

Review

Exercise, Prostaglandin E₂, and Cardiometabolic Health: From Molecular Signaling to Systemic Adaptation

Joseph Mannozi ^{1,2,3}, Mike M. Ravn Pedersen ^{3,4}, Shaheen Y. Bhat ^{3,4} and Timothy D. Bryson ^{3,4,*}

¹ Cardiovascular Medicine, Henry Ford Health, 48202 Detroit, MI, USA

² College of Human Medicine, Michigan State University, 49503 Lansing, MI, USA

³ Department of Physiology, Wayne State University School of Medicine, 48202 Detroit, MI, USA; shaheenyawarhat@wayne.edu (S.Y.B.)

⁴ Department of Internal Medicine, Hypertension and Vascular Research Division, Henry Ford Health, 49503 Detroit, MI, USA

* Correspondence: tbryson1@hfhs.org; Tel.: +1-313-432-7258

Abstract

Exercise is a cost-effective cornerstone therapy available to all for the treatment of cardiometabolic disorders, yet the molecular mediators linking physical activity to systemic metabolic and cardiovascular adaptations remain incompletely defined. Prostaglandin E₂ (PGE₂) is a bioactive lipid derived from arachidonic acid metabolism and has recently emerged as a critical regulator of inflammation, vascular function, mitochondrial remodeling, and glucose–lipid homeostasis. This review synthesizes current evidence on PGE₂ biosynthesis and signaling in the context of exercise, with a focus on its broader role in cardiometabolic health and disease.

Keywords: prostaglandin E₂; exercise; cardiometabolic disease; inflammation; EP receptors; metabolic syndrome

1. Cardiometabolic Disorders

1.1. Burden of Cardiometabolic Disorders and the Role of Exercise

Cardiometabolic disease (CMD) is an all-encompassing term that refers to comorbid disorders affiliated with traditional cardiovascular disease pathologies. These metabolic comorbid components include obesity, metabolic dysfunction-associated steatotic liver disease (MASLD), type 2 diabetes mellitus (T2DM), and metabolic syndrome. Importantly, these diseases are often coupled with ischemic heart disease and heart failure (HF). Moreover, the increasing prevalence of sedentary lifestyles, obesity, and metabolic comorbidities of cardiovascular disease has exacerbated the overall burden of CMD. Cardiovascular disease accounted for 915,973 deaths in the United States alone in 2023 [1] and presents a significant economic challenge in the coming years, as it is estimated to exceed \$500 billion annually [1]. Furthermore, these estimates only take into consideration increases in traditional cardiovascular disease burden. Thus, these numbers are likely to further increase, especially with the observed increases in cardiometabolic pathologies, which typically present with poorer long-term outcomes and more expensive treatment regimens.

Pharmacological interventions for CMD are complicated by the complexity of various comorbidities associated with the different conditions that make up CMD.

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Addressing these conditions thus requires an understanding of the shared pathways between the various disorders and the development of novel, cost-effective therapies. One such therapy that has been proven over time to be effective for the treatment of cardiovascular and metabolic diseases, both in isolation and when combined in the context of CMD, is exercise. The term *exercise*, for the purpose of this review, encompasses any physical movement defined by structure and planned purpose (i.e., increasing physical fitness).

In general, exercise training is known to positively regulate insulin and glucose balance, improve body composition, and reduce waist circumference [2–4]. The magnitude of these effects, however, may vary depending upon the population, specific disease state, and the type of exercise being performed (i.e., aerobic, resistance, or combination training, discussed in more detail below). In addition to global metabolic benefits, exercise can also improve chronic inflammation, which can be an underlying factor that potentiates many cardiometabolic disorders [5]. Unfortunately, traditional markers of inflammation are too general to identify specific characteristic shifts in inflammatory status. Thus, a necessary remaining area of research in the field of CMD is to identify more precise biomarkers that can be used to specifically identify metabolic-related inflammation. As the healthcare system continues to be burdened by rising costs related to CMD, shifting the public's focus towards prevention with lifestyle interventions like exercise should be a priority. At present, the recommended amount of exercise by the American Heart Association (AHA) for healthy individuals is 150–300 min per week. However, when it comes to obesity and CMD, the AHA recommends that the timeframe increase to 225–420 min of moderate-intensity aerobic activity per week for clinically meaningful weight loss, in combination with strength training and diet interventions [6]. Thus, even though exercise presents an excellent therapeutic intervention and prevention mechanism, if prevention is not achieved prior to the development of CMD, the burden on the patient to perform the prescribed exercise becomes greater and more difficult to maintain.

Besides weight loss, exercise is crucial for improving cardiorespiratory fitness (CRF); low CRF is a risk factor for CVD, CVD mortality, and all-cause mortality [7], especially in individuals with obesity and CMD. The Aerobics Center Longitudinal Study examined changes in fitness (metabolic equivalents; METs) and CVD mortality in 14,345 men. They identified that for every 1-met improvement, there was a 15% and 19% lower risk of all-cause and CVD mortality, respectively [7].

From a clinical standpoint, understanding the patients' cardiometabolic risk factors can help guide the exercise regimen prescribed. To improve resting blood pressure, it has been shown that aerobic training, resistance training, or the combination of both have similar positive effects on resting systolic/diastolic blood pressure in adults, independent of obesity [8–10]. However, different exercise modalities (aerobic, resistance, or a combination) may induce distinct metabolic and inflammatory adaptations. Furthermore, the combination of aerobic and anaerobic resistance training has been shown to achieve moderate improvements in insulin sensitivity and glycemic control in type 2 diabetics [8], with an added benefit of improved lipid profiles [11]. Interestingly, for improving fat mass and CRF, aerobic training or a combination of aerobic and resistance training has a greater, more favorable effect than resistance training alone. For fat mass specifically, a combination approach provides the greatest benefits [12–14]. Aerobic training alone improves CRF in a dose-dependent fashion, whereby higher-intensity aerobic training increases CRF more than moderate-intensity training [15].

For patients currently suffering from CMD, understanding the molecular mechanisms of exercise-induced benefits is of utmost importance. Moreover, this would allow researchers to potentially develop novel exercise mimetics to supplement current

pharmacological treatments for those patients who cannot participate in traditional exercise therapy due to the severity of comorbidities.

Understandably, the question of how exercise perpetuates improvements in CMD has been of considerable interest for researchers in recent years. Recent studies have shown that plasma from exercised mice, administered to older, cognitively deficient mice, mediated improved cognitive functions and reduced brain inflammation. This suggests that the effects of exercise are of a humoral nature (secreted factors termed *exerkines*), in addition to the known stimuli (increased cardiac output, increased vasoconstriction, shear stress, stretch receptor activation, etc.) [16].

A central challenge in the field of exercise mimetics is that not a single pathway but rather a system-level stimulus coordinates changes in skeletal muscle, cardiovascular function, metabolism, immunity, endocrine signaling, etc. Most studies examining exercise mimetics only target one or a few of the aforementioned pathways. This makes it particularly challenging to reproduce in translational studies. Moreover, at the human level, exercise intensity, sex, age, genetics, and disease state all play a role in shaping how these exercise-induced molecules may affect the system as a whole. There is considerable enthusiasm surrounding some key myokines like irisin, IL-15, apelin and others. However, the causal evidence remains heterogeneous as circulating levels are difficult to reliably measure and the mechanism of action for many of the potential candidates is poorly understood [17]. Given that PGE2 has both pro- and anti-inflammatory effects depending upon the tissue and stimulus, we propose a role for the bioactive lipid prostaglandin E2 in conferring exercise improvements (discussed in more detail in later sections).

1.2. Exercise-Induced Lipid Response

Ample evidence from the literature suggests that exercise training has positive effects on both the prevention and the treatment of cardiovascular disease. Importantly, one way that exercise reduces the burden of cardiovascular disease is through its impact on blood lipid concentrations. In general, exercise training reduces total triglyceride levels and increases high-density lipoprotein (HDL) cholesterol, while lowering low-density lipoprotein (LDL) cholesterol. The type of exercise is important, as a meta-analysis by Smart et al. [18] recently showed that when the types of exercise were set as covariates in the analysis, aerobic training significantly reduced total cholesterol, LDL, triglycerides, and very-low-density lipoprotein (VLDL) cholesterol. In contrast, resistance training only provided improvements in HDL. The effect of combined training was similar to that of aerobic training alone, via reductions in cholesterol, LDL, VLDL, and triglycerides, with a concomitant increase in HDL. Thus, the type, intensity, and duration of exercise are key factors that influence its beneficial effects.

Besides the beneficial changes in the species of lipoproteins, studies in both human and animal models have recorded changes in lipid mediators in response to exercise. Lipid mediators are bioactive signaling molecules that are derived from fatty acids to help coordinate the body's response to acute and chronic exercise training. During and after exercise, the production of prostaglandins, leukotrienes, lipoxins, and other pro-resolving mediators (e.g., resolvins) helps to regulate inflammation, vascular tone, and adaptation. Among these mediators is prostaglandin E2, the focus of this review article (Table 1) [19–24].

Table 1. Studies examining lipids in response to exercise.

Study	Design	Cohort	Lipids Measured	Key Findings
Jurado-Fasoli et al., 2022 [19]	12-week RCT	Middle-aged sedentary adults	Oxylipins (AA-derived: 12-HETE, 15-HETE; DHA/EPA-derived: resolvin precursors); Endocannabinoids, eCB and eCB-like molecules	No significant change in fasting plasma levels of Omega-3/6 oxylipins, nor any change in eCBs or eCB-like molecules.
Nieman et al., 2019 [20]	Crossover cycling trial	Endurance-trained cyclists	CYP oxylipins (EpOMEs, DiHOMEs), LOX oxylipins (HETEs, HODEs)	Prolonged exercise elevated 43 out of 45 metabolites analyzed; carbohydrate intake attenuates the increase.
van Doorslaer et al., 2023 [21]	Acute + training intervention	Healthy & prediabetic adults	Endocannabinoids (AEA, 2-AG, OEA, PEA); CB1/CB2 protein in muscle	Exercise modality-specific changes in ECs: Increase after endurance exercise, decrease after resistance training.
Zemski-Berry et al., 2025 [22]	Exercise + weight loss	Adults with obesity	DAG species (C16:0/18:1), sphingolipids (ceramides: Cer d18:1/16:0), triglycerides	Subcellular lipid redistribution linked to improved insulin sensitivity with weight loss.
Fabre et al., 2025 [23]	Mechanistic (animal + in vitro)	Mouse + muscle cells	Prostaglandins (PGD ₂ , 15Δ-PGJ ₂), SPMs (Protectin D1)	Lipid mediator class switching controls myogenesis and regeneration.
Liu et al., 2025 (Review) [24]	Training/mechanistic	Human/animal muscle	Lipid droplet proteins (PLIN2, PLIN5) associated with triglyceride pools	Exercise remodels lipid droplets and enhances mitochondrial coupling.

