

# **High-Salt, Low-Potassium Diets May Increase Risk for Type 2 Diabetes via Marinobufagenin-Mediated Potentiation of Glucolipototoxicity in Pancreatic Beta Cells**

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## **Abstract**

Finnish epidemiology has linked high-salt diets to an increased risk for type 2 diabetes. Conversely, lower risk for diabetes has been observed in people consuming potassium-rich diets. Yet severe salt restriction has often been reported to impair insulin sensitivity, whereas a high salt intake often improves it, if only transiently. Hence, modulation of insulin sensitivity is not a likely explanation for the increased risk of diabetes associated with salty diets. There is however reason to suspect that high-salt, low-potassium diets might adversely affect pancreatic beta cell function. In salt-sensitive subjects, such diets induce the production of natriuretic factors – most notably marinobufagenin (MBG) – which achieve adaptive natriuresis via inhibition of renal tubular sodium pumps. However, MBG can also interact with certain isoforms of the sodium pump – those containing alpha-1 subunits – to transmit intracellular signals that, in some cells, induce oxidative stress, likely via activation of NADPH oxidase. It is notable that beta cells express the alpha-1 subunit of the sodium pump, as well as the other proteins known to be required for MBG-mediated intracellular signaling. Moreover, activation of NADPH oxidase in beta cells is now believed to play a key role in driving the cellular dysfunction and apoptosis induced by glucolipototoxicity during the onset of diabetes. It is therefore proposed that salty, low-potassium diets have the potential to impose an oxidative stress on beta cells via MBG-mediated activation of NADPH oxidase; this may exacerbate the oxidative stress imposed by glucolipototoxicity in pre-diabetics, potentially hastening beta cell failure.

## **High-Salt, Low-Potassium Diets May Increase Diabetes Risk**

In 2005, Finnish researchers examined subsequent incidence of type 2 diabetes in nearly 2,000 subjects who in 1982 or 1987 had received a physical exam, filled out a health/diet questionnaire, and had provided 24-hour urine samples; the sodium and potassium content of these urine samples had been measured. Diabetes developed in 129 of these subjects during roughly 18 years of follow-up. The researchers discovered that risk for diabetes was notably higher in the subjects whose 24-hour sodium excretion had been in the top quartile, relative to those in the other quartiles; after adjustments for a wide range of potentially confounding variables, such as BMI, exercise, and saturated fat intake, the hazard ratio for type 2 diabetes incidence was found to be 2.05 in the top quartile of sodium excretion vs the bottom 3 quartiles. A trend toward lower risk in the upper quartiles of potassium excretion did not achieve statistical significance. The authors noted that this was the first epidemiological study to attempt to correlate dietary sodium intake (as quantified most reliably by 24-hour sodium excretion) with subsequent risk for type 2 diabetes.<sup>1</sup>

Several years later, a different group of Finnish epidemiologists examined the impact of meat consumption on risk for type 2 diabetes in subjects enrolled in the Alpha-Tocopherol, Beta-Carotene

Cancer Prevention Study. They found that consumption of processed meat specifically was linked to increased diabetes risk after appropriate multivariate adjustments. Further analysis suggested to them that the sodium content of the processed meat may have been largely responsible for this association.<sup>2</sup>

Dietary potassium exerts a natriuretic effect, and is thought to counteract to some extent the pathogenicity of salt-rich diets. An analysis of data from the prospective Nurses' Health Study revealed that risk for onset of new diabetes was 0.62 in the upper quintile of estimated dietary potassium intake, relative to the bottom quintile.<sup>3</sup>

### **Modulation of Insulin Sensitivity is Unlikely to Explain this Effect**

It has previously been suggested that natural potassium-rich diets might aid insulin sensitivity because they are typically high in metabolizable anionic compounds that exert a systemic alkalinizing effect.<sup>4, 5</sup> However, a recently clinical study found that 3 months of supplementation with potassium bicarbonate, sufficient to alkalinize the urine and exert a favorable impact on calcium metabolism, had no impact on the insulin sensitivity (HOMA) of non-diabetic individuals over 50.<sup>6</sup> Hence, any impact of high dietary potassium on diabetes risk seems unlikely to reflect improved insulin sensitivity.

Analogously, a number – though not all<sup>7</sup> – clinical studies have found that a low-sodium diet tends to impair insulin sensitivity; conversely, increased insulin sensitivity has been observed when volunteers are switched to high-sodium diets.<sup>8-12</sup> Hormone-modulatory effects of sodium restriction – such as increased sympathetic activity and activation of the renin-angiotensin-aldosterone pathway – are suspected to play some role in this effect. Fortunately, the adverse impact of salt restriction on insulin sensitivity tends to wane markedly during subsequent weeks, and in any case is minimal when salt restriction is moderate.<sup>13</sup>

The proposition that salty diets increase diabetes risk, while potassium-rich diets decrease this risk, evidently requires evaluation in additional large prospective data bases before it can be taken as firmly established; nonetheless, the limited epidemiological evidence currently available appears to support this view. If we take this proposition as a given, what mechanism could explain it? The data cited above suggest that high-salt, low-potassium diets are not detrimental to insulin sensitivity, at least in the short term; indeed, high-salt diets may at least transiently improve the efficiency of insulin-stimulated glucose disposal.

