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Review

Bradykinin Receptors in Metabolic Disorders: A Comprehensive Review

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Abstract

The kallikrein–kinin system and its B1 and B2 receptors are key regulators in metabolic disorders such as obesity, diabetes, and insulin resistance. Obesity, a chronic and multifactorial condition often associated with comorbidities like type 2 diabetes and dyslipidemia, remains poorly understood at the metabolic level. The kinin B2 receptor (B2R) is involved in blood pressure regulation and glucose metabolism, promoting glucose uptake in skeletal muscle via bradykinin. Studies in B2R-KO mice demonstrate that the absence of this receptor predisposes animals to glucose intolerance under a high-fat diet and impairs adaptive thermogenesis, indicating a protective role for B2R in metabolic homeostasis and insulin sensitivity. In contrast, the kinin B1 receptor (B1R) is inducible under pathological conditions and is activated by kinin metabolites. Mouse models lacking B1R exhibit improved metabolic profiles, including protection against high-fat diet-induced obesity and insulin resistance, enhanced energy expenditure, and increased leptin sensitivity. B1R inactivation in adipocytes enhances insulin responsiveness and glucose tolerance, supporting its role in the development of insulin resistance. Moreover, B1R deficiency improves energy metabolism and thermogenic responses to adrenergic and cold stimuli, promoting the activation of brown adipose tissue and the browning of white adipose tissue. Collectively, these findings suggest that B1R and B2R represent promising therapeutic targets for the treatment of metabolic disorders.

Keywords: bradykinin receptors; kallikrein–kinin system; kinin B1 receptor; kinin B2 receptor; metabolism; metabolic disorders; obesity; diabetes; insulin resistance; adipose tissue

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1. Introduction

In recent years, obesity has emerged as one of the most pressing and costly chronic health conditions worldwide, primarily due to its strong association with several metabolic disorders. These include type 2 diabetes, insulin resistance, dyslipidemia, cardiovascular disease, and even certain types of cancer [1–5]. Although excessive caloric intake combined with physical inactivity is often cited as the main cause, the underlying metabolic mechanisms contributing to the deleterious effects of obesity remain not fully understood [2].

These metabolic disorders not only affect energy balance but also compromise important regulatory systems, such as the immune and endocrine systems. For example, hormones secreted by white adipocytes, including leptin and adiponectin, play central roles

in the regulation of appetite, insulin sensitivity, and lipid metabolism. Dysregulation in these secretions, common in obesity, contributes to metabolic dysfunction and exacerbation of related comorbidities [6–8].

A growing body of evidence highlights the relevance of the kallikrein–kinin system in the pathophysiology of metabolic diseases, particularly through the actions of its receptors. Recent studies suggest that this system plays a direct role in regulating adiposity, improving insulin sensitivity, and enhancing glucose tolerance. The activation or inhibition of kinin receptors can substantially modulate the metabolic response, indicating a link between inflammatory pathways, adipose tissue function, and the development of metabolic disorders [9–11].

Therefore, understanding the interaction between obesity-related metabolic disturbances and the kallikrein–kinin system could open new therapeutic avenues. This perspective not only deepens insight into obesity pathophysiology but also highlights novel molecular targets for the development of more effective strategies to prevent and manage its metabolic complications.

2. Metabolic Disorders

Obesity is a complex and chronic metabolic condition driven by a combination of genetic, environmental, psychological, and social factors, and represents a major threat to global public health. It is characterized by an imbalance between energy intake and expenditure, resulting in the excessive accumulation of dysfunctional and pathological adipose tissue [2,12,13]. Beyond its high prevalence, obesity is particularly concerning due to its strong association with a broad spectrum of comorbidities, including type 2 diabetes mellitus (T2DM), insulin resistance, dyslipidemia, and cardiovascular diseases [2,14,15]. The common perception is that this range of diseases is driven mainly by positive energy balance, including excess caloric intake combined with insufficient energy expenditure—which leads to an excessive accumulation and impaired handling of lipids. This imbalance can lead to cellular dysfunction, including mitochondrial function, stress signaling, inflammation, and reactive oxygen species generation [16].

The increasing prevalence of obesity has drawn attention to the problem of long-term global imbalance. Currently, approximately 2.2 billion people are overweight and 712 million are considered obese, representing almost one-third and 10% of the world population, respectively [17,18]. Obesity exerts a significant impact on systemic glucose homeostasis, largely through its effects on tissue insulin sensitivity. In obese individuals, adipose tissue releases elevated levels of glycerol, non-esterified fatty acids, pro-inflammatory cytokines, and other bioactive factors that contribute to the development of insulin resistance [19].