Representative human and animal studies examining changes in bioactive lipid mediators in response to acute and chronic exercise. The table summarizes study design, participant characteristics, lipid classes measured (including oxylipins, endocannabinoids, sphingolipids, and prostaglandins), and key findings. Studies include both circulating (plasma/serum) lipid measurements and skeletal muscle lipidomic or signaling responses, highlighting systemic and tissue-specific adaptations to exercise.

2. Overview of Prostaglandin E2 Biology

Biosynthesis and Metabolic Pathways

PGE₂ is a bioactive lipid mediator belonging to the eicosanoid family, derived from arachidonic acid and synthesized through a tightly regulated, multi-step enzymatic process. It typically acts in a paracrine and/or an autocrine fashion and plays critical roles in inflammation, fever, pain sensitization, vascular tone regulation, and gastrointestinal protection. The biosynthesis of PGE₂ occurs in most mammalian cell types and is typically initiated in response to physiological stimuli such as cytokines, growth factors, or mechanical injury [25]. The first and rate-limiting step in PGE₂ synthesis involves the mobilization of arachidonic acid from membrane phospholipids. This cleavage is catalyzed primarily by cytosolic phospholipase A₂ (cPLA₂), which is activated by increases in intracellular calcium and phosphorylation via mitogen-activated protein kinases (MAPKs). Upon activation, cPLA₂ selectively hydrolyzes the sn-2 position of glycerophospholipids, releasing free arachidonic acid into the cytosol [26]. This step is highly regulated, ensuring that prostaglandin synthesis is closely linked to cellular activation states. Once liberated, arachidonic acid is converted to prostaglandin H₂ (PGH₂) via the cyclooxygenase (COX) enzymes, which exist in two main isoforms: COX-1 and COX-2. COX-1 is constitutively expressed in many tissues and is responsible for basal prostaglandin production involved in homeostatic functions such as gastric mucosal

protection and platelet aggregation. In contrast, COX-2 is an inducible enzyme, upregulated during inflammation in response to pro-inflammatory cytokines (e.g., IL-1 β , TNF- α) [27,28] and other stimuli [29]. The COX enzymes catalyze a two-step reaction. First, arachidonic acid is oxygenated and cyclized to form prostaglandin G₂ (PGG₂), a hydroperoxide intermediate. This reaction requires molecular oxygen and involves the insertion of two oxygen molecules. Subsequently, the peroxidase activity of the same enzyme reduces PGG₂ to PGH₂. PGH₂ serves as a common precursor for all major prostanoids, including prostacyclin (PGI₂), thromboxane A₂ (TXA₂), and various prostaglandins such as PGE₂.

The final step in PGE₂ biosynthesis is the isomerization of PGH₂ to PGE₂, catalyzed by prostaglandin E synthases (PGES). There are three known isoforms of PGES. Microsomal PGES-1 (mPGES-1): This glutathione-dependent enzyme is inducible and functionally coupled to COX-2 [30]. It is the primary enzyme responsible for elevated PGE₂ production during inflammatory responses. Microsomal PGES-2 (mPGES-2): Constitutively expressed and less well-characterized, it may contribute to both basal and inducible PGE₂ synthesis. Cytosolic PGES (cPGES): A cytosolic form typically associated with COX-1 and responsible for housekeeping levels of PGE₂. mPGES-1 is considered the dominant isoform during inflammation and is often upregulated alongside COX-2, creating a coordinated pathway for increased PGE₂ production under pathological conditions.

The enzymes involved in PGE₂ biosynthesis are strategically localized within the cell. cPLA₂ translocates to perinuclear and endoplasmic reticulum membranes upon activation, where it releases arachidonic acid in proximity to COX enzymes. COX-1 and COX-2 are primarily membrane-bound enzymes located in the endoplasmic reticulum and nuclear envelope, facilitating efficient substrate channeling. Similarly, mPGES-1 is associated with these membranes, forming a functional complex with COX-2.

Regulation of PGE₂ biosynthesis occurs at multiple levels, including enzyme expression (transcriptional control of COX-2 and mPGES-1), enzyme activation (phosphorylation of cPLA₂), substrate availability, and feedback mechanisms. Nonsteroidal anti-inflammatory drugs (NSAIDs) exert their effects by inhibiting COX activity, thereby reducing PGE₂ production [31].

PGE₂ exerts its biological effects through four distinct G protein-coupled receptors (EP1–EP4), each linked to different intracellular signaling pathways [32–34]. Classically, EP2 and EP4 signal through G_{as}, activating adenylate cyclase and increasing cAMP levels within the cell. In contrast, EP3 signals through G_{ai} to inhibit adenylate cyclase. EP1 signals through G_{aq} to increase Ca²⁺ levels in the cell. The diversity of receptor subtypes allows PGE₂ to mediate a wide range of physiological and pathological responses depending on the tissue context and receptor expression profile [35,36].

3. Exercise as a Mediator of PGE₂ Production

3.1. Effect of Exercise on PGE₂ Production

Several studies [37–43] have examined changes in prostaglandins, including PGE₂ specifically, after exercise (summarized in Table 2). Trappe and colleagues reported that administration of the NSAIDs ibuprofen and acetaminophen at maximal doses can inhibit skeletal muscle protein synthesis after resistance exercise [37,38]. They followed up this study by showing that production of PGE₂ in healthy young men was significantly attenuated after exercise when treated with acetaminophen specifically. The ibuprofen group had a trending reduction, but the data were not statistically significant. These results were confirmed when Naruse et al. examined the effects of low-dose aspirin on skeletal muscle PGE₂ production after resistance training. In both men and women, low-dose aspirin inhibited muscle PGE₂ production significantly compared to standard-dose

aspirin [39]. Interestingly, the skeletal muscle of men was 60% more sensitive to the effects of aspirin. This warrants future studies on the COX/PGE2 pathway in the skeletal muscle of men and women and the broader impact of sex differences in the long-term consumption of NSAIDs, as inhibiting PGE2 would likely contribute to deleterious effects on exercise.

Taken together, these findings suggest that PGE2 is not simply a marker of the acute inflammatory response to exercise but rather an important mediator of skeletal muscle adaptation during training. The observations that NSAIDs attenuate exercise-induced PGE2 production indicate that COX-derived prostaglandin signaling may contribute to the anabolic response to exercise. Moreover, the differential sensitivity to aspirin observed between men and women raises the possibility that sex-specific regulation of the COX–PGE2 axis influences training adaptation and recovery. In the broader context of exercise physiology, these data support a model whereby transient increases in PGE2 following exercise serve as a physiological signal that promotes muscle repair and regeneration. In contrast, chronic pharmacological suppression of the pathway (e.g., NSAID use) likely blunts the beneficial adaptations to training. Thus, PGE2 represents a key mechanistic link between acute exercise and long-term structural/metabolic adaptations that improve overall muscle function and health.

Additional studies have examined the role of PGE2 and its four G-protein-coupled receptors on skeletal muscle and skeletal muscle stem cells (muscle satellite cells). These studies are described in more detail in Section 3.2, and while direct evidence may not be available, we cautiously explore how activity of the receptors may be linked to cardiometabolic disorders.

Table 2. Studies examining prostaglandins in response to exercise.

Study	Design	Cohort	Compartment	Measurement	Key Findings on PGE2
Trappe et al., 2001 [37]	Acute eccentric resistance exercise ± NSAIDs	Healthy young adults	Skeletal muscle	Muscle biopsy (PGE2, PGF2α)	Eccentric exercise increased skeletal muscle PGE2 production
Trappe et al., 2002 [38]	Acute resistance exercise ± NSAIDs	Young adults	Skeletal muscle	Muscle prostaglandin signaling	Inhibition of PGE2 alters muscle remodeling signaling after exercise
Naruse et al., 2021 [39]	Acute resistance exercise + aspirin	Healthy adults (men vs. women)	Skeletal muscle	Ex vivo muscle PGE2 production	PGE2 reduced with aspirin; no significant change at 3.5 h post-exercise
Liu et al., 2016 [40]	Cross-sectional	Young and older adults (men vs. women)	Skeletal muscle	COX enzymes, PGE2 synthases, EP receptors	Confirms muscle capacity for PGE2 production relevant to adaptation and muscle fiber type
Ho et al., 2017 [41]	Muscle injury model	Mouse	Skeletal muscle	Satellite cell signaling	PGE2 required for regeneration after contraction-related injury
Palla et al., 2020 [42]	Pharmacologic elevation of PGE2 using 15-PGDH	Aged mice	Skeletal muscle	PGE2 signaling	Elevated PGE2 restores muscle mass and exercise capacity
Wang et al., 2025 [43]	Exercise + PGE2 treatment	Aged mice	Skeletal muscle	Stem cell signaling	PGE2 enhances exercise-induced regeneration

Studies examining prostaglandin E₂ (PGE₂) responses to exercise across biological compartments. The table distinguishes measurements in skeletal muscle, plasma, and urine, including direct quantification of PGE₂ or its metabolites (e.g., urinary PGE-M). The majority of evidence derives from skeletal muscle biopsy or ex vivo production assays, whereas urinary metabolites reflect

systemic prostaglandin turnover and plasma measurements remain limited. This compartmental stratification highlights differences between local (muscle) and systemic PGE2 responses to various exercise training paradigms.

