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MINI REVIEW

Role of BMP7 in appetite regulation, adipogenesis, and energy expenditure

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Abstract Bone morphogenetic protein 7 (BMP7), also known as osteogenic protein-1 (OP-1) is a member of Transforming growth factor-β (TGF-β) family of proteins. Bone morphogenetic proteins were discovered in 1965 by Marshal Urist, of which BMP7 is of particular interest in this review being a leptin-independent anorexinogen and having role in energy expenditure in the brown adipose tissue, which makes it a potential target for preventing/treating obesity. As it has been established that Obesity displays a state of leptin-resistance, thus a protein-like BMP7 which acts through a leptin-independent pathway could give new therapeutic directions. This review will also discuss the synthesis and action of BMP7, along with its receptors and signal transduction. A brief note about BMP7-mediated brown fat development and energy balance is also discussed.

Keywords BMP7 · Adipogenesis · Energy expenditure · Appetite loss

Introduction

Bone morphogenetic protein 7 (BMP7), which is a member of TGF-β superfamily [1–4], is well known for its osteogenic properties [5–7]. It is a glycosylated disulfide-linked 36 kDa homodimeric protein [8], having role in the induction, development, and regulation of adipocytes, especially brown adipose tissue (BAT) [5, 9, 10]. Neurotropic factors—brain-derived neurotropic factor (BDNF) and cilliary-derived neurotropic factor having role in appetite regulation and energy balance, [11–15] functionally resemble BMP7 [16]. Recently, the members of BMP family have been found to be associated with regulation of appetite. BMP7 is identified as an anorexinogen which acts through a leptin-independent central mTOR pathway in the hypothalamus [16]. This multifunctional cytokine [6] is involved in mitochondrial biogenesis [6, 9, 17] and energy expenditure in BAT [6, 16], which makes it a potential therapeutic agent for combating obesity [18]. OP1 (brand name for human recombinant BMP7) has clinical uses like bone fracture treatment, spinal fusions, etc [19]. In 2001, OP1 implant has been Food and Drug Administration (FDA) approved under humanitarian device exemption program as an alternative to autograft, though in 2008 some complications were reported in the cervical spine fusion [20, 21]. Although till date no clinical data are available for BMP7 in relation to obesity [19], but in near future eyeing BMP7 interventions could provide a hope for losing weight. The aim of this review is to summarize and explore the role of BMP7 in adipogenesis, energy expenditure, and this leptin-independent anorexinogen in treating diseases like obesity which is associated with leptin resistance.

Site of synthesis and action of BMP7

During embryogenesis and postnatal development, kidney is the major site of BMP7 synthesis [8]. In adults,

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collecting tubules and glomeruli of kidney, bone, cartilage, heart, urinary bladder, etc., express BMP7 [22–24]. BMP7, which is a secreted signaling protein is also synthesized in the adipose tissue by the stromal vascular cells [25, 26] and also expressed in various regions of brain including hypothalamus, cortex, hippocampus, leptomeninges, and habenular nucleus [27]. Cerebrospinal fluid (CSF) has an ample concentration of this bioactive neurotropic factor [16, 27]. BMP7 concentration in CSF is regulated in the choroid plexus as it has high amount of BMP7 mRNA [27–30]. Hypothalamus which is well known to be the major site involved in the modulation of feeding behavior and metabolism for homeostatic regulation [16, 31, 32], is the major site of action of BMP7 in brain [16, 27, 33].

BMP7 receptors and signal transduction

The TGF-β family ligand, BMP7 receptors are transmembrane heterodimers and are also known to regulate food intake [5, 16, 34]. They are serine/threonine kinase glycoproteins and consist of: (1) Three Type I receptors and (2) Three Type II receptors [5, 16]. BMPR1a, BMPRIb, and ALK2 are among Type I, and BMPRII, ActRIIa, ActRIIb among Type II receptors. BMPRII of the Type II receptors are widespread in the brain while Type I receptors are expressed in hypothalamus [3, 16]. BMPRIa mRNA has been found in visceral and subcutaneous adipose tissue [1].

BMPRIa and BMPRII receptors have been found to be correlated with human obesity. mRNA expression of both of these receptors in adipose tissue is relatively higher in obese and overweight individuals as compared to normal adults [1, 2]. BMPR2 is also associated with insulin sensitivity, adipogenesis, and glucose metabolism [2].

Signal transduction of TGF-β ligands requires both Type I and Type II receptors. Heteromeric complex formation of BMPR1 and BMPR2 [1, 2, 35–37], finally activate SMAD proteins which results in expression of a number of target genes [5, 38]. Apart from the SMAD protein pathway, the other downstream signaling cascade is p38 mitogen-activated protein kinase (p38 MAPK)/activating transcription factor 2 (ATF2) pathway [2, 5, 17, 38]. The involvement of these two pathways in the signaling of BMP7 is reported from the experiments where brown adipocytes were treated with BMP7, and there was an enhancement in the phosphorylation of SMAD1/5/8 and also p38MAPK and ATF2 [5, 6, 16, 17]. Further treatment with SMAD-inhibitor and a p38-MAPK inhibitor supported the results of involvement of these two pathways [17]. BMP7 treatment did not altered the phospho-AMPK levels, phospho-Akt, or total phospho ACC levels which suggest that these pathways are not activated by BMP7 [17].