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disease characterized by hyperglycemia resulting from peripheral insulin resistance and impaired insulin action [6]. It is currently estimated that 463 million people are living with diabetes, and projections suggest this number could rise to 700 million by 2045 if current trends continue [6]. Insulin resistance—often a precursor to T2DM—is closely associated with obesity and typically arises in the context of excessive weight gain, sedentary behavior, and/or chronic hyperlipidemia [20].

While significant advances have been made in understanding the relationship between obesity, insulin resistance, and T2DM, critical gaps remain in our knowledge of the molecular mechanisms that link these conditions. In response, there is growing interest in novel therapeutic strategies aimed at restoring metabolic balance. Some promising approaches target the adipose tissue itself, which is now recognized not only as the body's primary energy reservoir but also as an active endocrine organ with critical regulatory func-

tions [21,22]. The behavior and impact of adipose tissue vary according to its anatomical location and cellular composition, and its role in obesity and metabolic diseases continues to be a focus of extensive investigation [21].

Modern lifestyles, characterized by high-calorie diets, physical inactivity, and prolonged sedentary behavior, strongly contribute to the rising incidence of obesity and its metabolic complications [21]. Given the spread of obesity-associated disorders, significant efforts are underway to develop anti-obesity therapies that can alleviate the growing medical burden. Although a few pharmacological agents aimed at improving insulin sensitivity and glucose metabolism have been approved in specific countries or regions, their clinical efficacy has often fallen short of expectations [6].

Current treatment strategies for obesity predominantly focus on reducing energy intake (via diet, bariatric surgery, or pharmacotherapy) and/or increasing energy expenditure through physical activity. However, these interventions typically require substantial and sustained lifestyle changes, which may pose adherence challenges for many patients [21–23].

On the other hand, glucagon-like peptide-1 (GLP-1) receptor agonists have emerged as a groundbreaking therapy in the treatment of obesity, offering substantial and sustained weight loss that rivals outcomes typically associated with bariatric surgery, as highlighted in the review by Jastreboff and Kushner (2023) [24]. Initially designed for managing type 2 diabetes, agents like semaglutide have shown robust effects on appetite suppression and energy regulation by acting on key pathways within the central nervous system [24]. Thereby, GLP-1-based therapies represent a paradigm shift in obesity treatment, offering new hope for long-term weight control with relatively favorable safety profiles.

By understanding how receptors influence physiological processes such as hunger, glucose metabolism, and fat storage, it becomes possible to identify novel therapeutic targets and develop more precise treatments for complex conditions like obesity, diabetes, and metabolic syndrome.

Recent research has shed light on the potential involvement of the kallikrein–kinin system, particularly kinin receptors, in metabolic regulation. These findings suggest that this system may play a previously underappreciated role in the development and progression of metabolic disorders, a topic that will be explored in the following sections.

3. Overview of Kallikrein–Kinin System (KKS)

The kallikrein–kinin system (KKS) is a peptide system that has been described as an important mediator of physiological processes, with reported involvement in inflammatory processes, maintenance of tissue homeostasis, blood pressure control, cell proliferation, and pain transmission processes [25]. This system is basically composed of enzymes, receptors, and peptides: precursor protein substrate (kininogen), serine protease enzymes (kallikreins), pro-inflammatory peptide mediators (kinins), kinin B1 and B2 receptors, kininase enzymes, and inactive peptides (Figure 1).

Kininogen encodes two different proteins produced mainly in the liver, one of high molecular weight kininogen (HMWK) and one of low molecular weight kininogen (LMWK). To date, only the *Kng1* gene has been described in humans, while the *Kng2* gene has also been identified in mice, with a sequence identity of approximately 89% [26]. There are two types of kinin-generating enzymes that are encoded by two different genes: tissue kallikrein, expressed in most tissues, and plasma kallikrein, expressed in the liver [27]. HMWK is released into the bloodstream and processed by plasma kallikrein, producing the active peptide bradykinin (BK). LMWK is cleaved by tissue kallikrein, releasing kallidin (Lys-bradykinin) or BK into the blood [28].