3.2. Role of EP Receptors in Skeletal Muscle

3.2.1. EP1 Receptor (Ptger1)

The EP1 receptor is expressed at detectable, albeit relatively low, levels in human skeletal muscle and forms part of the broader COX–PGE2 signaling pathway that regulates muscle physiology. In a study from Liu et al., human muscle biopsy samples were obtained from the soleus (mainly type I fibers) and the vastus lateralis (> type 2 fibers than the soleus). Expression of EP1 and EP2 was not different between muscle types [40]. In a parallel experiment, samples from the same regions were also obtained from a sedentary group of young vs. old participants. EP1 (along with EP3 and EP4) has been shown to have reduced expression with aging, suggesting it may mediate muscle adaptation processes [40]. Unlike EP2 and EP4 (discussed below), EP1 has not been directly linked to muscle growth or regeneration pathways. Instead, it is thought to play a more modulatory role within the PGE2 signaling network. Based on its classically recognized signaling cascade, EP1 is hypothesized to contribute to Ca²⁺-dependent signaling, inflammation, and perhaps counter-regulation of anabolic pathways. This could subsequently promote endothelial dysfunction, vascular stiffness, insulin resistance, and ultimately an increased risk of cardiometabolic disease. However, direct evidence in skeletal muscle remains limited and incomplete and thus warrants further investigation.

3.2.2. EP2 Receptor (Ptger2)

Muscle satellite cells are stem cells that are specific to skeletal muscle. These are adult stem cells that are situated between the muscle basal lamina and the sarcolemma. Upon injury, they are activated, enter the cell cycle (normally existing in a quiescent G₀ state), undergo proliferation and differentiate into newly formed myofibers. They can also fuse with existing damaged myofibers for repair. These cells also play an important role in postnatal growth of muscle and hypertrophy, such as after exercise (via the Yap1/Taz-Thbs1-CD47 pathway) [44]. Their quiescence, however, is important as it prevents the loss and exhaustion of the cellular pool. Reports show that quiescence of muscle satellite cells is regulated by factors such as Wnt4 [45], N/M-cadherins [46], and Notch–Notch interactions [47]. Moreover, it was previously reported that the PGE2 EP2 receptor was upregulated in human muscle progenitors via Notch signaling mechanisms [48]. In a very recent study by Maruyama and colleagues, the authors elegantly show that EP2 is essential for the maintenance of muscle satellite cells, and its deficiency actually leads to their activation and loss, thereby impairing muscle regeneration. These actions of EP2 were via reduced phosphorylation of ERK1/2, similar to the actions of PTEN. Interestingly, the authors noted that EP2 and PTEN may have similar roles in the maintenance of the skeletal muscle pool, warranting further investigation into this novel relationship [49].

3.2.3. EP3 Receptor (Ptger3)

EP3 receptor expression in skeletal muscle has been shown to be ~2-fold higher in the soleus (type 1 fiber) vs. the more glycolytic vastus lateralis muscle (type 2 > type 1), and, like EP1, was shown to decline ~30–33% with age [40]. Within skeletal muscle physiology, PGE2 signaling broadly regulates protein turnover and exercise adaptation. By analogy to its canonical signaling and effects in other tissues, EP3 is thought to bias responses toward reduced cAMP/PKA signaling, pro-inflammatory activity, and potentially catabolic or anti-anabolic effects, rather than regeneration or hypertrophy. Much like the EP1 receptor, direct mechanistic studies in skeletal muscle are lacking for EP3, but EP3 is

strongly linked in other systems to inflammation [50], vascular contractility [51–54], and stress signaling [55–58] and mediates processes such as immune activation and cell stress responses via Gi/PLC pathways. Taken together, the available evidence supports a model in which EP3 acts as a modulatory or inhibitory arm of PGE₂ signaling in skeletal muscle, contributing to the regulation of protein turnover and inflammatory tone, but with comparatively sparse direct evidence defining its specific functional role relative to the better-characterized EP2/EP4 pathways.

3.2.4. EP4 Receptor (Ptger4)

The EP4 receptor is one of the most well-characterized PGE₂ receptors in skeletal muscle and plays a central role in muscle regeneration [43], growth [41], and metabolic regulation [59]. EP4 is primarily a G_{as}-coupled GPCR that stimulates adenylate cyclase, increasing cAMP and activating downstream PKA/CREB signaling pathways, affecting target genes such as Nurr1 (*Nr4a2*) [41] and *Orai1* [60], which share common functions in immune activation and metabolism. Similarly, a very recent report by Jiang et al. showed that in *migrasomes* (these are membranous organelles released from migrating cells), upregulation of PGE₂ induced an SPP1+ (secreted phosphoprotein 1) macrophage phenotype [61]. The authors did not explore the specific PGE₂ receptor mediating this response; however, this agrees with previously reported roles for the EP4 receptor in the cancer literature [62–64]. In skeletal muscle, EP4 signaling has been shown to be essential for muscle satellite cell function, where PGE₂ acting through EP4 promotes myoblast proliferation, satellite cell expansion, and efficient regeneration after injury, with genetic deletion of EP4 impairing regeneration and reducing muscle strength. In the study from Wang et al., the authors generated a satellite cell-specific EP4 knockout and showed an accelerated aging phenotype characterized by atrophy and loss of strength [43]. Mechanistically, EP4-mediated cAMP signaling aligns with broader evidence that cAMP pathways drive hypertrophy, regeneration, and metabolic adaptation in skeletal muscle, including the regulation of fiber size and oxidative phenotype. Importantly, EP4 signaling is also altered with aging, with reduced EP4 activity in aged muscle stem cells contributing to impaired regeneration. Moreover, it has been reported that PGE₂ levels themselves are reduced with aging due to increased expression of 15-hydroxylprostaglandin dehydrogenase (15-PGDH), an enzyme that degrades prostaglandins [42], appropriately termed a *gerozyme* [65]. In contrast, restoring PGE₂–EP4 signaling improves muscle repair and function [41]. From a cardiometabolic perspective, EP4 exerts dual and context-dependent effects: on one hand, it can be beneficial by supporting tissue repair and suppressing inflammation in some settings (e.g., improving insulin sensitivity via anti-inflammatory actions in obesity models); on the other hand, emerging evidence in skeletal muscle cells indicates that EP4 activation can impair insulin signaling and glucose uptake via NF-κB-mediated inflammatory pathways, contributing to lipid-induced insulin resistance. Together, these findings support a model in which EP4 is a key anabolic and regenerative receptor in skeletal muscle, but when dysregulated, particularly under conditions of chronic inflammation, lipid overload, or aging, it may also contribute to metabolic dysfunction and insulin resistance, linking muscle biology to broader cardiometabolic disease risk.

4. PGE₂ Response to Exercise in Adipose Tissue

PGE₂ has emerged as an important regulator of adipose tissue physiology, particularly in the context of lipolysis, inflammation, and metabolic adaptation. A key feature of PGE₂ signaling in adipose tissue is its tight coupling to lipid mobilization. Although relatively few studies have directly examined PGE₂ responses in adipose tissue following acute or chronic exercise, a substantial body of work in adipocyte biology and

related physiological conditions (i.e., fasting, lipolysis, COX-2 activation) provides mechanistic insights that may be relevant to exercise adaptation. Therefore, much of the following discussion should be interpreted as hypothesis-generating and based on indirect evidence rather than direct demonstrations of exercise-induced adipose PGE2 signaling.

For example, lipolytic stimulation of adipocytes has been shown to increase PGE2 production via activation of classical PLA2 and COX pathways. This indicates that PGE2 is generated as part of the adipocyte response to triglyceride breakdown. This is particularly relevant to exercise, where catecholamine-driven lipolysis is a well-known dominant metabolic process. However, direct evidence that exercise-induced lipolysis increases adipose tissue PGE2 production in humans remains limited.

PGE₂ signaling through its EP receptors, especially EP4, can modulate basal lipolysis and interact with insulin signaling, suggesting a role in fine-tuning fatty acid release during dynamic energy demand. However, this proposed role during exercise is currently inferred from adipocyte and pharmacological studies rather than direct exercise experiments. Consistent with this, exogenous PGE2 has been shown to inhibit β -adrenergic-stimulated lipolysis in adipocytes, further supporting a feedback limit on excessive lipid mobilization [66–68].

In addition to its metabolic regulation, PGE2 plays a significant role in adipose immune function. Adipocyte-derived PGE2 acts as a chemoattractant and signaling mediator that promotes macrophage recruitment during lipolysis, linking lipid mobilization to immune cell trafficking. Importantly, this effect appears to be largely anti-inflammatory or regulatory rather than overtly pro-inflammatory, consistent with other recently discovered functions of the EP4 receptor [66,69,70]. Indeed, PGE2 signaling through EP4 receptors suppresses chemokine production, dampens inflammatory gene expression in adipose tissue and can reduce the expression of cytokines such as IL-6 and MCP-1 in human adipose explants [71]. These findings align with the well-established anti-inflammatory effects of regular exercise in adipose tissue and raise the possibility that PGE2 contributes to exercise-induced improvements in adipose immune tone. However, direct studies measuring adipose PGE2 signaling alongside exercise-induced immune remodeling are currently lacking. Moreover, any contribution of PGE2 to exercise-mediated adipose immune adaptations remains speculative at present.

PGE2 also influences adipose tissue remodeling and thermogenic programming, which are especially important in the context of exercise and obesity. Adult humans with detectable levels of brown fat have a reduced incidence of hypertension [72]. In both human and experimental models, PGE2 promotes the expression of brown/beige adipocyte markers, including uncoupling protein 1 (UCP1) and PR domain zinc finger protein 16 (PRDM16), indicating a role in adipose browning and adaptive thermogenesis. This is particularly relevant to exercise physiology, as endurance training is known to enhance mitochondrial capacity and promote beige adipocyte formation. Whether PGE2 directly mediates these exercise-induced adaptations in adipose tissue has not been established. Very recently, Koenen et al. elegantly showed that in adipocyte-specific *Prdm16* knockout mice, characterized by a loss of beige adipocyte identity, there was marked remodeling of perivascular adipose tissue, increased vascular reactivity, and elevated blood pressure [73]. Furthermore, PGE2 production appears to restrain adipogenesis and adipose tissue expansion. In contrast, loss of COX-2 signaling increases adipocyte size and number, whereas PGE2 suppresses adipogenesis through PKA-dependent pathways (e.g., EP4 signaling) and reduces fat accumulation. A timely, relevant study was performed by Jingyi Li et al. [74] using a glucagon-like peptide-1 receptor agonist (GLP-1RA), Liraglutide. The authors showed that Liraglutide reduced body weight, improved metabolic insulin resistance and increased the expression of

browning-related markers like PGC1 α , UCP1, and ATGL. Importantly, COX-2 signaling and prostaglandin levels were increased in subcutaneous tissues. COX-2 inhibition abolished the effects of Liraglutide. These results confirmed that targeting the COX-2 pathway is important to consider when treating obese patients with GLP-1RAs. Together, these findings position PGE2 as a regulator not only of acute metabolism but also of long-term tissue remodeling [74,75]. However, definitive evidence supporting a similar role during exercise-induced adipose remodeling remains limited.

