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Šoša, Ivan; Grubešić, Aron

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Putative hormone with anti-obesogenic and insulin-sensitizing effect

Ivan Sosa[1] and Aron Grubesic[2]

Abstract

It was confirmed that bone morphogenetic protein-9 (BMP-9), like insulin, improves glycemia in diabetic mice and regulates glucose metabolism in hepatocytes, which is why it is proposed as a candidate for the hepatic insulin-sensitizing substance (HISS). Regarding the fact that BMP-9 has a signaling pathway similar to other BMPs as well as insulin, it is expected that BMP-9 would also have certain effects on the liver. In our 2011 hypothesis, we aimed towards BMP-9 as a possible "hepatic insulin-sensitizing substance" (HISS) and in this article, we provide further evidence, derived from existing studies, suggesting that this putative hormone might in fact be none other than BMP-9.

Keywords

BMP-9, endothelium, NO

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Bone morphogenetic protein-9 (BMP-9) is a member of transforming growth factor beta (TGF-β) superfamily of cytokines that regulate cell growth and differentiation during embryogenesis. BMP-9 binds to hepatocytes and shows strong immunoreactivity in liver non-parenchymal cells, which corresponds with our attempt to investigate immunolocalization of BMP-9 in the human liver. Indeed in our 2011 hypothesis,[1] we aimed towards BMP-9 as a possible "hepatic insulin-sensitizing substance" (HISS) mainly due to experimental work of Lautt[2] and that of Alam and Sollinger.[3] Furthermore, this hypothesis had been supported and experimentally proven in 2008 by Caperuto et al.[4] It is interesting that Caperuto takes reference on insulin influencing the release of HISS (whatever it may be) through a mechanism which includes the creation of nitric oxide,[1,4] stimulated by acetyl choline. On this role as well as the role of NO as an intermediary in glucose regulation rather than as a new candidate molecule for HISS, Lautt and Caperut are in agreement. Even Lautt's opinion on the role of NO in glucose level regulation has not changed when considering his earlier papers.[2,5]

In addition to BMP-9's inhibition of gluconeogenesis, Cheng et al. have also established it to have an effect on the metabolism of lipids by changing the expression of key enzymes – malic enzyme (ME) and the fatty acid synthase (FAS).[6] From Chen's findings, and also according to Alamo et al., the effect of BMP-9 on glucose metabolism is similar to that of insulin. Its effect is only weaker in terms of gluconeogenesis, which is, it would seem the key metabolic link affected by NO derived from nitric oxide synthase 3 (NOS3) enzyme (endothelial NOS or eNOS).

The fact that the endothelial form of NOS is involved in glucose metabolism along with BMP-9 is indeed indicative. BMP-9 has for some time now been called a circulating vascular quiescence factor[7] and most BMPs are also attributed with a certain angiogenic effect of which Huylebrock wrote all the way back in 2007.[8] The key role of endothelia in-between HISS, insulin, gluconeogenesis, obesity, and type 2 diabetes should always be observed in relation with BMP-9, more so as it exercises most of its effect through the ALK1 receptor.[7] These

[1]Clinical Hospital Center Rijeka, Rijeka, Croatia
[2]Department of Internal Medicine, Clinical Hospital Center Rijeka, Rijeka, Croatia

Corresponding author:
Ivan Sosa, Clinical Hospital Center Rijeka, Kresimirova 42, Rijeka, 51000, Croatia.
Email: ivan.sosa@medri.uniri.hr

receptors, apart from activating SMAD phosphorylation as part of the BMP signal pathway[9] also incite endothelial migration and proliferation.

We, unfortunately, did not aim to document hypoglycemic effect of BMP-9 but rather relied upon observations of Chen et al., where BMP-9 inhibited gluconeogenesis and activated expression of pivotal enzymes in lipid metabolism after a single subcutaneous injection.

Considering the above stated as well as the mitogenic activity of the hepatocytes stimulated by insulin when reversing fibrosis due to porto-caval shunt, we believe that anti-obesogenic and insulin-sensitizing effect that Sansbury and Hill[10] have recently attributed to NO should not be seen monochromatically, more so as it has been becoming clear for years that this putative hormone might in fact be none other than BMP-9.

Declaration of conflicting interests

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