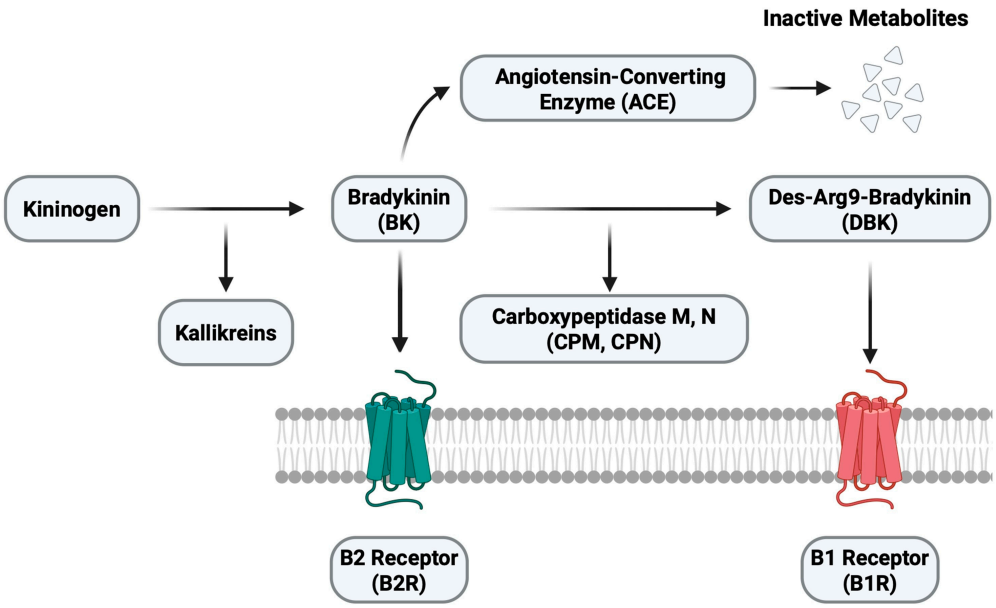

Figure 1. Kallikrein–kinin system—KKS (created by the author).

Kinins produced by kallikreins accumulate in damaged tissues, where they trigger inflammation and associated symptoms such as pain, vasodilation, and increased endothelial permeability. These effects often result in classic signs of inflammation, including redness, swelling, and infiltration of inflammatory cells [27]. Bradykinin (BK) is the primary active peptide of this system and plays a key role in the regulation of blood pressure and blood flow. Its signaling occurs via the kinin B2 receptor (B2R), which is constitutively expressed in various tissues under physiological conditions, including the cardiovascular system and nociceptive neurons. As such, B2R is involved in pain modulation and the relaxation of vascular smooth muscle [29].

Importantly, BK can also enhance systemic insulin sensitivity. When released by skeletal muscle, BK binds to B2R and promotes glucose uptake. BK and kallidin, a peptide that is functionally and pharmacologically equivalent to bradykinin, can be degraded by type I kininases (carboxypeptidases), yielding des-Arg^9-bradykinin (DBK) and des-Arg^9-kallidin, respectively [29]. These degradation products are the principal agonists of the kinin B1 receptor (B1R), which is typically expressed at low levels under physiological conditions [30]. Additionally, kinins can be inactivated by type II kininases, particularly angiotensin-converting enzyme (ACE), which cleaves them into inactive fragments.

Both B1R and B2R are G protein-coupled receptors (GPCRs) that activate intracellular signaling cascades, including calcium mobilization, inositol phosphate hydrolysis, arachidonic acid release, and nitric oxide (NO) production. Kinin receptors also stimulate mitogen-activated protein kinases (MAPKs) via Gs-dependent pathways [31,32]. The primary distinction between the two receptors lies in their expression patterns: while B2R is constitutively expressed across a wide range of tissues and cell types, B1R is generally absent under basal conditions and is instead induced during pathological states. B1R expression is upregulated following exposure to pro-inflammatory cytokines, oxidative stress (e.g., due to hyperglycemia), and tissue injury [30,33].

4. Kinin B2 Receptor (B2R)

The kinin B2 receptor (B2R), encoded by the Bdkrb2 gene, belongs to the G protein-coupled receptors (GPCR) superfamily and mediates the physiological responses of kinins [34]. Among the kinins, the bioactive peptides bradykinin and kallidin, generated by the kallikrein–kinin system, are the main ligands at the receptor [35,36]. B2R performs

a central role in several physiological processes such as the regulation of blood pressure, hydroelectrolytic homeostasis, vascular permeability, pain, and inflammation [31,34,37]. With a wide expression, B2R is constitutively and ubiquitously expressed in various tissues and cell types, including vascular endothelial cells, renal proximal tubules cells, the nervous system, and cells of the immunological system [38–41].

Structurally, B2R presents seven transmembrane domains, a singular characteristic of GPCRs, with a binding site for kinins in the extracellular domain. G-protein-coupled receptors are membrane receptors that present a single polypeptide chain and comprise seven transmembrane helices with three extracellular loops and three intracellular loops. The N-terminal of the polypeptide chain is exposed to the extracellular environment, while the C-terminal tail is intracellularly exposed [31].

