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Hypothesis

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Hepatoregenerative role of bone morphogenetic protein-9

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Summary

Bone morphogenetic protein-9 (BMP-9) is a member of the transforming growth factor beta (TGF-β) superfamily of cytokines, which regulate cell growth and differentiation during embryogenesis. Apart of that, the hypoglycemic potential of BMP-9 is of great interest. It has been confirmed that BMP-9, like insulin, improves glycemia in diabetic mice and regulates directional glucose metabolism in hepatocytes; therefore it is proposed to be a candidate hepatic insulin-sensitizing substance (HISS). In liver fibrosis, due to the portocaval shunt, insulin bypasses the organ and the liver undergoes atrophy. Parenteral administration of insulin reverses atrophy by stimulating mitogenic activity of the hepatocytes. Because BMP-9 has a signaling pathway similar to other BMPs and insulin, it is to be expected that BMP-9 has a certain regenerative role in the liver, supporting the above-mentioned is evidence of BMP-9 expression in Dissè's spaces and BMP-7's mitogenic activity in mucosal cells. However, further studies are needed to confirm the possible regenerative role of BMP-9.

key words: **liver organization • bone morphogenetic protein-9 • Insulin**

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HYPOTHESIS

We suggest that BMP-9 has a regenerative role in the human liver. In favor of its establishment in Dissè's spaces and supported additionally by presence of BMP-9's receptors on the surface of human hepatocytes, we have reason to believe that BMP-9 exerts the same effects on hepatocytes themselves [1]. Our hypothesis is additionally based on the fact that rhBMP-9 binds to human hepatoma cells and stimulates their DNA synthesis [2,3]. Properties that BMP-9 exerts locally and systemically resemble physiological effects of insulin [4–6], especially in protecting peripheral tissues in states of hyperglycemia such as diabetes.

EVIDENCE FOR THE HYPOTHESIS

Bone morphogenetic proteins (BMPs) are members of transforming growth factor beta (TGF-β) a superfamily of cytokines that regulate cell growth and, differentiation during embryogenesis. Some BMPs, such are BMP-2/4,-3, -5, -6 and -7, justify their name as they regulate skeletal tissue formation and repair [7–10]. BMP-2 is supplementally involved in formation of vascular calcifications [11], while BMP-7 deficiency plays a role in progression of chronic renal failure [12,13]. Another TGF-β superfamily member, growth differentiation factor 15 (GDF-15), although weak in osteogenic potential, has been implicated in playing an essential role in progression of congestive heart failure [12,14,15]. These facts open a new chapter on BMPs and their role in pathogenesis of human non-skeletal diseases. The mechanism of action of bone morphogenetic protein-7 (BMP-7) is most likely the one understood the best. Accordingly, anti-inflammatory action on intestinal mucosal cells (most likely suppressing interleukin-6 [IL-6]) is shown [16].

Two types of BMP receptors (BMPR) mediate activation of protein kinase and consecutive phosphorylation of amino-acids, phosphatidylinositol as 3-kinase and phospholipase C in insulin [17,18]. The receptors are commonly composed of 2 transmembrane chains. The various combinations of types of chains can generate a broad range of effects in response to the same ligand [4]. Phospholipase C generates inositol 1,4,5-triphosphate (IP3) and diacylglycerol (DAG) from phosphatidylinositol 4, 5-biphosphate [5]. IP3 is a universal calcium-mobilized second messenger, while DAG activates protein kinase C. Both paths aim to increase Ca^{2+} influx and/or uptake. The model of transmembrane receptors and phosphorylation of certain "second messengers" depicts the action of the BMP/BMPR system [19]. Just like other tissue-specific BMPs, the effect of BMP-9 depends on the receptor chains expressed by each target cell. Consequently, data suggest that BMP-9 is a potent alleviative of cartilage advance *in vitro,* and it has a significant role in forebrain embryogenesis, in cancer biology, in iron metabolism and in glucose homeostasis [17,20,21].