As mentioned previously, exercise is a key mechanism for reducing obesity, insulin resistance, inflammation, and ultimately cardiometabolic syndrome. Although direct PGE2 measurements in adipose tissue following exercise are scarce, studies using related physiological paradigms such as fasting, lipolysis-inducing interventions, genetic models, and pharmacological manipulation provide a conceptual framework for understanding how PGE2 may participate in exercise adaptation. Importantly, these studies do not establish that exercise elicits identical PGE2-dependent mechanisms in adipose tissue. The beneficial effects of PGE2 on immune and metabolic adaptations observed during intermittent fasting share several physiological features with endurance exercise. However, extrapolation between these conditions should be interpreted cautiously because the underlying signaling responses may not be identical. Future studies directly measuring adipose PGE2 responses to acute and chronic exercise in humans will be important to confirm and expand upon this framework [66–68,71].

5. Preclinical Large-Animal Evaluations of PGE2 and Implications for Sensitization of Autonomic Response Mechanisms in Humans

PGE2 has been examined with regard to cardiovascular function in a variety of large-animal model systems, including leporine, feline, canine, porcine, ovine, and bovine models [76–80]. Although PGE2 has been evaluated comparatively across multiple models, conclusions vary regarding cardiovascular function outcomes. Specifically, there are variations in results related to how PGE2 function is altered depending on the study design and the specific portion of the prostaglandin pathway being evaluated [76,77,79,81–83]. For instance, early studies in large animals have shown that prostaglandins (PGE2 specifically) can modulate autonomic responses, contribute to ventricular remodeling following a myocardial infarction, and participate in ischemia–reperfusion preconditioning [77,84–88]. Studies evaluating baroreflex activity and intracoronary PGE2 infusion have shown that PGE2 is capable of impairing baroreflex function independently of chemoreflex activity, and this is likely driven by cardiac c-fiber afferent activity [76]. Coincidentally, inhibition of the COX pathway with the COX inhibitor indomethacin was shown to blunt cardiac afferent responses to bradykinin in dogs with congestive heart failure [88]. Together, these results imply that PGE2 activity increases cardiac afferent activity and impairs baroreflex activity [89–92]. Beyond direct autonomic alterations, studies utilizing large animals have also shown that the inhibition of enzymes responsible for PGE2 synthesis, specifically COX-2, leads to exaggerated vasoconstriction, impaired response to myocardial infarction, and abolition of ischemia–reperfusion preconditioning. Although studies utilizing exercise per se are limited, these aforementioned studies highlight the potentially beneficial impact of PGE2 signaling in response to exercise (e.g., vasoconstriction) and myocardial injury [77–79,87].

In contrast to cardiac function, the skeletal muscle response to PGE2 in preclinical models is far less understood. Current evidence is largely limited to the potential role of PGE2 signaling in skeletal muscle afferent nerves, as well as its release and downstream systemic effects. Even within the studies on afferent activity, preclinical relevance remains unclear, in part because there is no clearly defined stimulatory pathway by which prostaglandins can directly regulate autonomic function. Nevertheless, prostaglandins

remain an important topic of discussion regarding autonomic function, particularly in the context of cardiometabolic disease.

Studies evaluating cardiac sympathetic afferent activity have identified a potential role for PGE2 and/or COX-2 inhibition as described above, illustrating the potent impact of prostaglandin activity on cardiac afferent activation within the heart and cardiac circulation as well as its robust impact on baroreflex function [77,82,83,93–96]. However, it remains unclear whether prostaglandins act within the cardiac afferent system directly or through other pathways (i.e., skeletal muscle, renal afferents). Moreover, given the limited studies of PGE2 and altered autonomic activity, it is possible that the effects are a result of the actions of prostacyclin (or another COX-1/2-derived prostanoid). Based on the current evidence, it is likely that COX-derived mediators act primarily to sensitize or desensitize neural responses to more potent autonomic mediators, as opposed to being direct stimulators of autonomic activity themselves. However, their innate signaling capacity has yet to be investigated. Regarding indirect alterations in autonomic function, relatively recent studies of prostaglandins have shown that they can sensitize or enhance responses mediated by common receptors (TRPV1, P2X3, and ASIC) located on type III and IV unmyelinated afferent fibers, which are known to contribute to both pain signaling and cardiovascular response patterns [97–102]. This capacity to sensitize afferent receptor subtypes is especially important as several cardiovascular and metabolic conditions result in elevated inflammatory responses, in which PGE2 is likely involved. In the context of exercise and exercise capacity in disease, the potential effects of PGE2 expression are especially important. For instance, studies have shown that skeletal muscle-mediated cardiovascular responses via various afferent receptor subtypes (i.e., P2X3, TRPV1, and ASIC) are impaired and/or exaggerated in various disease pathologies such as diabetes, heart failure, hypertension, obesity, and others [96,103–107]. Given the inflammatory nature of these conditions, PGE2 signaling could be a mechanism that accounts for variations in autonomic response patterns from skeletal muscle during exercise, although direct evidence for this is currently lacking. In hypertension, for example, cardiac performance increases along with systemic vasoconstriction [108]. Additionally, in heart failure, cardiac performance improves minimally, yet vasoconstriction is profoundly exaggerated [109]. In the context of diabetes, pressor responses are exaggerated during exercise along with limited cardiac improvements relative to the other conditions, which is unexpected given the lack of existing hypertension [110]. Overall, the variations in the response patterns and severity of perfusion limitation in disease induced by autonomic afferent signaling may be modifiable via PGE2 and/or COX-2 modulation.

Studies in humans with heart failure have shown that when exercise training is not limited by intolerance and can be used as an adjunct therapy, mediators of autonomic dysfunction may normalize, which correlates with reductions in COX-2 pathway activation [98]. Subsequent studies have observed that afferent expression of both initiators of autonomic signaling (PGE2 and/or COX-2) is upregulated in individuals with reduced exercise capacity due to training status and disease [111]. However, this is not direct evidence in a conscious model, but the potential of prostaglandins as amplifiers and/or sensitizers of afferent signaling is plausible. Furthermore, the work in large animals and humans thus far has mainly centered on neurogenic mechanisms. Investigations on the effects of PGE2 and/or COX-2 in skeletal muscle itself regarding exercise capacity are limited. Thus, the unanswered questions regarding PGE2 signaling and autonomic function provide significant justification for further studies and evaluation as a therapeutic target for exercise intolerance.

6. Conclusions and Perspectives

The purpose of this review is to highlight the complex and context-dependent role of PGE2 in cardiovascular disease, exercise, and, importantly, its broader implications for cardiometabolic disease. The evidence presented here suggests that PGE2 signaling can play a protective and adaptive role in cardiovascular function (depending on which receptor subtype is activated and in which tissue), obesity, and inflammation, and can contribute to the modulation of autonomic responses. At the same time, inhibition of PGE2-producing pathways can exacerbate vasoconstriction and impair recovery following cardiac injury, highlighting its physiological importance. Preclinically, its role in skeletal muscle and afferent signaling remains less clearly defined, with current data suggesting that prostaglandins may act primarily as sensitizers of neural pathways rather than direct regulators of autonomic output. This concept is particularly relevant to cardiometabolic disease, where dysregulated autonomic function, chronic inflammation, and impaired exercise capacity intersect. The observed upregulation of COX-2 and prostaglandin-sensitive signaling pathways in individuals with reduced exercise tolerance suggests that altered PGE2 signaling may contribute to the autonomic imbalance and reduced cardiovascular adaptability characteristic of cardiometabolic conditions. Thus, PGE2 may represent a key intermediary linking inflammatory signaling, neural control, and cardiovascular dysfunction within the broader cardiometabolic disease framework, highlighting its potential as both a biomarker and therapeutic target.

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References

1. Palaniappan, L.P.; Allen, N.B.; Almarzooq, Z.I.; Anderson, C.A.M.; Arora, P.; Avery, C.L.; Baker-Smith, C.M.; Bansal, N.; Currie, M.E.; Earlie, R.S.; et al. 2026 Heart Disease and Stroke Statistics: A Report of US and Global Data from the American Heart Association. *Circulation* **2026**, *153*, 109087. <https://doi.org/10.1161/cir.0000000000001412>.
2. Church, T.S.; Blair, S.N.; Cocroham, S.; Johannsen, N.; Johnson, W.; Kramer, K.; Mikus, C.R.; Myers, V.; Nauta, M.; Rodarte, R.Q.; et al. Effects of aerobic and resistance training on hemoglobin A1c levels in patients with type 2 diabetes: A randomized controlled trial. *JAMA* **2010**, *304*, 2253–2262. <https://doi.org/10.1001/jama.2010.1710>.
3. Schwingshackl, L.; Missbach, B.; Dias, S.; König, J.; Hoffmann, G. Impact of different training modalities on glycaemic control and blood lipids in patients with type 2 diabetes: A systematic review and network meta-analysis. *Diabetologia* **2014**, *57*, 1789–1797. <https://doi.org/10.1007/s00125-014-3303-z>.
4. Donnelly, J.E.; Hill, J.O.; Jacobsen, D.J.; Potteiger, J.; Sullivan, D.K.; Johnson, S.L.; Heelan, K.; Hise, M.; Fennessey, P.V.; Sonko, B.; et al. Effects of a 16-month randomized controlled exercise trial on body weight and composition in young, overweight men and women: The Midwest Exercise Trial. *Arch. Intern. Med.* **2003**, *163*, 1343–1350. <https://doi.org/10.1001/archinte.163.11.1343>.
5. Soták, M.; Clark, M.; Suur, B.E.; Börgeson, E. Inflammation and resolution in obesity. *Nat. Rev. Endocrinol.* **2025**, *21*, 45–61. <https://doi.org/10.1038/s41574-024-01047-y>.
6. Swift, D.L.; Ross, L.M.; Laddu, D.R.; Conroy, M.B.; German, C.A.; Evangelista, L.S.; Marvel, F.A.; Jerome, G.J. Role of Physical Activity in Obesity Treatment and Cardiometabolic Health: A Scientific Statement from the American Heart Association. *Circulation* **2026**, *154*, 1. <https://doi.org/10.1161/cir.0000000000001441>.
7. Ross, R.; Blair, S.N.; Arena, R.; Church, T.S.; Després, J.P.; Franklin, B.A.; Haskell, W.L.; Kaminsky, L.A.; Levine, B.D.; Lavie, C.J.; et al. Importance of Assessing Cardiorespiratory Fitness in Clinical Practice: A Case for Fitness as a Clinical Vital Sign: A