In endothelial cells, receptor activation triggers intracellular signaling, leading to the activation of phospholipase C (PLC), which hydrolyzes phosphatidylinositol-(4,5)-bisphosphate (PIP2), producing diacylglycerol (DAG) and inositol-(1,4,5)-triphosphate (IP3). DAG is a lipophilic structure positioned at the membrane and is responsible for protein kinase C activation (PKC). The IP3 released into the cytosol acts on the IP3 receptor (IP3R) present in the endoplasmic reticulum (ER) membrane, which mediates the mobilization of Ca^{2+} from intracellular reserves. Increased intracellular Ca^{2+} levels induce the formation of the Ca^{2}+-calmodulin complex, promoting the activation of Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII), calcineurin, endothelial nitric oxide synthase (eNOS), and phospholipase A2 (PLA) enzymes, leading to the release of NO (nitric oxide) and prostaglandins by endothelial cells into adjacent smooth muscle cells, resulting in vasodilation and increased vascular permeability [42]. Additionally, B2R is also able to form heterodimers or functionally interact with other receptors, including the angiotensin II AT1 receptor, representing an important association with the renin–angiotensin system (RAS), particularly relevant in blood pressure regulation, vascular tone, inflammation, and glucose metabolism [43].

4.1. Kinin B2 Receptor Knockout Mice

Much of the current understanding of B2R function in physiological and pathophysiological contexts has been derived from studies using B2R knockout (B2R-KO) animal models. These mice were generated through homologous recombination, in which the entire coding sequence of the *Bdkrb2* gene was deleted. Homozygous B2R-KO mice exhibit a phenotype largely similar to that of wild-type animals, maintaining normal fertility and life expectancy consistent with their species [44].

One of the defining characteristics of B2R-KO mice is the complete loss of physiological responses to exogenous bradykinin. This is evidenced by impaired contractility of the uterus and ileum, as well as the absence of receptor function in the superior cervical sympathetic ganglia [44]. The deletion of *Bdkrb2* also leads to several cardiovascular and renal alterations, including increased susceptibility to salt-sensitive hypertension [45], reduced renal blood flow, and elevated renal vascular resistance [46]. These mice show an exaggerated vasopressor response to angiotensin II (Ang II), and chronic treatment with AT1 receptor antagonists results in decreased blood pressure [47]. Furthermore, B2R-KO mice are more prone to developing mineralocorticoid-induced hypertension [48]. Neonatal B2R-KO mice also display decreased *renin* mRNA expression compared to wild-type counterparts. When exposed to salt stress in utero, knockout embryos show suppressed renin expression, abnormal kidney development, and early-onset postnatal hypertension [45,49]. Additionally, B2R deficiency exacerbates renal tubulointerstitial fibrosis following ureteral obstruction [50].

Some studies have reported that the absence of B2R leads to the compensatory upregulation of kinin B1R in tissues where it is normally expressed at low levels, such as the kidney and heart. This suggests a functional interplay between the two receptors [51,52]. For instance, in B2R-KO mice, B1R expression is elevated under basal conditions, and insulin infusion further increases *B1R* mRNA levels [51].

Moreover, B2R deletion is associated with reduced leukocyte recruitment and diminished production of pro-inflammatory cytokines [53]; these mice also exhibit delayed wound healing following skin excision, characterized by impaired angiogenesis, reduced collagen deposition, and delayed re-epithelialization [54].

4.2. Contribution of Kinin B2 Receptor to Insulin Sensitivity and Glucose Homeostasis

Glucose metabolism and insulin signaling are essential physiological processes that maintain energy homeostasis and metabolic balance [55]. Disruptions in these pathways contribute to insulin resistance, a key feature of various metabolic disorders, including type 2 diabetes and obesity [56–58]. Several signaling pathways and receptors regulate insulin sensitivity, and evidence suggests that components of the kallikrein–kinin system, particularly the bradykinin B2 receptor (B2R), play a modulatory role [51,59]. Glucose and insulin dynamics have been more thoroughly assessed using the hyperinsulinemic euglycemic clamp technique in B2R knockout (B2R-KO) mice. These mice exhibit normal fasting glucose and insulin levels compared to wild-type controls, though a trend toward elevated insulin levels was observed in the B2R-KO group. However, B2R-KO mice require higher steady-state insulin levels to maintain euglycemia and show impaired glucose disposal, indicating insulin resistance [51].

Interestingly, B2R deficiency has also been associated with protection against diabetic nephropathy in a streptozotocin (STZ)-induced diabetes model. Compared to diabetic wild-type controls (B2R_D), B2R-KO diabetic mice (B2R-KO_D) exhibit significant protection from both structural and functional renal impairments. Histological evaluations revealed reductions in mesangial matrix expansion, glomerular basement membrane thickening, and interstitial fibrosis. These mice also displayed decreased albuminuria, reduced glomerular injury, and preserved renal function. Moreover, expression levels of key pro-inflammatory and pro-fibrotic markers, TGF-β1, collagen IV, and MCP-1, were markedly downregulated in B2R-KO diabetic mice [60]. Notably, B2R antagonism with HOE-140 failed to reverse hyperglycemia in diabetic models, whereas blockade of the B1 receptor with des-Arg9-BK normalized blood glucose levels, implicating B1R as a major contributor in hyperglycemia under diabetic conditions [61].

