. Common functionalities among these factors led us in 1999 to suggest general principles of intracrine action including the notion of intracrine memory or intracrine differentiation.[19,20] Because many intracrines can upregulate their own synthesis or the synthesis of components of their signaling systems, they have the capacity to establish long-lived self-sustaining positive feedback loops. This upregulation in many cases involves intracellular intracrine action. Early on, we showed high-affinity angiotensin II receptors on hepatic nuclei and demonstrated that angiotensin II binding to these receptors was associated with increased RNA synthesis.[21–23] Others then demonstrated that when applied to isolated hepatic nuclei, angiotensin II directly upregulates transcription of angiotensinogen, renin, and platelet-derived growth factor. These, and similar observations, led us to postulate RAS positive feedback loops involving some intracellular RAS (iRAS) action. The observations of Johnson noted previously demonstrating upregulation of multiple RAS components and related receptors provide more recent support for the existence of these feedforward loops, whether they involve intracellular peptide action or not. In regard to the Berecek phenomenon, early on, we also identified chromatin angiotensin II receptors, and binding of angiotensin II to these sites altered chromatin conformation and susceptibility to micrococcal nuclease. These results are consistent with changes in chromatin structure affecting gene transcription and/or producing epigenetic