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Review

Exploring the Emerging Link Between Obesity-Induced Meta-Neuroinflammation and Osteoarthritis Pain Mechanisms

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Abstract

Obesity is a complex, heterogeneous, chronic and progressive disease, which correlates with an augmented risk to develop several comorbidities with an enhanced risk of death. In addition to metabolic and cardiovascular diseases, obesity is related to depressive disorders and neurodegenerative diseases, in which gut microbiota dysbiosis plays a central role in triggering the meta-neuroinflammation through the gut-brain axis. In obese patients, the release of inflammatory mediators by dysfunctional adipocytes and the oxidative stress induces meta-neuroinflammation, which have been identified as the main physio-pathological pathway underlying chronic pain syndromes, particularly osteoarthritis, low back pain, fibromyalgia, headache, and painful diabetic peripheral neuropathy. Both the peripheral and the central nervous system are involved in neuroinflammatory processes, leading to central sensitization and pain chronification. Meta-neuroinflammation is also a potential peripheral target of treatment in degenerative joint disease, in order to minimize the traditional pharmacological approaches use. The ultramicrosized palmitoylethanolamide is able to control the body weight, to exert neuroprotective, anti-neuroinflammatory and analgesic actions, and to restore intestinal eubiosis, with beneficial effects on mental disorders via the gut-brain axis. Finally, adelmidrol, as a PEA congener, available for intra-articular injection associated with hyaluronic acid, has been shown to modulate meta-neuroinflammation in knee osteoarthritis.

Keywords: obesity; chronic pain; meta-neuroinflammation; low back pain; osteoarthritis; oxidative stress; palmitoylethanolamide; gut microbiota; gut dysbiosis; cognitive impairment

1. Epidemiology of Obesity and Chronic Pain Syndromes

1.1. Obesity and Its Comorbidities

Obesity is a complex, heterogeneous, chronic, and progressive disease, which substantially affects more than 890 million (13%) adults [1]. According to the World Health Organization (WHO), the diagnosis of overweight is made by measuring a Body Mass Index (BMI) greater than or equal to 25 kg/m² and obesity by a BMI greater than or equal to 30 kg/m². Central obesity is defined by a waist circumference greater than 102 cm in men and 88 cm in women. In 2022, 2.5 billion adults worldwide were overweight and about 16% of population were obese [2].

Worldwide, obesity is a major public health problem associated with increased morbidity and mortality for all-causes [3]. Although obesity is recognized as a high-risk condition for the development of other chronic degenerative non-communicable diseases, this pathology has been declared as a disease per se that leads to a reduction in the quality and expectancy of life [4]. In obesity patients, the adipocyte hypertrophy, visceral and ectopic adiposity, increased production of adipokines with anorexigenic function, such as leptin, and of a plethora of pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin (IL) -6, IL-1 β , and resistin, predisposes the organism to the adiposopathy (or “sick fat”) [5]. The latter is defined as a “pathologic adipose tissue (AT) anatomic/functional disturbances induced by positive caloric balance in genetically susceptible individuals that results in adverse endocrine and immune responses that may cause or worsen metabolic dysfunction” [3]. This alteration is also sustained by dysfunctional adipocytes, resulting in an imbalance between the production of pro-inflammatory and anti-inflammatory cytokines, in favor of the first. This condition predisposes the body to the chronic low-grade inflammation or meta-inflammation, which is observed in all tissues involved in energy homeostasis [6]. The low-grade inflammation is also sustained by infiltration of bone marrow-derived immune cells that signal via the production of cytokines and chemokines. Despite its low-grade nature, meta-inflammation negatively impacts remote organ function, a phenomenon that is considered causative of the complications of obesity. The visceral and ectopic fat, either in the liver, muscle or heart, can increase the risk of developing insulin resistance, type 2 diabetes mellitus (DM), and cardiovascular diseases (CVDs) [7]. In fact, the obesity correlates with an augmented risk of several comorbidities that exponentially increase the risk of death. In this regard, the risk of all-cause mortality increases as the number of years lived with obesity increases, regardless of the current BMI [8]. Notably, two-thirds of obesity-related mortality is attributable to CVDs, including atherosclerotic disease, heart failure, thromboembolic disease, arrhythmias, and sudden cardiac death. In fact, for every additional 2 years lived with obesity, the risk of cardio-vascular mortality rises significantly by 7% [8]. CVDs are followed by type 2 DM, cancer (especially esophagus, colon, rectum and liver), and chronic kidney disease (CKD) [9,10]. Obesity contributes to the development of CKD among 15–30% of patients, though direct and indirect mechanisms [11]. Among the direct mechanisms, the altered secretion of adipokines and the lipotoxicity lead to the accumulation of perirenal AT and of fatty acids in the renal parenchyma. The result is a tubule-Interstitial damage, that involves either the proximal tubular epithelial cells and endothelial cells [12]. The hemodynamic changes, such as glomerular hyperfiltration and microvascular stretching, and the hyperactivation of renin-angiotensin-aldosterone system are the other two direct mechanisms contributing to inflammation, oxidative stress and fibrosis [13,14]. This triad is exacerbated if the patient presents type 2 DM, arterial hypertension and atherosclerosis, namely comorbidities and indirect mechanisms of obesity itself, that are responsible for the development and progression of CKD [15].