B2R also plays a pivotal role in hepatic glucose regulation, especially in obesity. In studies involving B2R-deficient obese mice (obB2KO), animals exhibited elevated fasting glycemia, hyperinsulinemia, and impaired glucose tolerance compared to wild-type obese controls (obWT), indicating heightened insulin resistance. These effects were accompanied by increased hepatic gluconeogenesis, evidenced by enhanced glucose output in pyruvate tolerance tests and elevated hepatic expression of gluconeogenic genes such as *Foxo1*, *G6Pase*, *PEPCK*, and *PGC-1α*. Bradykinin administration in wild-type mice suppressed hepatic *Foxo1* and *PEPCK* expression, confirming its inhibitory role in gluconeogenesis. These findings underscore the protective function of the kallikrein–kinin system (KKS) in type 2 diabetes through the suppression of hepatic glucose production via Foxo1 [62].

Transcriptomic analyses in B2R-KO diabetic mice further reveal alterations in numerous signaling pathways, including those related to glucose and insulin metabolism. In particular, the expression of insulin-like growth factor binding proteins *Igfbp-1* and *Igfbp-4* was significantly altered, highlighting the impact of B2R disruption on diabetic pathophysiology [63].

The interaction between high-fat diets (HFDs), exercise, and metabolic outcomes has also been explored in B2R-KO models. While glucose tolerance did not differ significantly between wild-type and B2R-KO mice under a control diet, B2R-KO mice developed glucose intolerance under HFD conditions, suggesting increased susceptibility to diet-induced metabolic dysfunction. Paradoxically, these mice exhibited improved insulin sensitivity under HFD, with no differences observed under the control diet. Baseline muscle glucose uptake was comparable between groups, but insulin-stimulated glucose uptake and glycogen storage were significantly enhanced in B2R-KO mice [64].

A systematic review integrating findings from both animal and human studies confirms the involvement of B2R in glucose regulation under physiological and pathological conditions. B2R activation enhances glucose uptake in skeletal muscle and adipose tissue by promoting GLUT4 translocation to the cell membrane. This effect occurs through an insulin-independent mechanism involving the nitric oxide (NO)/AMPK signaling axis, which also synergizes with the canonical IRS1/PI3K/Akt insulin pathway. The activation of NO, AMPK, and cGMP-dependent protein kinase (PKG) supports glycemic control and energy balance. The review also emphasizes that metabolic disturbances can skew signaling toward pro-inflammatory pathways via the B1 receptor (B1R) and inducible nitric oxide synthase (iNOS), leading to excessive NO production and metabolic dysfunction [65].

Finally, the role of B2R in exercise-mediated metabolic adaptations has also been explored. B2R is not required for exercise-induced reductions in blood glucose or plasma insulin levels, as both B2R-KO and wild-type mice exhibit similar declines in glucose following exercise. However, post-exercise plasma insulin levels were lower in B2R-KO mice, suggesting a potential role in modulating insulin clearance or sensitivity during physical activity [66].

4.3. Participation of B2 Receptor in Thermogenic Activation and Energy Expenditure

Thermogenesis is a critical physiological process for maintaining thermal homeostasis, regulating energy balance, and enabling cold adaptation. This response involves several signaling pathways, notably the activation of brown adipose tissue (BAT) and the browning of inguinal white adipose tissue (WAT), leading to the emergence of beige adipocytes. A key molecular marker of thermogenesis is uncoupling protein 1 (UCP1), a mitochondrial protein highly expressed in BAT and beige adipocytes. UCP1 plays a crucial role in thermoregulation and energy expenditure by dissipating energy as heat instead of storing it as ATP [67].

A recent study investigated the role of B2R in mice lacking this receptor in both BAT and WAT (referred to as B2R-AKO mice). While previous studies have shown that adrenergic stimulation during cold exposure induces *Ucp1* expression [68], cold exposure alone failed to upregulate *Ucp1* expression in BAT or promote WAT browning in B2R-AKO mice, despite elevated bradykinin (BK) levels. These findings suggest that BK alone is not sufficient to trigger thermogenic responses; rather, B2R signaling is essential for the activation of adaptive thermogenesis. Moreover, upon bradykinin administration, B2R-AKO mice exhibited significantly reduced browning of subcutaneous WAT compared to control mice [69].

