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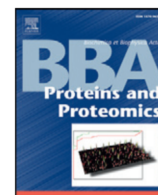

Review

The catalytic function of renalase: A decade of phantoms☆,☆☆

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ABSTRACT

Ten years after the initial identification of human renalase the first genuinely catalytic substrates have been identified. Throughout the prior decade a consensus belief that renalase is produced predominantly by the kidney and catalytically oxidizes catecholamines in order to lower blood pressure and slow the heart has prevailed. This belief was, however, based on fundamentally flawed scientific observations that did not include control reactions to account for the well-known autoxidation of catecholamines in oxygenated solutions. Nonetheless, the initial claims have served as the kernel for a rapidly expanding body of research largely predicated on the belief that catecholamines are substrates for this enzyme. The proliferation of scientific studies pertaining to renalase as a hormone has proceeded unabated despite well-reasoned expressions of dissent that have indicated the deficiencies of the initial observations and other inconsistencies.

Our group has very recently identified isomeric forms of β-NAD(P)H as substrates for renalase. These substrates arise from non-specific reduction of β-NAD(P)$^+$ that forms β-4-dihydroNAD(P) (β-NAD(P)H), β-2-dihydroNAD(P) and β-6-dihydroNAD(P); the latter two being substrates for renalase. Renalase oxidizes these substrates with rate constants that are up to 10^4-fold faster than any claimed for catecholamines. The electrons harvested are delivered to dioxygen via the enzyme's FAD cofactor forming both H_2O_2 and β-NAD(P)$^+$ as products. It would appear that the metabolic purpose of this chemistry is to alleviate the inhibitory effect of β-2-dihydroNAD(P) and β-6-dihydroNAD(P) on primary metabolism dehydrogenase enzymes. The identification of this genuinely catalytic activity for renalase calls for re-evaluation of much of the research of this enzyme, in which definitive links between renalase catecholamine consumption and physiological responses were reported.

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1. Introduction

At the time of publication of this review, renalase has been known of and studied for a decade. During this period a clear divergence in the literature pertaining to renalase has developed. One line of investigation has attempted to establish and defend a link between renalase activity and catecholamine neurotransmitter oxidation in blood [1–5]. Another set of articles describes skepticism of this link and has offered well-reasoned arguments and experimental evidence that undermine it [6–10]. The preponderance of the renalase literature, however, pivots from passive acceptance of the catalytic link to catecholamines in blood and has pursued physiological consequences and correlations as indirect evidence of function (for a recent comprehensive review and analysis of such findings see Malyszko et al. [10]).

The scientific conjecture surrounding renalase has led to an exponential accumulation of research articles and reviews since its discovery in 2005. The proliferation of renalase articles is founded on early reports that claim the protein is secreted by the kidney to lower blood pressure and slow heart rate by catabolizing circulating catecholamines, chiefly epinephrine and dopamine [11,12]. However, in vitro enzymological investigations of renalase chemistry have generally failed to observe activity with catecholamines (or any other substrate) [9,13,14] and links between this proposed chemistry of renalase and its physiological function(s) have remained diffuse, often contrary and/or tenuous. This review attempts to offer a corrective summary of the renalase literature that is presented in the light of newly identified substrates for this

Abbreviations: HPLC, high performance liquid chromatography; FAD, flavin adenine dinucleotide; β-NADPH, reduced nicotinamide adenine dinucleotide phosphate; β-NADH (4DHNAD), reduced nicotinamide adenine dinucleotide; β-NAD, oxidized nicotinamide adenine dinucleotide; 2DHNAD, 2-dihydronicotinamide adenine dinucleotide; 6DHNAD, 6-dihydronicotinamide adenine dinucleotide; NMR, nuclear magnetic resonance; CD, circular dichroism.