Obesity is also related to structural and functional abnormalities that reduced patients quality of life (QoL). These include gastrointestinal reflux disease, gallbladder disease, osteoarthritis (OA), obstructive sleep apnea/obesity hypoventilation syndrome, psychological and eating behavior disorders, anxiety and depression and impairment of the physical performance [16]. In fact, obese patients often have impaired cognitive functioning and present a major depressive disorder, with negative effects on measures of processing speed and executive function, as evidenced by mood assessment questionnaires and neuropsychological tests [17]. Furthermore, obesity appears to be associated with greater emotional dysregulation, compared to normal-weight condition. In fact, obesity shares many psychological features with eating disorders, especially with binge eating disorder and alexithymia [18].

1.2. Obesity and Chronic Pain

Chronic pain is a widespread health issue, which affects over 20% of adult population [19]. In obese patients, chronic pain syndromes are among the most common observed comorbidities, with their relevant psychosocial consequences. These two phenomena are closely related, with each

condition adversely impacting the other, because of limited mobility, mood disorders, and common chemical mediators [20].

Numerous studies investigated the relationship between OA-related pain and obesity, which is the focus of this review. Among older people, long-term obesity has been identified as a significant predictor of pain, particularly with an increased risk of back, hip, and knee pain [21], which are the most common sites of OA. Among OA-related pain syndromes, low back pain (LBP) has the highest prevalence in general population, affecting over 600 million people globally. LBP is supposed to be a major determinant of age-standardized disability-adjusted life-years (DALYs) in the next 25 years, while improvement of BMI has been proposed as one of the strategies for improving life expectancy [22]. Overweight and obesity have been recognized as risk factors for LBP. Obesity increased the incidence of LBP, with an odd ratio of 1.36 and 1.4, respectively in men and women [23]. In a recent cohort study conducted in Norway, higher values of BMI have been associated with higher incidence of LBP, particularly among very obese women [24], however the exact magnitude of this phenomenon is still under investigation.

Advancing age and adiposity also contribute to musculoskeletal degenerative diseases, which lead to sarcopenic obesity (SO), a condition that links osteopenia/osteoporosis, muscle loss, and obesity [25]. SO is associated with reduced physical activity, loss of independence among older adults and is a determinant risk factor for frailty [26]. In postmenopausal women, SO had greater effect on knee OA compared to obesity without sarcopenia and to sarcopenia without obesity [27].

Obesity has been also associated also with other pain syndromes, such as painful diabetic peripheral neuropathy [28], headache [29], and fibromyalgia [30].