5. Kinin B1 Receptor (B1R)

The kinin B1 receptor belongs to the G protein-coupled receptor (GPCR) superfamily and differs notably from B2R in terms of expression patterns and activation mechanisms [70]. While B2R is constitutively expressed under physiological conditions, B1R is absent or minimally expressed in healthy tissues, with its expression being strongly

upregulated in pathological states such as inflammation, hypoxia, ischemia, and hyperglycemia [71–74].

B1R is activated mainly by kinin metabolites, specifically Des-Arg9-Bradykinin (Des-Arg9-BK) and Lys-Des-Arg9-Bradykinin (Lys-Des-Arg9-BK) [70–72,74]. These ligands are generated during inflammation via the enzymatic activity of carboxypeptidases, which cleave bradykinin and kallidin [71,72]. Notably, species-specific variations exist in ligand preference: Lys-Des-Arg9-BK is predominant in humans and rabbits, whereas Des-Arg9-BK is more relevant in rodents [72].

Structurally, B1R shares approximately 36% amino acid identity with B2R. The human Bdkrb1 gene encoding B1R comprises three exons, with the entire coding region contained in exon 3. The *Bdkrb1* and *Bdkrb2* genes are organized in tandem within a compact genomic locus, with *Bdkrb2* located 12 kb upstream of *Bdkrb1* [31].

Functionally, B1R is critically involved in pathological processes, especially those related to inflammation and pain [27,70–72,74]. Its activation promotes vasodilation, edema formation, and leukocyte recruitment to inflamed tissues [72]. Studies using B1R knockout mice have demonstrated hypoalgesia and reduced inflammatory responses, highlighting its role in the initiation of inflammation and in modulating spinal cord plasticity involved in central pain sensitization [27].

Beyond its role in inflammation, B1R also participates in metabolic regulation. It influences glucose homeostasis and interferes with both leptin and insulin signaling pathways [65]. In liver disease, B1R expression is markedly increased in the fibrotic livers of mice and has been implicated in the development of hepatic fibrosis and portal hypertension [73]. Pharmacological blockade of B1R has been shown to attenuate fibrosis and portal pressure, reduce the expression of pro-fibrotic proteins and growth factors, and diminish levels of inflammatory cytokines and chemokines [73].

5.1. Kinin B1 Receptor Knockout Mice

Similarly to B2R-KO mice, B1 receptor knockout (B1R-KO) mice were generated through homologous recombination in embryonic stem cells, leading to the deletion of the BDKRB1 gene [27]. This genetic modification prevents the expression of the B1 receptor protein, allowing researchers to study its physiological roles in vivo.

The use of B1R-KO mice has been instrumental in uncovering the complex functions of this receptor across multiple systems. These models have revealed phenotypic changes affecting energy metabolism, inflammation, pain perception, renal physiology, and bone homeostasis.

B1R activation is critical for the development of neuropathic pain. Mice lacking B1R show significant reductions in the early stages of mechanical allodynia and thermal hyperalgesia [75]. In the context of tissue remodeling, B1R-deficient mice display increased bone loss and elevated osteoclast numbers, along with enhanced osteoclast differentiation and efficient resorption of calcium phosphate substrates [76].

In kidney injury models, B1R-KO mice demonstrate protection against cisplatin-induced acute kidney damage, associated with altered immune cell migration and reductions in serum and blood creatinine levels [77]. In the cardiovascular system, these mice exhibit reduced myocardial infarct size following ischemia–reperfusion injury [78]. Additionally, they show increased angiotensin-converting enzyme (ACE) activity in bone marrow non-hematopoietic cells compared to wild-type controls [79].

Metabolically, B1R deletion reduces hepatic lipid accumulation and lipogenesis in response to a high-fat diet, indicating an indirect regulatory effect of adipose tissue B1R on liver metabolism, potentially mediated by leptin and insulin signaling pathways [80].

To investigate the specific role of B1R in adipocytes, aP2-B1/B1R-KO mice were created by crossing B1R-overexpressing mice (in white adipose tissue) with B1R knockout mice [10]. Findings by Mori et al. (2012) revealed that adipocyte B1R plays a central role in whole-body insulin sensitivity and glucose regulation [10]. B1R expression in white adipose tissue also modulates glucose tolerance and susceptibility to obesity [10].

Given the relationship between the kinin B1 receptor and adipocytes, Sales et al. (2019) transplanted visceral white adipose tissue from wild-type donors into the subcutaneous region of B1R-KO mice [11]. These recipient mice developed obesity under a high-fat diet but did not show glucose intolerance or insulin resistance, although they had elevated fasting glucose levels. Moreover, changes in the expression of metabolic genes (such as *Adipoq*, *Fabp4*, *Pparγ*, *Glut1*) and normalization of serum levels of leptin, insulin, and EGF were observed. These findings suggest that B1R in adipose tissue exerts systemic, non-autonomous effects on body weight and metabolism [11].