### **Marinobufagenin May Induce Oxidative Stress in Pancreatic Beta Cells**

I wish to suggest that high-salt, low-potassium diets may increase diabetes risk in salt-sensitive subjects by increasing the production of endogenous digitalis-like substances – notably marinobufagenin (MBG) – which in turn acts directly on pancreatic beta cells to potentiate their susceptibility to the glucolipotoxicity that impairs beta cell function and precipitates onset of type 2 diabetes. In particular, I suggest that MBG does this by boosting NADPH oxidase-mediated oxidative stress in beta cells.

Much of the pathogenicity of high-salt diets is now thought to be mediated by endogenous digitalis-like substances – MBG and ouabain - produced in the brain and adrenal glands, which aid natriuresis via inhibition of sodium pumps (Na/K-ATPase) in renal tubules.<sup>14, 15</sup> A number of mechanisms aid appropriate natriuresis when individuals ingest a salt load; when these mechanisms are suboptimally effective –as they appear to be in many “salt-sensitive” individuals, sequential production of ouabain and

MBG, in the brain and adrenal gland, respectively, provides a back-up mechanism to insure adequate natriuresis. Unfortunately, the interaction of these hormones with sodium pumps in other tissues can exert adverse health effects. For example, MBG-mediated inhibition of sodium pumps in vascular smooth muscle can increase muscle tone, and may be largely responsible for the elevation of blood pressure evoked by salty diets in salt-sensitive humans and rodents. Remarkably, administration of antibodies to MBG exacerbates and prolongs the fluid retention induced by salty diets in salt-sensitive rodents – while eliminating the hypertensive response to such diets.<sup>16</sup>

MBG and ouabain may also exert hormonal effects on other tissues via their interaction with the sodium pump.<sup>14, 17-20</sup> Remarkably, these effects are seen at concentrations of these factors too low to notably impair the pumping activity of the pump; in effect, the sodium pump can act as a membrane hormone receptor for which MBG and ouabain serve as potent agonists. Interaction of MBG with sodium pumps containing alpha1 subunits elicits an intracellular signaling pathway that entails activation of Src, transactivation of the epidermal growth factor receptor (EGFR), and induction of oxidative stress.<sup>14</sup> There is reason to suspect that NADPH oxidase is a key mediator of this oxidative stress.<sup>21</sup> Rodent studies have provided cogent evidence that such signaling may mediate the left ventricular hypertrophy associated with chronic renal failure and induced by salty diets in salt-sensitive subjects - independent of any impact of salt on blood pressure.<sup>22, 23</sup> Moreover, it has been suggested that MBG-mediated oxidative stress in vascular endothelium may be partially responsible for the increased risk for heart attack and stroke associated with high-salt, low-potassium diets.<sup>21</sup>

There is growing evidence that activation of NADPH oxidase in pancreatic beta cells may be a key mediator of the glucolipotoxicity thought to precipitate beta cell failure during the induction of type 2 diabetes.<sup>24-28</sup> In this regard, Inoguchi and colleagues have recently demonstrated that oral administration of biliverdin – which, via its metabolite bilirubin, functions to inhibit certain isoforms of NADPH oxidase – can suppress onset of diabetes in db/db mice, a rodent model of obesity-linked type 2 diabetes.<sup>29</sup>

Pancreatic beta cells express sodium pumps that consume a high proportion of the ATP generated by these cells – and these pumps contain the alpha1 subunit.<sup>30, 31</sup> Hence, beta cells are potentially a target for the hormonal action of MBG. Moreover, beta cells also express other key proteins which transmit MBG signals intracellularly – notably Src, caveolin-1, and EGFR – as well as the Nox2 isoform of NADPH oxidase.<sup>27, 32-38</sup> Hence, it is reasonable to postulate that MBG has the potential to activate NADPH oxidase in beta cells. If so, this effect would likely complement the activation of beta cell NADPH oxidase induced by glucolipotoxicity, and thus presumably increase the propensity of beta cells to fail in the face of such toxicity.

This hypothesis could quite readily be tested by exposing primary pancreatic beta cells – or cell lines derived from such cells – to physiologically pertinent concentrations of MBG, and determining whether this activates NADPH oxidase in these cells or induces other intracellular signaling effects.

It should be noted, however, that angiotensin II, whose production is increased during severe salt restriction, can also impose an oxidative stress on beta cells via NADPH oxidase.<sup>24, 39</sup> Hence, even if salty diets do have the potential to hasten beta cell failure in pre-diabetics, it may not necessarily follow that severe salt restriction will be beneficial in this respect. Indeed, in the Finnish study linking salty diets to increased diabetes risk, the lowest risk for diabetes was seen in the second quartile of sodium excretion; risk in the first quartile was non-significantly higher.<sup>1</sup>

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