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Defective Wnt Signaling: A Potential Contributor to Cardiometabolic Disease?

Diabetes 2015;64:3342–3344 | DOI: 10.2337/db15-0822

COMMENTARY

Hypertension is a major public health problem associated with the increased risk for heart disease and stroke, leading causes of death worldwide. Despite recent treatment advances, hypertension remains present in approximately one-third of adults in the U.S. (1). The majority of hypertensive subjects are now obese and many suffer from insulin resistance, which exacerbates the risk for cardiovascular disease. While there is a well-established clinical association, the mechanisms linking hypertension and insulin resistance are not fully understood. A better understanding of hypertension mechanisms and related metabolic comorbidities will improve targeted treatment approaches and health-related outcomes in this disease.

Aberrant Wnt pathway signaling may be one such mechanism linking hypertension, obesity, and type 2 diabetes. The Wnt family of secreted glycoprotein ligands is highly implicated in embryonic development and regulates numerous physiological processes including body axis patterning and cellular adhesion, migration, and differentiation. As shown in Fig. 1, in the canonical pathway (2), Wnt proteins bind the Frizzled G-protein–coupled receptor and coreceptors, such as LDL receptor–related protein (LRP) 5 and 6. Activation of these receptors signals the intracellular phosphoprotein Dishevelled to traffic the destruction complex (including glycogen synthase kinase 3β [GSK-3β]) to the plasma membrane. This allows for stabilization and translocation of β-catenin to the nucleus to coactivate T-cell factor (TCF) and lymphoid enhancing factor transcription factors. Noncanonical Wnt pathways, which are independent of β-catenin, have also been identified and play a role in the regulation of cell polarity and intracellular calcium levels.

Defective Wnt signaling has been implicated in numerous conditions including cancer, aging, osteoporosis, Alzheimer disease, and cardiometabolic disease. Polymorphisms of LRP5 are associated with obesity (3), and LRP6 mutations result in coronary artery disease and features of metabolic syndrome, including hypertension in clinical studies (4,5). Carriers of LRP6 mutations also exhibit hyperinsulinemia and reduced insulin sensitivity, associated with diminished insulin signaling in skeletal muscle (6). Mutations in the transcription factor 7-like 2 gene also increase the risk for type 2 diabetes (7). In animal models, the Wnt/β-catenin signaling pathway has been shown to contribute to the modulation of insulin secretion, β-cell function, energy expenditure, and cholesterol metabolism in various tissues (8–11). While these findings suggest that the Wnt pathway is important in metabolic regulation, studies examining its importance to whole-body metabolism are limited. Furthermore, there is no information on the effects of Wnt signaling on blood pressure regulation and related mechanisms.

In this issue of *Diabetes,* Cheng et al. (12) determine the effects of central Wnt administration on blood pressure in well-established animal models of hypertension. Interactions between Wnt and insulin signaling pathways within the nucleus tractus solitarii (NTS), an autonomic brainstem region integral to cardiovascular control, were also examined. This study included normotensive Wistar Kyoto (WKY), spontaneously hypertensive (SHR), and fructose-fed rats. Animals received chronic 14-day intracerebroventricular infusion of vehicle, Wnt3a (a highly transforming Wnt protein), the LRP antagonist Dickkopf-1 (DKK1), or the GSK-3β inhibitor TWS119. Systolic blood pressure and heart rate were measured at baseline and during treatment by the tail-cuff method. Levels of insulin, nitric oxide, and insulin and Wnt signaling pathway components were determined in NTS tissue sections.

The findings from this study suggest that *1*) hypertension is associated with downregulation of canonical Wnt signaling pathways within the NTS, *2*) central infusion of Wnt3a lowers blood pressure and increases nitric oxide within the NTS of hypertensive rats through LRP coreceptor activation, *3*) Wnt3a infusion enhances

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See accompanying article, p. 3413.