Diabetic neuropathy is the most common complication of DM, affecting about 50% of diabetes patients and about 70% of patients with diabetic neuropathies receive medications for neuropathic pain [31]. Visceral obesity is an independent risk factor for diabetic peripheral neuropathy [32].

Different studies investigated obesity as a risk factor for headache/migraine. Although migraine frequency was not associated with BMI, obese patients seem to have an higher prevalence of frequent and severe migraine headaches [33]. The exact relationship between these two comorbidities is not fully understood, however, there is evidence that obesity could be a consequence of migraine, through the effect of inflammatory mediators, adipokines, and alterations of gut microbiota [34].

Finally, 35% of adults with fibromyalgia are obese and obesity impacts most of the clinical features of fibromyalgia, such as tenderness and stiffness, fatigue, physical functioning, sleep, and cognitive function, leading to a reduced QoL [35]. Among women suffering from fibromyalgia, obese patients displayed higher levels of anxiety and depression, compared with the normal-weight subjects [36]. Even in this case, it is not possible to understand whether obesity is a cause or a consequence of fibromyalgia [30].

2. Mechanisms Underlying Obesity and Osteoarthritis: Role of Oxidative Stress and Meta-Neuroinflammation

2.1. Obesity and Neuroinflammation

AT is an endocrine organ distributed throughout the body and is characterized by high metabolic and dynamic activity [37]. AT regulates several physiological mechanisms through the secretion of adipocytokines (also called adipokines) into the bloodstream, creating a communication with other tissues and organs [38]. In adult mammals, AT is classified in two different types: white and beige. White AT (WAT) accounts for the largest percentage of AT in the human body and is localized around the viscera, subcutis, and perivascular. WAT stores excess energy in the form of triglycerides and secretes adipokines and vasoactive factors. Its phenotype changes in patients affected by obesity, becoming hyperplastic and hypertrophic, suffering the infiltration of the immune cells and secreting vasoconstrictor factors. Beige AT (BAT) mainly surrounds the thoracic aorta. It possesses anti-inflammatory and cardioprotective properties and is involved in the thermogenesis, dissipating energy as heat. For this reason, BAT has anti-obesogenic and anti-diabetic properties,

ensuring cardio-metabolic health [39]. Lean individuals with normo-metabolic function present an increased production of anti-inflammatory ILs (like IL-10, IL-5, IL-4, IL-13, IL-25, IL-33) and anti-inflammatory adipokines (such as adiponectin, omentin, apelin and secreted frizzled-related protein-Sfrp-5) [40]. Moreover, in a healthy AT, macrophages constitute 5-10% of the cells, of which only a small part is in a pro-inflammatory state (M1), because the remainder of the resident macrophages is in an anti-inflammatory state (M2) [41]. During chronic low-grade inflammation, which characterizes patients with obesity, AT is mainly characterized by hypertrophic adipocytes that accumulate lipid droplets, secrete pro-inflammatory adipokines (like leptin, resistin, and visfatin), and amplify the infiltration into AT itself of pro-inflammatory cells (such as M1 macrophages, T helper 1 cells, natural killer cells, CD8⁺ T cells, neutrophils, and mast cells).