- Scientific Statement from the American Heart Association. *Circulation* **2016**, *134*, e653–e699. <https://doi.org/10.1161/cir.0000000000000461>.
8. Battista, F.; Ermolao, A.; van Baak, M.A.; Beaulieu, K.; Blundell, J.E.; Busetto, L.; Carraça, E.V.; Encantado, J.; Dicker, D.; Farpour-Lambert, N.; et al. Effect of exercise on cardiometabolic health of adults with overweight or obesity: Focus on blood pressure, insulin resistance, and intrahepatic fat-A systematic review and meta-analysis. *Obes. Rev.* **2021**, *22*, e13269. <https://doi.org/10.1111/obr.13269>.
 9. Cornelissen, V.A.; Smart, N.A. Exercise training for blood pressure: A systematic review and meta-analysis. *J. Am. Heart Assoc.* **2013**, *2*, e004473. <https://doi.org/10.1161/jaha.112.004473>.
 10. Inder, J.D.; Carlson, D.J.; Dieberg, G.; McFarlane, J.R.; Hess, N.C.; Smart, N.A. Isometric exercise training for blood pressure management: A systematic review and meta-analysis to optimize benefit. *Hypertens. Res. Off. J. Jpn. Soc. Hypertens.* **2016**, *39*, 88–94. <https://doi.org/10.1038/hr.2015.111>.
 11. Mann, S.; Beedie, C.; Jimenez, A. Differential effects of aerobic exercise, resistance training and combined exercise modalities on cholesterol and the lipid profile: Review, synthesis and recommendations. *Sports Med.* **2014**, *44*, 211–221. <https://doi.org/10.1007/s40279-013-0110-5>.
 12. Paluch, A.E.; Boyer, W.R.; Franklin, B.A.; Laddu, D.; Lobelo, F.; Lee, D.C.; McDermott, M.M.; Swift, D.L.; Webel, A.R.; Lane, A. Resistance Exercise Training in Individuals with and Without Cardiovascular Disease: 2023 Update: A Scientific Statement from the American Heart Association. *Circulation* **2024**, *149*, e217–e231. <https://doi.org/10.1161/cir.0000000000001189>.
 13. Schwingshackl, L.; Dias, S.; Strasser, B.; Hoffmann, G. Impact of different training modalities on anthropometric and metabolic characteristics in overweight/obese subjects: A systematic review and network meta-analysis. *PLoS ONE* **2013**, *8*, e82853. <https://doi.org/10.1371/journal.pone.0082853>.
 14. Powell-Wiley, T.M.; Poirier, P.; Burke, L.E.; Després, J.P.; Gordon-Larsen, P.; Lavie, C.J.; Lear, S.A.; Ndumele, C.E.; Neeland, I.J.; Sanders, P.; et al. Obesity and Cardiovascular Disease: A Scientific Statement from the American Heart Association. *Circulation* **2021**, *143*, e984–e1010. <https://doi.org/10.1161/cir.0000000000000973>.
 15. Piercy, K.L.; Troiano, R.P.; Ballard, R.M.; Carlson, S.A.; Fulton, J.E.; Galuska, D.A.; George, S.M.; Olson, R.D. The Physical Activity Guidelines for Americans. *JAMA* **2018**, *320*, 2020–2028. <https://doi.org/10.1001/jama.2018.14854>.
 16. Jin, L.; Diaz-Canestro, C.; Wang, Y.; Tse, M.A.; Xu, A. Exerkines and cardiometabolic benefits of exercise: From bench to clinic. *EMBO Mol. Med.* **2024**, *16*, 432–444. <https://doi.org/10.1038/s44321-024-00027-z>.
 17. Zhang, J.; Shao, Q.; Cheng, T.; Lin, J.; Tang, Y.; Lu, H.; Zhang, Y.; Yu, Z.; Cao, L. Exercise mimetics: Molecular mechanisms, biological and therapeutic effects. *Mol. Biomed.* **2026**, *7*, 81. <https://doi.org/10.1186/s43556-026-00483-8>.
 18. Smart, N.A.; Downes, D.; van der Touw, T.; Hada, S.; Dieberg, G.; Pearson, M.J.; Wolden, M.; King, N.; Goodman, S.P.J. The Effect of Exercise Training on Blood Lipids: A Systematic Review and Meta-analysis. *Sports Med.* **2025**, *55*, 67–78. <https://doi.org/10.1007/s40279-024-02115-z>.
 19. Jurado-Fasoli, L.; Yang, W.; Kohler, I.; Dote-Montero, M.; Osuna-Prieto, F.J.; Di, X.; Hankemeier, T.; Krekels, E.H.J.; Harms, A.C.; Castillo, M.J.; et al. Effect of Different Exercise Training Modalities on Fasting Levels of Oxylipins and Endocannabinoids in Middle-Aged Sedentary Adults: A Randomized Controlled Trial. *Int. J. Sport Nutr. Exerc. Metab.* **2022**, *32*, 275–284. <https://doi.org/10.1123/ijsnem.2021-0332>.
 20. Nieman, D.C.; Gillitt, N.D.; Chen, G.Y.; Zhang, Q.; Sakaguchi, C.A.; Stephan, E.H. Carbohydrate intake attenuates post-exercise plasma levels of cytochrome P450-generated oxylipins. *PLoS ONE* **2019**, *14*, e0213676. <https://doi.org/10.1371/journal.pone.0213676>.
 21. van Doorslaer de Ten Ryen, S.; Dalle, S.; Terrasi, R.; Koppo, K.; Muccioli, G.G.; Deldicque, L. Regulation of the endocannabinoid system by endurance and resistance exercise in hypoxia in human skeletal muscle. *J. Appl. Physiol.* **2023**, *134*, 569–580. <https://doi.org/10.1152/jappphysiol.00645.2022>.
 22. Zemski Berry, K.; Garfield, A.; Whytock, K.L.; Macias, E.; Zarini, S.; Jambal, P.; Stepaniak, T.; Bowen, S.; Perreault, L.; Johnson, C.; et al. Combined Weight Loss and Exercise Training Alters Skeletal Muscle Subcellular Lipid Localization and Intermuscular Adipose Tissue Cellular Composition. *Diabetes* **2025**, *74*, 2249–2263. <https://doi.org/10.2337/db25-0492>.
 23. Fabre, P.; Molina, T.; Larose, J.; Greffard, K.; G  n  reux-Gamache, G.; Deprez, A.; Mokhtari, I.; Pellerito, O.; Duchesne, E.; Dort, J.; et al. Bioactive lipid mediator class switching regulates myogenic cell progression and muscle regeneration. *Nat. Commun.* **2025**, *16*, 5578. <https://doi.org/10.1038/s41467-025-60586-8>.
 24. Liu, Z.; Zhao, Y. PLINs-mediated organelle interactions: A key of exercise-mediated improvement of skeletal muscle lipid metabolism disorders. *Front. Endocrinol.* **2025**, *16*, 1700668. <https://doi.org/10.3389/fendo.2025.1700668>.