The first evidence of BMP-9 was found in the mouse liver, where it was expressed during embryonic development [22,23]. Further investigations revealed that BMP-9 binds on human hepatoma cells and primary rat hepatocytes, inducing a proliferative response in both cell lines [24]. Although BMP-9 was not detectable in rat hepatocytes, a high level of BMP-9 messenger RNA is expressed in non-parenchymal cells of the liver (ie, endothelial, Kupffer, and stellate cells). Since cells of the hepatic reticuloendothelial system showed high binding affinity for BMP-9, a possible autocrine-paracrine role is proposed for this morphogen in the liver [1].

This was supported by Chen et al., who found BMP-9 inhibits gluconeogenesis and activated expression of pivotal enzymes of lipid metabolism after a single subcutaneous injection of BMP-9 [25]. The hypoglycemic effect of BMP-9 was first established in transcription inhibition in rat hepatoma cells. Both BMP-9 and insulin regulate directional glucose metabolism in hepatocytes. Their effects, however, differ. While BMP-9 as potently as insulin regulates total glucose production, insulin's effect on gluconeogenesis is more potent [25]. BMP-9 has been demonstrated to improve glycemia in diabetic mice, which can be proven by *in-situ* exposition of hepatocytes to the combination of glucose and insulin and oral glucose in fasted rats [26], and is proposed as a candidate for the hepatic insulin-sensitizing substance (HISS).

The process of hepatic regeneration has evoked wide interest since antiquity. Despite many models of liver injury (eg, CCl_4), the most popular is partial hepatectomy introduced by Higgins and Anderson. Hepatic regeneration has been witnessed in various species, but the exact mechanism and control over liver growth are unclear [27–29]. It is proposed that regenerative capacities of the hepatocytes are dependent on the supply of oxygen and nutrients [30,31]. The liver lobule is divided into 3 zones (metabolic heterogeneity) [32]: zone I is the periportal part, which gets the maximum of oxygen and nutrients; zone II is the middle part of the liver lobule; and zone III surrounds the branches of hepatic vein and gets the minimum of oxygen and nutrients. Hepatocytes that are closer to the periportal zone have better regenerative abilities compared to those hepatocytes in the central zone. During liver regeneration, hepatocyte proliferation starts in the areas of the lobules surrounding the portal triads and then proceeds to the pericentral areas by 36 to 48 hours. Any explanation of this process has to take into account various blood-stream driven molecules: calcium, hepatocyte growth factor, epidermal growth factor, IL-6, transforming growth factor-alpha, and tumor necrosis factor-alpha [2,27]. Insulin and norepinephrine, with limited effect on DNA synthesis by themselves, are capable of altering growth factors induced liver regeneration [2]. The kinetics of both cell proliferation and the growth factors produced by proliferating hepatocytes suggest that hepatocytes provide the mitogenic stimuli leading to proliferation of the other cells.

Based on findings of the BMP-9's expression in the human liver, we hypothesize effects of BMP-9 to be dependent on blood supply (Cvijanovic et al.). It is crucial to distinguish whether the localization of this protein is zone dependent? If compared to the central zone, higher levels of the BMP-9's expression in periportal hepatocytes would indicate its possible hepatoregenerative role.

Our suggestion of BMP-9's wide employability is supported by previously established scientific knowledge. Thus, in orthopedics it needs to be applied in vast quantities, and in more adoptable quantities, it is active in soft-tissue locations - including the liver, nervous system and bone marrow. BMP-9 like insulin, but less potently, regulates directional

glucose metabolism in hepatocytes [25]. Postprandial action of BMP-9 needs to be proven more definitely. The high-throughput approach presented by Chen et al. is an extremely powerful tool that should help establishing possible therapeutic potential of BMP-9 in the treatment of type 2 diabetes [25,33].