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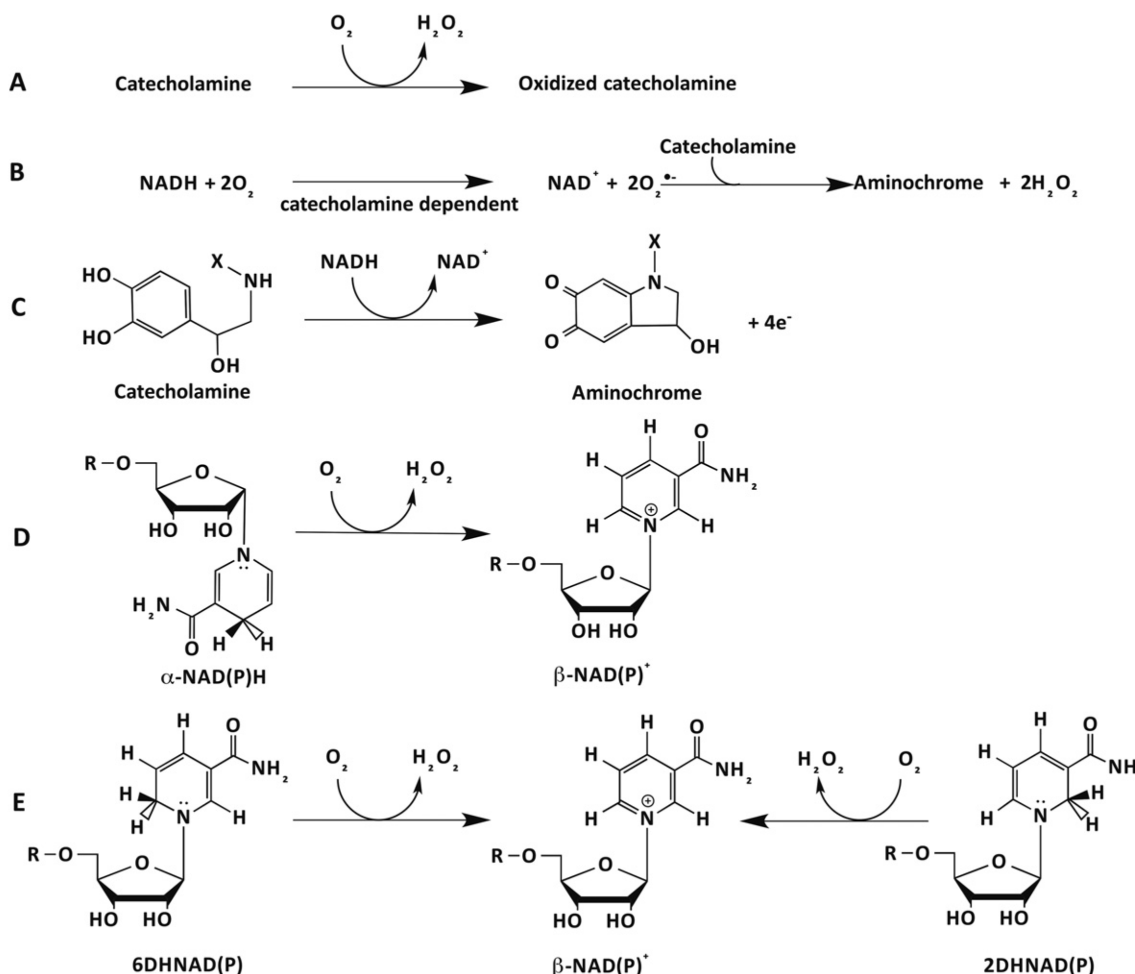
enzyme. It is not intended to be a comprehensive chronology as recent scholarly synopses of the reported physiological and biochemical observations for renalase are available [10,15,9].

2. Status quo

The current majority belief for the catalytic function of renalase is unsupported by experimental observation. The context for its role in nature was set askew by the very first observations made with this protein and these misconceptions continue to permeate the literature. The initial publication describing renalase claimed both to discover the enzyme and its catalytic function, a remarkable feat given a near infinite number of possibilities for potential substrates. This initial notion, that renalase is an enzyme/hormone that suppresses vascular tone, has largely confined the search for its catalytic function to the blood where, as it transpires, it is highly unlikely that renalase has a catalytic role.

Renalase was identified by the Desir nephrology group at Yale School of Medicine. In the first report, renalase was proposed to be a kidney-derived hormone that consumes neurologically active catecholamines [11]. The partial basis for this assertion was that the renalase primary structure resembled (albeit poorly) that of monoamine oxidases (MAOs). When tested for activity with a number of catecholamines and primary amines using a generic Amplex Red hydrogen peroxide (H_2O_2) detection assay, exceedingly low rates of H_2O_2 evolution were detected. The putative catecholamine substrates yielded 5–7-fold more H_2O_2 in the presence of renalase than did the primary amines and this was the basis for the substrate(s) identification. The difficulty with this claim was that no controls for (facile) autoxidation of these molecules were reported (Scheme 1A). This early assertion was then modified in subsequent reports to include NAD(P)H as a cosubstrate and it was proposed that the catecholamine substrate was oxidized by two electrons and cyclized to form molecules known as aminochromes that are neurologically inactive (Scheme 1B & C) [1]. This was an unprecedented reaction in which an obligate two-electron reductant was required to oxidize the catechol by two-electrons. The stoichiometry of this transformation was not demonstrated and once again appropriate controls for the proposed chemistry were not reported [3].

The known propensity for autoxidation of catecholamines in the presence of molecular oxygen [16–18] dictates that control reactions must be employed and most particularly when the reported activity is low. Moreover, the reduction potential differences for the redox active molecules in the reaction (NADH vs FAD, $\Delta E° \sim 180$ mV; NADH vs O_2, $\Delta E° \sim 1130$ mV; catechol vs O_2, $\Delta E° \sim 430$ mV) would yield non-specific production of H_2O_2 and superoxide from flavin hydroquinone autoxidation [19] and catechol autoxidation [20,21] (see red species in Scheme 2). Non-specific production of such powerful oxidants would then promote further oxidation of catecholamines. It is reasonable to conclude that the abundance of non-catalytic facile exothermic reactions possible in the presence of NAD(P)H, flavin adenine dinucleotide (FAD), catechol and O_2 demands the use of control reactions in order to establish catalysis. As such it appears at least probable that the foundational observations for renalase activity were scientifically deficient. The inadequacy of these initial activity claims has been clearly stated in the literature [6,14,22]. Moreover, in 2010, Pandini et al. reported that renalase yielded no added H_2O_2 production in the presence of



Scheme 1. Activities claimed for renalase in chronological order.

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