25. Park, J.Y.; Pillinger, M.H.; Abramson, S.B. Prostaglandin E2 synthesis and secretion: The role of PGE2 synthases. *Clin. Immunol.* **2006**, *119*, 229–240. <https://doi.org/10.1016/j.clim.2006.01.016>.
26. Funk, C.D. Prostaglandins and leukotrienes: Advances in eicosanoid biology. *Science* **2001**, *294*, 1871–1875. <https://doi.org/10.1126/science.294.5548.1871>.
27. Ricciotti, E.; FitzGerald, G.A. Prostaglandins and inflammation. *Arterioscler. Thromb. Vasc. Biol.* **2011**, *31*, 986–1000. <https://doi.org/10.1161/atvbaha.110.207449>.
28. Samuelsson, B.; Goldyne, M.; Granstrom, E.; Hamberg, M.; Hammarstrom, S.; Malmsten, C. Prostaglandins and thromboxanes. *Annu. Rev. Biochem.* **1978**, *47*, 997–1029. <https://doi.org/10.1146/annurev.bi.47.070178.005025>.
29. Masuko-Hongo, K.; Berenbaum, F.; Humbert, L.; Salvat, C.; Goldring, M.B.; Thirion, S. Up-regulation of microsomal prostaglandin E synthase 1 in osteoarthritic human cartilage: Critical roles of the ERK-1/2 and p38 signaling pathways. *Arthritis Rheum.* **2004**, *50*, 2829–2838. <https://doi.org/10.1002/art.20437>.
30. Watanabe, K.; Kurihara, K.; Tokunaga, Y.; Hayaishi, O. Two types of microsomal prostaglandin E synthase: Glutathione-dependent and -independent prostaglandin E synthases. *Biochem. Biophys. Res. Commun.* **1997**, *235*, 148–152. <https://doi.org/10.1006/bbrc.1997.6708>.
31. Green, G.A. Understanding NSAIDs: From aspirin to COX-2. *Clin. Cornerstone* **2001**, *3*, 50–60. [https://doi.org/10.1016/s1098-3597\(01\)90069-9](https://doi.org/10.1016/s1098-3597(01)90069-9).
32. Sugimoto, Y.; Narumiya, S. Prostaglandin E receptors. *J. Biol. Chem.* **2007**, *282*, 11613–11617. <https://doi.org/10.1074/jbc.R600038200>.
33. Yamamoto, E.; Izawa, T.; Kuwamura, M.; Yamate, J. Immunohistochemical Expressions of Main PGE(2) Biosynthesis-related Enzymes and PGE(2) Receptor in Rat Nephrogenesis. *J. Toxicol. Pathol.* **2011**, *24*, 257–261. <https://doi.org/10.1293/tox.24.257>.
34. Breyer, M.D.; Breyer, R.M. Prostaglandin E receptors and the kidney. *Am. J. Physiol. Renal Physiol.* **2000**, *279*, F12–F23. <https://doi.org/10.1152/ajprenal.2000.279.1.F12>.
35. Yang, G.; Chen, L. An Update of Microsomal Prostaglandin E Synthase-1 and PGE2 Receptors in Cardiovascular Health and Diseases. *Oxidative Med. Cell. Longev.* **2016**, *2016*, 5249086. <https://doi.org/10.1155/2016/5249086>.
36. Bryson, T.D.; Harding, P. Prostaglandin E2 EP receptors in cardiovascular disease: An update. *Biochem. Pharmacol.* **2022**, *195*, 114858. <https://doi.org/10.1016/j.bcp.2021.114858>.
37. Trappe, T.A.; Fluckey, J.D.; White, F.; Lambert, C.P.; Evans, W.J. Skeletal muscle PGF(2)(alpha) and PGE(2) in response to eccentric resistance exercise: Influence of ibuprofen acetaminophen. *J. Clin. Endocrinol. Metab.* **2001**, *86*, 5067–5070. <https://doi.org/10.1210/jcem.86.10.7928>.
38. Trappe, T.A.; White, F.; Lambert, C.P.; Cesar, D.; Hellerstein, M.; Evans, W.J. Effect of ibuprofen and acetaminophen on postexercise muscle protein synthesis. *Am. J. Physiol. Endocrinol. Metab.* **2002**, *282*, E551–E556. <https://doi.org/10.1152/ajpendo.00352.2001>.
39. Naruse, M.; Fountain, W.A.; Claiborne, A.; Chambers, T.L.; Jones, A.M.; Stroh, A.M.; Montenegro, C.F.; Lynch, C.E.; Minchev, K.; Trappe, S.; et al. Influence of low-dose aspirin, resistance exercise, and sex on human skeletal muscle PGE(2)/COX pathway activity. *Physiol. Rep.* **2021**, *9*, e14790. <https://doi.org/10.14814/phy2.14790>.
40. Liu, S.Z.; Jemiolo, B.; Lavin, K.M.; Lester, B.E.; Trappe, S.W.; Trappe, T.A. Prostaglandin E2/cyclooxygenase pathway in human skeletal muscle: Influence of muscle fiber type and age. *J. Appl. Physiol.* **2016**, *120*, 546–551. <https://doi.org/10.1152/japplphysiol.00396.2015>.
41. Ho, A.T.V.; Palla, A.R.; Blake, M.R.; Yucel, N.D.; Wang, Y.X.; Magnusson, K.E.G.; Holbrook, C.A.; Kraft, P.E.; Delp, S.L.; Blau, H.M. Prostaglandin E2 is essential for efficacious skeletal muscle stem-cell function, augmenting regeneration and strength. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 6675–6684. <https://doi.org/10.1073/pnas.1705420114>.
42. Palla, A.R.; Ravichandran, M.; Wang, Y.X.; Alexandrova, L.; Yang, A.V.; Kraft, P.; Holbrook, C.A.; Schürch, C.M.; Ho, A.T.V.; Blau, H.M. Inhibition of prostaglandin-degrading enzyme 15-PGDH rejuvenates aged muscle mass and strength. *Science* **2021**, *371*, eabc8059. <https://doi.org/10.1126/science.abc8059>.
43. Wang, Y.X.; Palla, A.R.; Ho, A.T.V.; Robinson, D.C.L.; Ravichandran, M.; Markov, G.J.; Mai, T.; Still, C., 2nd; Balsubramani, A.; Nair, S.; et al. Multiomic profiling reveals that prostaglandin E2 reverses aged muscle stem cell dysfunction, leading to increased regeneration and strength. *Cell Stem Cell* **2025**, *32*, 1154–1169.e1159. <https://doi.org/10.1016/j.stem.2025.05.012>.
44. Kaneshige, A.; Kaji, T.; Zhang, L.; Saito, H.; Nakamura, A.; Kurosawa, T.; Ikemoto-Uezumi, M.; Tsujikawa, K.; Seno, S.; Hori, M.; et al. Relayed signaling between mesenchymal progenitors and muscle stem cells ensures adaptive stem cell response to increased mechanical load. *Cell Stem Cell* **2022**, *29*, 265–280.e266. <https://doi.org/10.1016/j.stem.2021.11.003>.

45. Eliazer, S.; Muncie, J.M.; Christensen, J.; Sun, X.; D'Urso, R.S.; Weaver, V.M.; Brack, A.S. Wnt4 from the Niche Controls the Mechano-Properties and Quiescent State of Muscle Stem Cells. *Cell Stem Cell* **2019**, *25*, 654–665. <https://doi.org/10.1016/j.stem.2019.08.007>.
46. Goel, A.J.; Rieder, M.K.; Arnold, H.H.; Radice, G.L.; Krauss, R.S. Niche Cadherins Control the Quiescence-to-Activation Transition in Muscle Stem Cells. *Cell Rep.* **2017**, *21*, 2236–2250. <https://doi.org/10.1016/j.celrep.2017.10.102>.
47. Bjornson, C.R.; Cheung, T.H.; Liu, L.; Tripathi, P.V.; Steeper, K.M.; Rando, T.A. Notch signaling is necessary to maintain quiescence in adult muscle stem cells. *Stem Cells* **2012**, *30*, 232–242. <https://doi.org/10.1002/stem.773>.
48. Yartseva, V.; Goldstein, L.D.; Rodman, J.; Kates, L.; Chen, M.Z.; Chen, Y.J.; Foreman, O.; Siebel, C.W.; Modrusan, Z.; Peterson, A.S.; et al. Heterogeneity of Satellite Cells Implicates DELTA1/NOTCH2 Signaling in Self-Renewal. *Cell Rep.* **2020**, *30*, 1491–1503. <https://doi.org/10.1016/j.celrep.2019.12.100>.
49. Maruyama, Y.; Nogami, K.; Motohashi, N.; Sakai-Takemura, F.; Elhussieny, A.; Uchiumi, F.; Aoki, Y.; Takeda, S.; Miyagoe-Suzuki, Y. Prostaglandin E2 receptor EP2 is indispensable for maintenance of skeletal muscle stem cells. *Stem Cells* **2026**, *44*, sxag012. <https://doi.org/10.1093/stmcls/sxag012>.
50. Toth, A.D.; Schell, R.; Levay, M.; Vettel, C.; Theis, P.; Haslinger, C.; Alban, F.; Werhahn, S.; Frischbier, L.; Krebs-Haupenthal, J.; et al. Inflammation leads through PGE/EP3 signaling to HDAC5/MEF2-dependent transcription in cardiac myocytes. *EMBO Mol. Med.* **2018**, *10*, EMM201708536. <https://doi.org/10.15252/emmm.201708536>.
51. Jadhav, V.; Jabre, A.; Lin, S.Z.; Lee, T.J. EP1- and EP3-receptors mediate prostaglandin E2-induced constriction of porcine large cerebral arteries. *J. Cereb. Blood Flow. Metab.* **2004**, *24*, 1305–1316. <https://doi.org/10.1097/01.Wcb.0000139446.61789.14>.
52. Kida, T.; Sawada, K.; Kobayashi, K.; Hori, M.; Ozaki, H.; Murata, T. Diverse effects of prostaglandin E₂ on vascular contractility. *Heart Vessels* **2014**, *29*, 390–395. <https://doi.org/10.1007/s00380-013-0374-6>.
53. Kobayashi, K.; Murata, T.; Hori, M.; Ozaki, H. Prostaglandin E2-prostanoid EP3 signal induces vascular contraction via nPKC and ROCK activation in rat mesenteric artery. *Eur. J. Pharmacol.* **2011**, *660*, 375–380. <https://doi.org/10.1016/j.ejphar.2011.03.032>.
54. Majima, M.; Matsuda, Y.; Watanabe, S.I.; Ohtaki, Y.; Hosono, K.; Ito, Y.; Amano, H. Prostanoids Regulate Angiogenesis and Lymphangiogenesis in Pathological Conditions. *Cold Spring Harb. Perspect. Med.* **2024**, *14*, a041182. <https://doi.org/10.1101/cshperspect.a041182>.
55. Furuyashiki, T.; Narumiya, S. Roles of prostaglandin E receptors in stress responses. *Curr. Opin. Pharmacol.* **2009**, *9*, 31–38. <https://doi.org/10.1016/j.coph.2008.12.010>.
56. Furuyashiki, T.; Narumiya, S. Stress responses: The contribution of prostaglandin E(2) and its receptors. *Nat. Rev. Endocrinol.* **2011**, *7*, 163–175. <https://doi.org/10.1038/nrendo.2010.194>.
57. Liu, Y.; Liu, R.; Huang, L.; Zuo, G.; Dai, J.; Gao, L.; Shi, H.; Fang, Y.; Lu, Q.; Okada, T.; et al. Inhibition of Prostaglandin E2 Receptor EP3 Attenuates Oxidative Stress and Neuronal Apoptosis Partially by Modulating p38MAPK/FOXO3/Mul1/Mfn2 Pathway after Subarachnoid Hemorrhage in Rats. *Oxidative Med. Cell. Longev.* **2022**, *2022*, 7727616. <https://doi.org/10.1155/2022/7727616>.
58. Lv, L.; Bai, D.; Ma, Y.; Liu, K.; Ma, Y. The PGE2 receptor EP3 plays a positive role in the activation of hypothalamic-pituitary-adrenal axis and neuronal activity in the hypothalamus under immobilization stress. *Brain Res. Bull.* **2021**, *168*, 45–51. <https://doi.org/10.1016/j.brainresbull.2020.12.014>.
59. Nisr, R.B.; Shah, D.S.; Hundal, H.S. EP4: A prostanoid receptor that modulates insulin signalling in rat skeletal muscle cells. *Cell. Signal.* **2025**, *126*, 111516. <https://doi.org/10.1016/j.cellsig.2024.111516>.
60. Osawa, K.; Umemura, M.; Nakakaji, R.; Tanaka, R.; Islam, R.M.; Nagasako, A.; Fujita, T.; Yokoyama, U.; Koizumi, T.; Mitsudo, K.; et al. Prostaglandin E(2) receptor EP4 regulates cell migration through Orai1. *Cancer Sci.* **2020**, *111*, 160–174. <https://doi.org/10.1111/cas.14247>.
61. Jiang, M.J.; Zhou, H.Y.; Bai, Y.T.; Chen, X.J.; Zhou, G. Migrasome-transported PTGES amplifies the PGE2 cascade in SPP1(+) macrophages to drive oral leukoplakia carcinogenesis. *Nat. Commun.* **2026**, *17*, 4753. <https://doi.org/10.1038/s41467-026-70824-2>.
62. Digiaco, G.; Ziche, M.; Dello Sbarba, P.; Donnini, S.; Roviola, E. Prostaglandin E2 transactivates the colony-stimulating factor-1 receptor and synergizes with colony-stimulating factor-1 in the induction of macrophage migration via the mitogen-activated protein kinase ERK1/2. *FASEB J. Off. Publ. Fed. Am. Soc. Exp. Biol.* **2015**, *29*, 2545–2554. <https://doi.org/10.1096/fj.14-258939>.
63. Legler, D.F.; Krause, P.; Scandella, E.; Singer, E.; Groettrup, M. Prostaglandin E2 is generally required for human dendritic cell migration and exerts its effect via EP2 and EP4 receptors. *J. Immunol.* **2006**, *176*, 966–973. <https://doi.org/10.4049/jimmunol.176.2.966>.
64. Majumder, M.; Nandi, P.; Omar, A.; Ugwuagbo, K.C.; Lala, P.K. EP4 as a Therapeutic Target for Aggressive Human Breast Cancer. *Int. J. Mol. Sci.* **2018**, *19*, 1019. <https://doi.org/10.3390/ijms19041019>.