Conclusions

The suggested work should expand our current understanding of BMPs' functions other than those concerning heading morphogenesis towards supporting tissue's formation [7–13]. The effect of BMP-9 suggests its importance other than merely a bone formation inducer, most obviously in metabolism of carbohydrates, but nonetheless, fats [6,25]. Such properties, in supporting tissues' organization could reform the clinical management of many musculoskeletal disorders, and its capability in differentiation of many other tissues warrants its popularity and attractiveness.

The expression of the BMP-9 was assessed in human liver. Precise determination of protein's expression is needed regarding zonal differences in normal and pathologically altered hepatocytes functions. Experimental study needs to be carried out in order to give rise to analysis of direct hepatoregenerative effect of BMP-9.

Therefore, our hypothesis predicts additional evidence to previously introduced ideas of BMP-9 as a local autocrine/paracrine factor in the liver or systemic protein with a possible effect on glucose sensitive peripheral tissues.

References:

1. Miller AF, Harvey SA, Thies RS, Olson MS: Bone morphogenetic protein-9. An autocrine/paracrine cytokine in the liver. J Biol Chem, 2000; 275(24): 17937–45
2. Fausto N, Laird AD, Webber EM: Liver regeneration. 2. Role of growth factors and cytokines in hepatic regeneration. FASEB J, 1995; 19(3): 1527–36
3. LaBrecque DR: The role of hepatotrophic factors in liver regeneration--a brief review including a preliminary report of the *in vitro* effects of hepatic regenerative stimulator substance (SS). Yale J Biol Med, 1979; 52(1): 49–60
4. Caperuto LC, Anhê GF, Cambiaghi TD et al: Modulation of bone morphogenetic protein-9 expression and processing by insulin, glucose, and glucocorticoids: possible candidate for hepatic insulin-sensitizing substance. Endocrinology, 2008; 149(12): 6326–35
5. Rodrigues MA, Gomes DA, Andrade VA et al: Insulin induces calcium signals in the nucleus of rat hepatocytes. Hepatology, 2008; 48(5): 1621–31
6. Saltiel AR, Kahn CR: Insulin signalling and the regulation of glucose and lipid metabolism. Nature, 2001; 414(6865): 799–806
7. Wang EA, Rosen V, D'Alessandro JS et al: Recombinant human bone morphogenetic protein induces bone formation. Proc Natl Acad Sci USA, 1990; 87(6): 2220–24
8. Cook SD, Baffes GC, Wolfe MW et al: The effect of recombinant human osteogenic protein-1 on healing of large segmental bone defects. J Bone Joint Surg Am, 1994; 76(6): 827–38
9. Aspenberg P, Basic N, Tägil M, Vukicevic S: Reduced expression of BMP-3 due to mechanical loading: a link between mechanical stimuli and tissue differentiation. Acta Orthop Scand, 2000; 71(6): 558–62
10. Fujimoto K, Sheng H, Shao J, Beauchamp RD: Transforming growth factor-beta1 promotes invasiveness after cellular transformation with activated Ras in intestinal epithelial cells. Exp Cell Res, 2001; 266(2): 239–49
11. Sweatt A, Sane DC, Hutson SM, Wallin R: Matrix Gla protein (MGP) and bone morphogenetic protein-2 in aortic calcified lesions of aging rats. J Thromb Haemost, 2003; 1(1): 178–85
12. Tobin JF, Celeste AJ: Bone morphogenetic proteins and growth differentiation factors as drug targets in cardiovascular and metabolic disease. Drug Discov Today, 2006; 11, 9–10
13. Davis BJ, Johnston CI, Burrell LM et al: Renoprotective effects of vasopeptidase inhibition in an experimental model of diabetic nephropathy. Diabetologia, 2003; 46(7): 961–71