In summary, the comparative analysis of phenotypes in B1 receptor knockout mouse models and their controls reveals a comprehensive function of this receptor in several physiological and pathophysiological pathways. B1R functions as a key regulator of energy balance, inflammation, pain signaling, renal and skeletal health, and hematopoiesis, positioning it as a promising therapeutic target in various clinical contexts.

5.2. Role of Kinin B1 Receptor in Insulin Resistance and Metabolic Dysfunction

The interplay between B1R, insulin resistance, and glucose homeostasis has been extensively investigated using B1R knockout (B1R-KO) models. Analyses of these models have consistently demonstrated that genetic ablation of B1R leads to a markedly improved metabolic phenotype, offering protection against several components of metabolic syndrome.

One of the most consistent and clinically relevant findings is the resistance of B1R-KO mice to high-fat diet (HFD)-induced obesity, a primary contributor to insulin resistance and type 2 diabetes [9,81]. In these models, B1R deficiency results in reduced fat mass and adiposity, elevated energy expenditure, increased spontaneous activity, reduced insulin levels regardless of diet, and resistance to diet-induced hyperleptinemia. These observations suggest that B1R plays a role in the development of leptin resistance during obesity [9,81]. This protection is particularly important since visceral adiposity is a major driver of systemic insulin resistance and metabolic dysfunction.

Improved insulin sensitivity is another hallmark of B1R-KO models. Studies have shown that these mice display enhanced insulin-stimulated glucose uptake in metabolically active tissues, such as adipose tissue and skeletal muscle [10].

The importance of B1R specifically in adipocytes was highlighted by Mori et al. (2012), who demonstrated that B1R expression in adipose tissue plays a crucial role in regulating systemic insulin action and maintaining glucose homeostasis. B1R in adipocytes has been implicated in fat accumulation, impaired glucose uptake, and insulin resistance in the context of HFD exposure [10]. Its inactivation enhances insulin responsiveness, supporting the idea that B1R signaling in adipocytes contributes to metabolic dysfunction [10]. Sales et al. (2019) further demonstrated that B1R in white adipose tissue functions in a non-autonomous manner, influencing systemic metabolism through inter-organ communication [11].

Concomitant with improved insulin sensitivity, B1R-KO mice exhibit markedly improved glucose tolerance. During glucose tolerance tests, they present lower blood glucose levels and faster glucose clearance, indicating a greater capacity to manage glucose loads and maintain glycemic balance [10]. This improved glucose regulation is a direct indication of improved glycemic homeostasis.

Interestingly, the effects of B1R on glucose homeostasis extend to hepatic metabolism. Although the liver does not express B1R under normal physiological conditions, systemic B1R deficiency leads to reduced hepatic lipid accumulation and decreased lipogenesis under HFD conditions [80]. This suggests that B1R in peripheral tissues, particularly adipose tissue, indirectly modulates liver function, likely via improved leptin and insulin sensitivity. Indeed, B1R-KO mice exhibit enhanced hepatic leptin signaling, reduced steatosis, and an overall healthier metabolic profile [80].

Collectively, studies employing B1R-KO models underscore a pivotal role for this receptor in regulating insulin sensitivity, glucose homeostasis, and energy metabolism. Although some evidence suggests that B1R deficiency may lead to the compensatory upregulation of B2R expression [82,83], the overall metabolic profile of B1R-KO mice is strongly protective. These models show resistance to obesity, improved peripheral and systemic insulin sensitivity, enhanced glucose tolerance, and favorable modulation of hepatic and central pathways. These findings position B1R as a promising therapeutic target for addressing obesity, insulin resistance, and type 2 diabetes.

5.3. Influence of B1 Receptor on Thermogenic Response

The investigation of the relationship between the B1 receptor (B1R) and thermogenesis has become an area of growing interest in understanding the regulation of energy expenditure and the pathophysiology of obesity. Studies using B1R knockout (B1R-KO) models have provided key insights into how the absence of this receptor influences the thermogenic capacity of adipose tissue.

Traditionally, kinins, ligands for the B1 and B2 receptors, have been primarily associated with inflammation and pain signaling [75,79]. However, recent studies using B1R-KO mice have revealed an unexpected role for B1R in regulating energy metabolism [9]. B1R deficiency has been consistently associated with reduced adiposity, resistance to diet-induced obesity, and improved leptin and insulin sensitivity [9,10,81]. These findings have led to the hypothesis that B1R may also play a regulatory role in energy expenditure, particularly through thermogenic mechanisms.