65. Bakooshli, M.A.; Wang, Y.X.; Monti, E.; Su, S.; Kraft, P.; Nalbandian, M.; Alexandrova, L.; Wheeler, J.R.; Vogel, H.; Blau, H.M. Regeneration of neuromuscular synapses after acute and chronic denervation by inhibiting the gerozyme 15-prostaglandin dehydrogenase. *Sci. Transl. Med.* **2023**, *15*, eadg1485. <https://doi.org/10.1126/scitranslmed.adg1485>.
66. Hu, X.; Cifarelli, V.; Sun, S.; Kuda, O.; Abumrad, N.A.; Su, X. Major role of adipocyte prostaglandin E2 in lipolysis-induced macrophage recruitment. *J. Lipid Res.* **2016**, *57*, 663–673. <https://doi.org/10.1194/jlr.M066530>.
67. Inazumi, T.; Yamada, K.; Shirata, N.; Sato, H.; Taketomi, Y.; Morita, K.; Hohjoh, H.; Tsuchiya, S.; Oniki, K.; Watanabe, T.; et al. Prostaglandin E(2)-EP4 Axis Promotes Lipolysis and Fibrosis in Adipose Tissue Leading to Ectopic Fat Deposition and Insulin Resistance. *Cell Rep.* **2020**, *33*, 108265. <https://doi.org/10.1016/j.celrep.2020.108265>.
68. García-Alonso, V.; Titos, E.; Alcaraz-Quiles, J.; Rius, B.; Lopategi, A.; López-Vicario, C.; Jakobsson, P.J.; Delgado, S.; Lozano, J.; Clària, J. Prostaglandin E2 Exerts Multiple Regulatory Actions on Human Obese Adipose Tissue Remodeling, Inflammation, Adaptive Thermogenesis and Lipolysis. *PLoS ONE* **2016**, *11*, e0153751. <https://doi.org/10.1371/journal.pone.0153751>.
69. Bryson, T.D.; Gu, X.; Khalil, R.M.; Khan, S.; Zhu, L.; Xu, J.; Peterson, E.; Yang, X.P.; Harding, P. Overexpression of prostaglandin E2 EP4 receptor improves cardiac function after myocardial infarction. *J. Mol. Cell Cardiol.* **2018**, *118*, 1–12. <https://doi.org/10.1016/j.yjmcc.2018.03.005>.
70. Bryson, T.D.; Ross, J.; Peterson, E.; Harding, P. Prostaglandin E2 and an EP4 receptor agonist inhibit LPS-Induced monocyte chemotactic protein 5 production and secretion in mouse cardiac fibroblasts via Akt and NF-kappaB signaling. *Prostaglandins Other Lipid Mediat.* **2019**, *144*, 106349. <https://doi.org/10.1016/j.prostaglandins.2019.106349>.
71. Tang, E.H.; Cai, Y.; Wong, C.K.; Rocha, V.Z.; Sukhova, G.K.; Shimizu, K.; Xuan, G.; Vanhoutte, P.M.; Libby, P.; Xu, A. Activation of prostaglandin E2-EP4 signaling reduces chemokine production in adipose tissue. *J. Lipid Res.* **2015**, *56*, 358–368. <https://doi.org/10.1194/jlr.M054817>.
72. Becher, T.; Palanisamy, S.; Kramer, D.J.; Eljalby, M.; Marx, S.J.; Wibmer, A.G.; Butler, S.D.; Jiang, C.S.; Vaughan, R.; Schöder, H.; et al. Brown adipose tissue is associated with cardiometabolic health. *Nat. Med.* **2021**, *27*, 58–65. <https://doi.org/10.1038/s41591-020-1126-7>.
73. Koenen, M.; Becher, T.; Pagano, G.; Del Gaudio, I.; Barrero, J.A.; Montezano, A.C.; Ruiz Ortiz, J.; Lin, Z.; Gómez-Banoy, N.; Amblard, R.; et al. Ablation of Prdm16 and beige fat identity causes vascular remodeling and elevated blood pressure. *Science* **2026**, *391*, 306–313. <https://doi.org/10.1126/science.ady8644>.
74. Li, J.; Wu, H.; Ma, W.; Yuan, T.; Chen, X.; Pan, Y. Activation of cyclooxygenase-2 signaling mediates liraglutide-induced adipose lipolytic activity. *Eur. J. Pharmacol.* **2025**, *1006*, 178133. <https://doi.org/10.1016/j.ejphar.2025.178133>.
75. Wang, C.; Zhang, X.; Luo, L.; Luo, Y.; Yang, X.; Ding, X.; Wang, L.; Le, H.; Feldman, L.E.R.; Men, X.; et al. Adipocyte-derived PGE2 is required for intermittent fasting-induced Treg proliferation and improvement of insulin sensitivity. *JCI Insight* **2022**, *7*, e153755. <https://doi.org/10.1172/jci.insight.153755>.
76. Panzenbeck, M.J.; Tan, W.; Hajdu, M.A.; Cornish, K.G.; Zucker, I.H. PGE2 and arachidonate inhibit the baroreflex in conscious dogs via cardiac receptors. *Am. J. Physiol.* **1989**, *256*, H999–H1005. <https://doi.org/10.1152/ajpheart.1989.256.4.H999>.
77. Hull, S.S., Jr.; Chimoskey, J.E. Mechanisms of central prostaglandin E2 hypertension in conscious dogs, sheep, and calves. *Am. J. Physiol.* **1984**, *247*, H218–H228. <https://doi.org/10.1152/ajpheart.1984.247.2.H218>.
78. Rossoni, G.; Muscara, M.N.; Cirino, G.; Wallace, J.L. Inhibition of cyclo-oxygenase-2 exacerbates ischaemia-induced acute myocardial dysfunction in the rabbit. *Br. J. Pharmacol.* **2002**, *135*, 1540–1546. <https://doi.org/10.1038/sj.bjp.0704585>.
79. Lipton, H.L.; Cassin, S.; Kadowitz, P.J. Comparative effects of PGD2 and PGE2 on vasoconstrictor responses in the feline intestinal vascular bed. *Prostaglandins Med.* **1980**, *5*, 297–305. [https://doi.org/10.1016/0161-4630\(80\)90032-4](https://doi.org/10.1016/0161-4630(80)90032-4).
80. Lipton, H.L.; Paustian, P.W.; Sporn, L.; Kadowitz, P.J. Comparative effects of PGD2 and PGE2 in the regional circulation of the cat. *Prostaglandins Med.* **1980**, *5*, 365–373. [https://doi.org/10.1016/0161-4630\(80\)90108-1](https://doi.org/10.1016/0161-4630(80)90108-1).
81. Sellers, R.S.; Radi, Z.A.; Khan, N.K. Pathophysiology of cyclooxygenases in cardiovascular homeostasis. *Vet. Pathol.* **2010**, *47*, 601–613. <https://doi.org/10.1177/0300985810364389>.
82. Neri Serneri, G.G.; Gensini, G.F.; Abbate, R.; Castellani, S.; Bonechi, F.; Dagianti, A.; Arata, L.; Fedele, F.; Iacoboni, C.; Prisco, D. Physiologic role of coronary PGI2 and PGE2 in modulating coronary vascular response to sympathetic stimulation. *Am. Heart J.* **1990**, *119*, 848–854. [https://doi.org/10.1016/s0002-8703\(05\)80322-9](https://doi.org/10.1016/s0002-8703(05)80322-9).
83. Staszewska-Barczak, J. Prostanoids and cardiac reflexes of sympathetic and vagal origin. *Am. J. Cardiol.* **1983**, *52*, 36a–45a. [https://doi.org/10.1016/0002-9149\(83\)90175-3](https://doi.org/10.1016/0002-9149(83)90175-3).
84. Baltzer, W.I.; Firshman, A.M.; Stang, B.; Warnock, J.J.; Gorman, E.; McKenzie, E.C. The effect of agility exercise on eicosanoid excretion, oxidant status, and plasma lactate in dogs. *BMC Vet. Res.* **2012**, *8*, 249. <https://doi.org/10.1186/1746-6148-8-249>.