14. Kempf T, Horn-Wichmann R, Brabant G et al: Circulating concentrations of growth-differentiation factor 15 in apparently healthy elderly individuals and patients with chronic heart failure as assessed by a new immunoradiometric sandwich assay. Clin Chem, 2007; 53(2): 284–91
15. Kempf T, Eden M, Strelau J et al: The transforming growth factor-beta superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury. Circ Res, 2006; 98(3): 351–60
16. Maric I, Poljak L, Zoricic S et al: Bone morphogenetic protein-7 reduces the severity of colon tissue damage and accelerates the healing of inflammatory bowel disease in rats. J Cell Physiol, 2003; 196(2): 258–64
17. Chen L, Jiang W, Huang J et al: Insulin-like growth factor 2 (IGF-2) potentiates BMP-9-induced osteogenic differentiation and bone formation. J Bone Miner Res, 2010; 25(11): 2447–59
18. Luo J, Tang M, Huang J et al: TGFbeta/BMP type I receptors ALK1 and ALK2 are essential for BMP9-induced osteogenic signaling in mesenchymal stem cells. J Biol Chem, 2010; 285(38): 29588–98
19. Chen D, Zhao M, Mundy GR: Bone morphogenetic proteins. Growth Factors, 2004; 22(4): 233–41
20. Takahashi T, Morris EA, Trippel SB: Bone morphogenetic protein-2 and -9 regulate the interaction of insulin-like growth factor-I with growth plate chondrocytes. Int J Mol Med, 2007; 20(1): 53–57
21. An C, Cheng Y, Yuan Q, Li J: IGF-1 and BMP-2 induces differentiation of adipose-derived mesenchymal stem cells into chondrocytes-like cells. Ann Biomed Eng, 2010; XXXVIII, 4): 1647–54
22. Celeste AJ, Iannazzi JA, Taylor RC et al: Identification of transforming growth factor beta family members present in bone-inductive protein purified from bovine bone. Proc Natl Acad Sci USA, 1990; 87(24): 9843–47
23. Wozney JM, Rosen V, Byrne M et al: Growth factors influencing bone development. J Cell Sci Suppl, 1990; 13: 149–56
24. Song JJ, Celeste AJ, Kong FM et al: Bone morphogenetic protein-9 binds to liver cells and stimulates proliferation. Endocrinology, 1995; 136(10): 4293–97
25. Chen C, Grzegorzewski KJ, Barash S et al: An integrated functional genomics screening program reveals a role for BMP-9 in glucose homeostasis. Nat Biotechnol, 2003; 21(3): 294–301
26. Alam T, Sollinger HW: Glucose-regulated insulin production in hepatocytes. Transplantation, 2002; 74(12): 1781–87
27. Michalopoulos GK, DeFrances M: Liver regeneration. Science, 1997; 276(60): 60–66
28. Francavilla A, Makowka L, Polimeno L et al: A Novel Model of Acute Hepatic Failure in Dogs With Implications for Transplantation Research. Transplant Proc, 1988; 20(1. Suppl.1): 713–15
29. Francavilla A, Ove P, Polimeno L, et al. Regulation of liver size and regeneration: importance in liver transplantation. Transplant Proc, 1988; 20(1. Suppl.1): 494–97
30. Chen L, Davis GJ, Crabb DW, Lumeng L: Intrasplenic transplantation of isolated periportal and perivenous hepatocytes as a long-term system for study of liver-specific gene expression. Hepatology, 1994; 19(4): 989–98
31. Gumucio JJ, May M, Dvorak C et al: The isolation of functionally heterogeneous hepatocytes of the proximal and distal half of the liver acinus in the rat. Hepatology. 1996; 6(5): 932–44
32. Gebhardt R: Metabolic zonation of the liver: regulation and implications for liver function. Pharmacol Ther, 1992; 53(3): 275–354
33. Cvijanovic O, Celic T, Peternel S et al: Expression of bone morphogenetic protein-9 in adult human liver. Abstracts of the 35th European Symposium on Calcified Tissues, In: Calcified Tissue International, 2008; 82(Suppl.1): S13–54 / Civitelli R (ed), New York, USA.: Springer Science; Business Media, 2008. S83
34. Groop L: Bringing diabetes therapeutics to the big screen. Nat Biotechnol, 2003; 21(3): 240–41