BAT adipogenesis mediated by BMP7

In the body, adipose tissue is an important endocrine organ. Earlier known as a passive reservoir of energy storage is now being known to have multiple roles in integration of appetite regulation, energy balance, glucose homeostasis, and secrete various adipocytokines essential for metabolism [9, 39, 40]. Two types of adipose tissue are present: (1) white adipose tissue (WAT) and (2) brown adipose tissue (BAT) [41]. With WAT having main function in energy storage [9], brown adipose tissue in particular is of importance in energy balance for its thermogenic, energy expending function [9, 10, 16, 17, 42] and insulin sensitivity [25, 43]. Highly vascularized BAT is derived from differentiation of mesenchymal stem cell [9, 44, 45] and has a large number of mitochondria for carrying out β-oxidation [17]. BAT is highly innervated by sympathetic nervous system (SNS) which is activated by hypothalamus upon sensing of stimulus (like cold, food) which inturn activate β-adrenoreceptors in BAT and downstream cGMP which causes immobilization of free fatty acids and leads to uncoupling protein 1 (UCP-1) activation [18, 46]. UCP-1 located in the inner mitochondrial membrane is unique to brown adipocytes [6, 9, 17, 25, 47]. This UCP-1 uncouple mitochondrial proton gradient from ATP production and generates heat (Fig. 1) [10, 48–50].

BMP7, among other members of the BMP family is known for induction, differentiation, and development of brown fat in particular [6, 9, 25, 51]. On one hand, where BMP7 knockout significantly reduced the BAT mass in mice [25], on the other hand, BMP7 induction or treatment promoted brown fat development, fatty acid oxidation, mitochondrial activity [17], and reduce body weight gain [6, 9, 25] along with induction of peroxisome proliferator-activated receptor gamma (PPAR-γ), peroxisome proliferator-activated receptor gamma coactivator 1 alpha (PGC1-α), nuclear respiratory factor 1 (NRF1), and cytochrome C expression [6]. GDF8, also known as myostatin, is an inhibitor of BMP7 signaling and inhibit adipogenesis and myogenesis [52–54]. BAT marker UCP1 expression is also increased upon BMP7 treatment [6, 18, 25, 26]. BMP7 is involved in browning of white fat by inducing UCP1 expression and brite cell formation [10, 18]. BAT which is involved in body weight regulation [9] and considered to disappear after infancy [55], have been observed in humans during post mortem [9, 56]. Small amounts of functionally active BAT are found by positron-emission tomography and computed tomography (PET-CT) imaging studies in humans, which can induce BAT formation and thus control

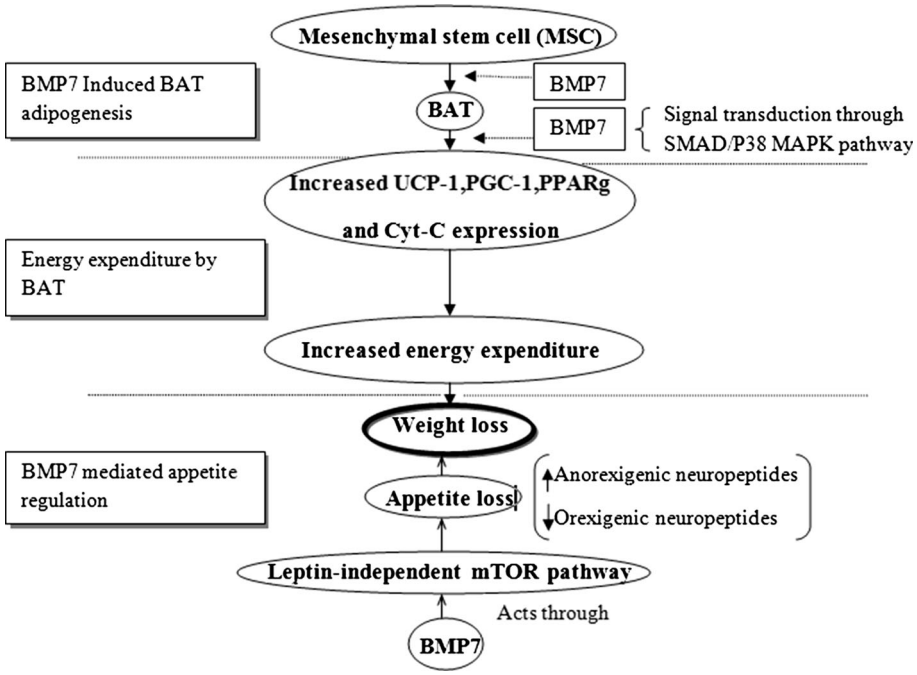

Fig. 1 Schematic representation of the role of BMP7 in BAT adipogenesis from embryonic MSC, increasing energy expenditure in BAT, weight loss and appetite loss through leptin independent mTOR pathway

weight gain [9, 56, 57]. Hence, the property of BMP7 in promoting brown fat lineage can be exploited as a target counteracting obesity and associated morbidities.