85. Young, E.W.; Sparks, H.V. Prostaglandin E release from dog skeletal muscle during restricted flow exercise. *Am. J. Physiol.* **1979**, *236*, H596–H599. <https://doi.org/10.1152/ajpheart.1979.236.4.H596>.
86. Young, E.W.; Sparks, H.V. Prostaglandins and exercise hyperemia of dog skeletal muscle. *Am. J. Physiol.* **1980**, *238*, H191–H195. <https://doi.org/10.1152/ajpheart.1980.238.2.H191>.
87. Berger, H.J.; Zaret, B.L.; Speroff, L.; Cohen, L.S.; Wolfson, S. Regional cardiac prostaglandin release during myocardial ischemia in anesthetized dogs. *Circ. Res.* **1976**, *38*, 566–571. <https://doi.org/10.1161/01.res.38.6.566>.
88. Wang, W.; Zucker, I.H. Cardiac sympathetic afferent reflex in dogs with congestive heart failure. *Am. J. Physiol.* **1996**, *271*, R751–R756. <https://doi.org/10.1152/ajpregu.1996.271.3.R751>.
89. Chen, W.W.; Xiong, X.Q.; Chen, Q.; Li, Y.H.; Kang, Y.M.; Zhu, G.Q. Cardiac sympathetic afferent reflex and its implications for sympathetic activation in chronic heart failure and hypertension. *Acta Physiol.* **2015**, *213*, 778–794. <https://doi.org/10.1111/apha.12447>.
90. Gao, L.; Schultz, H.D.; Patel, K.P.; Zucker, I.H.; Wang, W. Augmented input from cardiac sympathetic afferents inhibits baroreflex in rats with heart failure. *Hypertension* **2005**, *45*, 1173–1181. <https://doi.org/10.1161/01.HYP.0000168056.66981.c2>.
91. Gao, L.; Zhu, Z.; Zucker, I.H.; Wang, W. Cardiac sympathetic afferent stimulation impairs baroreflex control of renal sympathetic nerve activity in rats. *Am. J. Physiol. Heart Circ. Physiol.* **2004**, *286*, H1706–H1711. <https://doi.org/10.1152/ajpheart.01097.2003>.
92. Wang, W.; Zhu, G.Q.; Gao, L.; Tan, W.; Qian, Z.M. Baroreceptor reflex in heart failure. *Acta Psychol. Sin.* **2004**, *56*, 269–281.
93. Tune, J.D.; Gorman, M.W.; Feigl, E.O. Matching coronary blood flow to myocardial oxygen consumption. *J. Appl. Physiol.* **2004**, *97*, 404–415. <https://doi.org/10.1152/japplphysiol.01345.2003>.
94. Wang, W. Cardiac sympathetic afferent stimulation by bradykinin in heart failure: Role of NO and prostaglandins. *Am. J. Physiol.* **1998**, *275*, H783–H788. <https://doi.org/10.1152/ajpheart.1998.275.3.H783>.
95. Trappe, T.A.; Liu, S.Z. Effects of prostaglandins and COX-inhibiting drugs on skeletal muscle adaptations to exercise. *J. Appl. Physiol.* **2013**, *115*, 909–919. <https://doi.org/10.1152/japplphysiol.00061.2013>.
96. Stone, A.J.; Copp, S.W.; Kim, J.S.; Kaufman, M.P. Combined, but not individual, blockade of ASIC3, P2X, and EP4 receptors attenuates the exercise pressor reflex in rats with freely perfused hindlimb muscles. *J. Appl. Physiol.* **2015**, *119*, 1330–1336. <https://doi.org/10.1152/japplphysiol.00630.2015>.
97. Moriyama, T.; Higashi, T.; Togashi, K.; Iida, T.; Segi, E.; Sugimoto, Y.; Tominaga, T.; Narumiya, S.; Tominaga, M. Sensitization of TRPV1 by EP1 and IP reveals peripheral nociceptive mechanism of prostaglandins. *Mol. Pain* **2005**, *1*, 3. <https://doi.org/10.1186/1744-8069-1-3>.
98. Antunes-Correa, L.M.; Nobre, T.S.; Groehs, R.V.; Alves, M.J.; Fernandes, T.; Couto, G.K.; Rondon, M.U.; Oliveira, P.; Lima, M.; Mathias, W.; et al. Molecular basis for the improvement in muscle metaboreflex and mechanoreflex control in exercise-trained humans with chronic heart failure. *Am. J. Physiol. Heart Circ. Physiol.* **2014**, *307*, H1655–H1666. <https://doi.org/10.1152/ajpheart.00136.2014>.
99. Wang, C.; Gu, Y.; Li, G.W.; Huang, L.Y. A critical role of the cAMP sensor Epac in switching protein kinase signalling in prostaglandin E2-induced potentiation of P2X3 receptor currents in inflamed rats. *J. Physiol.* **2007**, *584*, 191–203. <https://doi.org/10.1113/jphysiol.2007.135616>.
100. Wang, C.; Li, G.W.; Huang, L.Y. Prostaglandin E2 potentiation of P2X3 receptor mediated currents in dorsal root ganglion neurons. *Mol. Pain* **2007**, *3*, 22. <https://doi.org/10.1186/1744-8069-3-22>.
101. Liviero, F.; Scarpa, M.C.; De Stefani, D.; Folino, F.; Campisi, M.; Mason, P.; Iliceto, S.; Pavanetto, S.; Maestrelli, P. Modulation of TRPV-1 by prostaglandin-E(2) and bradykinin changes cough sensitivity and autonomic regulation of cardiac rhythm in healthy subjects. *Sci. Rep.* **2020**, *10*, 15163. <https://doi.org/10.1038/s41598-020-72062-y>.
102. Zhou, Y.M.; Wu, L.; Wei, S.; Jin, Y.; Liu, T.T.; Qiu, C.Y.; Hu, W.P. Enhancement of acid-sensing ion channel activity by prostaglandin E2 in rat dorsal root ganglion neurons. *Brain Res.* **2019**, *1724*, 146442. <https://doi.org/10.1016/j.brainres.2019.146442>.
103. Greaney, J.L.; Wenner, M.M.; Farquhar, W.B. Exaggerated increases in blood pressure during isometric muscle contraction in hypertension: Role for purinergic receptors. *Auton. Neurosci.* **2015**, *188*, 51–57. <https://doi.org/10.1016/j.autneu.2014.12.003>.
104. O'Leary, D.S.; Mannozi, J.; Augustyniak, R.A.; Ichinose, M.; Spranger, M.D. Hypertension depresses arterial baroreflex control of both heart rate and cardiac output during rest, exercise, and metaboreflex activation. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2022**, *323*, R720–R727. <https://doi.org/10.1152/ajpregu.00093.2022>.
105. O'Leary, D.S.; Senador, D.; Augustyniak, R.A. Muscle metaboreflex-induced central blood volume mobilization in heart failure. *Am. J. Physiol. Heart Circ. Physiol.* **2019**, *316*, H1047–H1052. <https://doi.org/10.1152/ajpheart.00805.2018>.

106. Pinna, V.; Doneddu, A.; Roberto, S.; Magnani, S.; Ghiani, G.; Mulliri, G.; Sanna, I.; Serra, S.; Hosseini Kakhak, S.A.; Milia, R.; et al. Combined mental task and metaboreflex impair cerebral oxygenation in patients with type 2 diabetes mellitus. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2021**, *320*, R488–R499. <https://doi.org/10.1152/ajpregu.00288.2020>.
107. Stavres, J.; Aultman, R.A.; Brandner, C.F.; Newsome, T.A.; Vallecillo-Bustos, A.; Wise, H.L.; Henderson, A.; Stanfield, D.; Mannozi, J.; Graybeal, A.J. Hemodynamic responses to handgrip and metaboreflex activation are exaggerated in individuals with metabolic syndrome independent of resting blood pressure, waist circumference, and fasting blood glucose. *Front. Physiol.* **2023**, *14*, 1212775. <https://doi.org/10.3389/fphys.2023.1212775>.
108. Spranger, M.D.; Kaur, J.; Sala-Mercado, J.A.; Krishnan, A.C.; Abu-Hamdah, R.; Alvarez, A.; Machado, T.M.; Augustyniak, R.A.; O’Leary, D.S. Exaggerated coronary vasoconstriction limits muscle metaboreflex-induced increases in ventricular performance in hypertension. *Am. J. Physiol. Heart Circ. Physiol.* **2017**, *312*, H68–H79. <https://doi.org/10.1152/ajpheart.00417.2016>.
109. Mannozi, J.; Kaur, J.; Spranger, M.D.; Al-Hassan, M.H.; Lessanetwork, B.; Alvarez, A.; Chung, C.S.; O’Leary, D.S. Muscle metaboreflex-induced increases in effective arterial elastance: Effect of heart failure. *Am. J. Physiol. Regul. Integr. Comp. Physiol.* **2020**, *319*, R1–R10. <https://doi.org/10.1152/ajpregu.00040.2020>.
110. Roberto, S.; Milia, R.; Doneddu, A.; Pinna, V.; Palazzolo, G.; Serra, S.; Orrù, A.; Hosseini Kakhak, S.A.; Ghiani, G.; Mulliri, G.; et al. Hemodynamic abnormalities during muscle metaboreflex activation in patients with type 2 diabetes mellitus. *J. Appl. Physiol.* **2019**, *126*, 444–453. <https://doi.org/10.1152/japplphysiol.00794.2018>.
111. Smith, J.R.; Hart, C.R.; Ramos, P.A.; Akinsanya, J.G.; Lanza, I.R.; Joyner, M.J.; Curry, T.B.; Olson, T.P. Metabo- and mechanoreceptor expression in human heart failure: Relationships with the locomotor muscle afferent influence on exercise responses. *Exp. Physiol.* **2020**, *105*, 809–818. <https://doi.org/10.1113/ep088353>.

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