Peyrou et al. (2020) demonstrated that wild-type mice exhibit downregulation of B1 and B2 receptor expression in both interscapular brown adipose tissue (iBAT) and inguinal white adipose tissue (iWAT) following chronic cold exposure [84]. Their study highlighted a role for the kallikrein–kinin system in the plasticity of adipose tissue during thermogenic challenges [84]. Specifically, noradrenergic stimulation of thermogenesis, via the cAMP pathway, led to the increased release of kininogen (*Kng2*) and repression of kinin receptor expression, contributing to BAT activation. These results suggest a reciprocal regulatory relationship, whereby thermogenic activation suppresses kinin receptor signaling, and in turn, kinin signaling may inhibit thermogenic processes in BAT [84]. Nevertheless, the role of this system in beige adipose tissue thermogenesis remains largely unexplored.

A more recent and comprehensive study by Branquinho et al. (2024) directly investigated the role of B1R in thermogenesis [85]. Using B1R-KO mice, the authors reported enhanced energy metabolism, which was further amplified by β-adrenergic stimuli, such as the administration of the β3-adrenergic agonist CL-316,243 and chronic cold exposure. These interventions led to heightened thermogenic activation in both brown and beige adipose depots.

Selective β3-adrenergic receptor stimulation acutely increased respiratory metabolism and energy expenditure while upregulating thermogenic gene expression in the iWAT of B1R-KO mice. These findings suggest the recruitment of beige adipocytes in response to β3-adrenergic activation [85]. B1R-KO mice also exhibited improved cold tolerance, supporting the notion that B1R deficiency enhances thermogenic capacity. Chronic cold

exposure resulted in increased BAT activation, as evidenced by improved thermal regulation in the interscapular region, lowered blood glucose levels, BAT hypertrophy, and the upregulation of insulin signaling pathways. Additionally, WAT browning was significantly enhanced in B1R-KO mice, as demonstrated by the increased recruitment of multilocular adipocytes, the upregulation of thermogenic and mitochondrial genes, especially *Ucp1* and electron transport chain components, and the stimulation of classical energy metabolism pathways, including oxidative phosphorylation and the TCA cycle [85].

Interestingly, in a model lacking both B1 and B2 receptors (B1RB2R-KO), cold exposure led to BAT activation but failed to induce iWAT browning, in contrast to B1R-KO mice. This suggests that B1R plays a specific role in beige adipocyte recruitment and that the simultaneous deletion of both receptors disrupts coordinated adipose tissue thermogenic responses [84].

Although the precise molecular mechanisms through which B1R deficiency enhances thermogenesis are still under investigation, it is likely that B1R signaling modulates intracellular pathways governing mitochondrial biogenesis and the expression of key thermogenic proteins, such as UCP1. The current evidence suggests that under physiological conditions, B1R signaling may act as a brake on thermogenic activity in adipose tissue, and its absence permits enhanced heat production and energy dissipation.

These findings are of considerable significance, positioning B1R in adipose tissue as a promising target for the therapeutic manipulation of energy expenditure. Modulating B1R to increase thermogenesis may represent a novel approach to combat obesity and other metabolic disorders characterized by low energy expenditure and excessive fat accumulation.

6. Conclusions

The bradykinin B1 and B2 receptors of the kallikrein–kinin system are key modulators of metabolic processes, playing pivotal roles in glucose homeostasis, insulin sensitivity, and thermogenesis. These receptors are directly implicated in the pathophysiology of metabolic disorders such as obesity and type 2 diabetes. The activation of the B2 receptor (B2R) has been shown to enhance glucose uptake in metabolically active peripheral tissues, such as skeletal muscle and adipose tissue, via GLUT4 translocation and nitric oxide and AMPK-dependent pathways, underscoring its protective effects on glycemic control.

Conversely, genetic deletion or pharmacological inhibition of the B1 receptor (B1R) has been consistently associated with resistance to high-fat diet-induced obesity, improved insulin sensitivity, and increased energy expenditure, suggesting that B1R signaling contributes to insulin resistance and fat accumulation. Both receptors also influence thermogenic regulation: B2R is essential for adaptive thermogenesis, while B1R deficiency enhances energy metabolism and promotes higher thermogenic activity in adipose tissues.

Taken together, these findings position B1R and B2R as promising therapeutic targets in metabolic diseases. B1R blockade, by conferring protection against obesity and improving insulin action and glucose tolerance, supports the development of pharmacological strategies aimed at inhibiting this receptor to counteract metabolic syndrome. In parallel, harnessing the beneficial effects of B2R activation on glucose uptake and thermogenesis offers a complementary approach to restore glycemic balance and improve energy homeostasis.

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