BMP7 and energy expenditure

The balance between energy intake and energy expenditure regulates body weight [32, 58]. BMP7 increases energy expenditure in the brown adipose tissue [6, 9, 16, 18, 25]. Thus, BMP7 treatment both systemically and by adenoviral method resulted in an increase in body temperature, BAT-mediated energy expenditure, oxidative phosphorylation, fatty acid uptake, mitochondrial biogenesis and decrease in food intake, body weight gain, and the white fat content by inducing brite cell formation [6, 16–18, 25]. Brite cells in WAT play a key role in energy expenditure [18, 59]. BMP7 treatment also increased thermogenic capacity in BAT by activating SNS and thereby triggering a signal transduction cascade which leads to adaptive increase in brown fat marker UCP-1 expression in the inner mitochondrial membrane independent of environmental temperature, which generate heat instead of adenosine-ri-phosphate (ATP) by uncoupling reaction [6, 9, 16–18, 25]. According to a study by Boon et al. [18], sympathetic BAT activation by BMP7 occurs at subneutral temperature. p38 MAP kinase and PGC-1 play an important role in BMP7-induced thermogenic function [6, 60]. Upon intracerebroventricular (i.c.v) infusion of appetite-inhibiting peptides like POMC and α-MSH, thermogenesis increases [61]. Thus, it can be concluded that neuropeptides that inhibit food intake increases thermogenesis [62]. This property of BMP7 to induce thermogenesis and energy expenditure in brown adipose tissue can be exploited as a potential target for targetting obesity and diabetes in humans [6, 9, 17, 63].

Leptin-independent appetite regulation

Anorectic factors like leptin [64] reduce food intake by acting on hypothalamus by reducing the expression of anorexigenic neuropeptides like pro-opiomelanocortin (POMC), cocaine, and amphetamine transcript and decreasing expression of orexigenic neuropeptides like neuropeptide Y, agouti-related protein [31]. BMP7 is a novel anorectic factor which acts in hypothalamus and regulate feeding behavior [16]. Confocal microscopy showed that BMP7 and its receptors co-localized with appetite regulating neuropeptides in the brain. Peripheral treatment of mice with BMP7 adenovirus resulted in reduction of body weight [6, 16] and this reduction was more as compared to mice that received LacZ adenovirus [6]. In addition to the i.c.v administration of recombinant BMP7 to chow-fed mice [16], systemic treatment of BMP7 adenovirus to ob/ob mice [25] and administration to C57BL/6 mice, all individually resulted in a significant reduction in food intake [16]. Appetite regulatory effect of BMP7 is temperature dependent. BMP7 maintained its effect both in the DIO mice i.e., leptin-resistant mice plus in Ob mice i.e., leptin-deficient mice, which suggest that it mediate its signaling independent of leptin [16]. Additionally, for BMP7's anorectic activity, melanocortin pathway is not essential [16]. mTOR (mammalian target of rapamycin) signaling is well known in the regulation of

food intake [65–67] and BMP7 is able to reduce food intake by activating mTOR-p70S6 kinase pathway [16]. BMP7 treatment resulted in the phosphorylation of p70S6K (downstream target of mTOR) in the arcuate and paraventricular nucleus of hypothalamus, which are actively involved in appetite regulation [16]. The evidence for the role of mTOR signaling were reported by Townsend et al. [16] when i.c.v treatment with rapamycin, (mTOR pathway inhibitor) [68], completely rendered the food intake reducing capability of BMP7 in mice [16]. Myostatin (MSTN) gene expression is increased in the state of insulin resistance and obesity and soluble MSTN inhibitors could prevent these disorders [69, 70]. It has been proposed by a few lines of evidence that MSTN and BMP7 may compete each other in the hypothalamus [53, 71] and increased BMP7 signaling could be the cause of appetite loss in A-ZIP and Muscle-DN mice [72]. Studies reported so far indicate that BMP7's anorectic effect is leptin-independent and inhibited by MSTN and mTOR inhibitor rapamycin.

Conclusion and future perspectives

BMP7 is a multifunctional ligand and anorexinogen of the TGF-β family with an important role in bone induction, brown fat adipogenesis and energy expenditure, which act through a central mTOR pathway in leptin-independent manner to reduce food intake and body weight. Having characteristics of reducing appetite, increasing thermogenesis, and energy expenditure in brown fat by increasing UCP1 mRNA, BMP7 is of particular therapeutic interest in treatment of obesity, diabetes, and other associated metabolic and degenerative diseases. Human recombinant BMP7 has been approved by FDA in 2001 and after that BMP7 containing osteogenic implants are being used. Since thermogenically active BAT traces have been found in the adult humans by landmark imaging techniques recently, thus developing a BMP7 molecular mimic/agonist or BMP7 spinal implant which could stimulate BAT formation, could lead to weight loss in humans. Since obese subjects generally have a state of reduced leptin-sensitivity, so the leptin-independent action of BMP7 in appetite loss could appear as a novel obesity treating breakthrough in near future with further research in this field.

Conflict of interest Authors declare no conflict of interest.

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