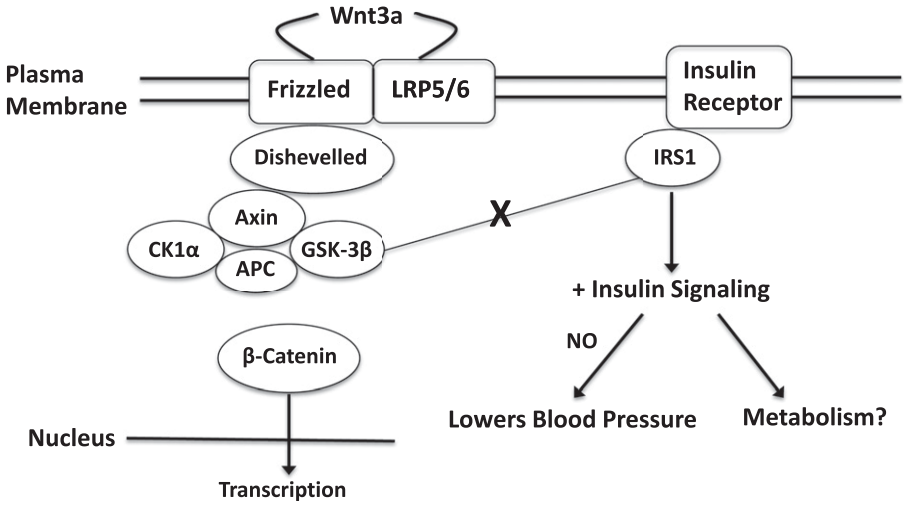

Figure 1— Proposed mechanism by which central Wnt3a administration lowers blood pressure in animal models of hypertension. Within the NTS, Wnt3a initiates canonical signaling by binding the Frizzled receptor and LRP coreceptor. This signals the phosphoprotein Dishevelled to traffic the destruction complex (Axin, CK1α, APC, GSK-3β) to the plasma membrane, allowing for translocation of β-catenin to the nucleus to activate transcription. The study by Cheng et al. (12) provides new evidence for cross talk between Wnt activation and insulin signaling within the NTS. Inhibition of GSK-3β activity by central Wnt administration prevents serine phosphorylation of IRS1. This allows IRS1 to undergo insulin-induced tyrosine phosphorylation and to activate subsequent insulin signaling pathways including nitric oxide (NO) release. While a beneficial blood pressure–lowering effect of central Wnt3a administration was shown, the impact of the activation of these pathways on metabolism remains unknown.

phosphorylation of Wnt and insulin signaling components within the NTS, and 4) Wnt3a-mediated blood pressure–lowering effects involve interruption of GSK-3β and insulin receptor substrate 1 (IRS1) interactions to promote activation of insulin signaling pathways. These findings provide new insight into the precise mechanisms and sites of action by which Wnt signaling may contribute to central cardiovascular regulation. The strengths of this study include the use of combined molecular biology and in vivo pharmacologic methods in two animal models of hypertension that are differentially driven by factors induced by genes versus environment. This suggests that aberrant Wnt signaling is a generalized phenomenon related to hypertension, which could be targeted regardless of underlying etiology. These studies also provide evidence for cross talk between Wnt and insulin signaling pathways within the brain for blood pressure regulation. Similar findings have been observed in skeletal muscle and preadipocytes (13,14), perhaps indicating that restoration of this pathway could serve to improve global cardiometabolic function.

This study raises several questions that necessitate further research. First, Wnt signaling pathways are expressed in multiple tissues and have pleiotropic effects. While central Wnt administration improves blood pressure, overactivation of this pathway promotes cardiac, vascular, and renal abnormalities. In fact, pharmacologic inhibition of Wnt signaling is proposed in the treatment of cardiac hypertrophy and renal injury (15,16). Central nervous system targeting of Wnt may therefore be necessitated in hypertension to avoid off-target effects in cardiovascular end organs. Second, as Wnt3a was administered via intracerebroventricular infusion, it is not clear whether other cardiovascular nuclei participated in the observed effects. Third, as SHR and fructose-fed rats exhibit insulin resistance, they provide ideal models to examine the effects of Wnt administration on insulin action. The ability of Wnt activation to enhance central insulin signaling pathways and nitric oxide release could positively impact metabolic function, particularly if drug administration reached hypothalamic sites of action. Finally, more information is needed on potential upstream mediators for Wnt effects on blood pressure in hypertension. The hypertension in SHR and fructose-fed rats is associated with the overactivation of the renin-angiotensin system. The prorenin receptor is increased in the NTS of hypertensive rats (17) and can serve as a cofactor for the Wnt receptor complex (18). Renin-angiotensin genes are also downstream targets of canonical Wnt signaling (19). The importance of these reciprocal interactions to blood pressure regulation is unclear.

Overall, the study by Cheng et al. (12) provides compelling evidence for a facilitatory relationship between Wnt and insulin signaling pathways within the central nervous system for blood pressure regulation. These findings improve our understanding of complex cardiovascular neural pathways and may provide a new link between hypertension and insulin resistance that could be targeted for treatment of cardiometabolic diseases.

Funding. A.C.A. and D.R. were supported by funding from the National Institutes of Health (K99 HL122507, P01 HL056693, and U54 NS065736).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

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