The dysbiosis of the gut microbiota also plays a central role in exacerbating AT inflammation, negatively impacting on distant organ function, such as the brain. In fact, despite its low-grade nature, chronic inflammation is the leitmotif that links obesity with neuroinflammation. The central nervous system (CNS) requires a highly controlled microenvironment to support its physiological functioning. This is possible thanks to the presence of three biological barrier at the blood-brain interface, that effectively separates the brain from the rest of the body [42]. These include the blood-brain barrier (BBB), the blood-cerebrospinal fluid barrier and the arachnoid barrier [43]. Brain microvascular endothelial cells display distinctive morphological, structural and functional characteristics that differentiate them from other vascular endothelia. In detail, these cells express: (i) the tight junctions (TJs), namely intercellular protein complexes that preserve tissue homeostasis and integrity through the control of paracellular pathways between adjacent endothelial cells, thus preventing the unregulated passage of polar molecules between the blood and the brain [44]; (ii) the absence of fenestrations [45]; (iii) the lack of pinocytic vesicles [46]; (iv) the active transport mechanisms, specifically expressed by the endothelial cells of the cerebral capillaries. These mechanisms ensure the transport of nutrients and essential amino acids into the CNS and the blockade of endogenous and xenobiotics molecules, that could be harmful to the ideal milieu for neural transmission [47]. For this reason, the BBB is an anatomo-functional structure that protects the CNS from systemic circulation, not allowing the pro-inflammatory factors, toxins, immune cells and pathogens to be translocated into the brain [48]. The integrity of the BBB is compromised in patients with obesity. Moreover, obese patients have as a comorbidity type 2 DM that downregulates the TJs proteins, leading to the destruction of claudin-5, zonula occludens-1 (ZO-1), occludin and caveolin [49]. The upregulation of the matrix metalloproteinases (MMPs) and tissue inhibitor of metalloproteinases (TIMPs) is observed in obese subjects, and it is associated with some obesity-related parameters, including BMI, waist circumference, blood pressure and endothelial-dependent response [50]. In addition, hyperglycemia leads to the amplification of oxidative respiration and the production of reactive oxygen species (ROS). ROS react with nitric oxide to produce peroxynitrite, which mediates MMPs activation and TIMPs inhibition, causing basement membrane (BM) degradation [51] (namely the second barrier of entry for the immune system) [52]. The BM regeneration is unable to compensate the protease activity of the MMPs. In fact, the increase in fibronectin, collagen IV and laminin compromises the attachment of cells to the BM and the downregulation of heparin-sulfated proteoglycans removes anionic protein binding sites, destabilizing the BM [53] and allowing the extravasation of leukocytes. Leukocytes express highly glycosylated molecules on their surface, namely the P-selectin glycoprotein ligand-1 (PSGL-1), consenting selectins adhesion receptors to bind them and triggering the neuroinflammation response through the microglia activation. The interaction between PSGL-1 and P-selectin and E-selectin mediate the initial capture and the rolling of leukocytes on the vascular endothelium in search of a point for extravasation, which can occur by paracellular and transcellular diapedesis. Most transmigration into the perivascular space occurs via a paracellular mechanism. The immune cells extend pseudopods and pass through the endothelium, thanks to the interaction with platelet endothelial cell adhesion molecule (PECAM) and junctional adhesion molecule-A (JAM-A). When leukocytes cannot find an endothelial junction, transcellular diapedesis occurs [54,55]. The leukocyte

extravasation into the brain parenchyma is also permitted by MMP-9, which remove away BM filaments [56]. The impaired BM also becomes thicker, leading to increased vascular permeability [57]. This process is favored by the activation of protein kinase C (PKC), advanced glycation end-products (AGEs), transforming growth factor β (TGF- β) and connective tissue growth factor [52]. AGEs act on AGE receptor (RAGE) to intensify nuclear factor kappa β activation (NF- $\kappa\beta$), increasing pro-inflammatory gene expression, including RAGE itself and pro-inflammatory cytokines, like TNF- α [58]. Astrocyte endfeet wrap around the entire CNS vascular tree and perform important functions in regulating the BBB, through the cerebral blood flow, nutrient uptake, and waste elimination [59]. During neuroinflammation, astrocytes produce and secrete a wide range of molecules and chemokines to attract circulating peripheral immune cells, including CD8⁺ T cells, B cells, NK cells, monocytes and macrophages into the CNS [60]. Conversely, astrocytes can boost effector functions of peripheral immune cells, including NK cells and CD8⁺ T cells, through the production of IL-15. TH 17 cells promote pathogenic activities of astrocytes by expressing receptor activator of nuclear factor-kappa β (RANK) ligand and granulocyte-macrophage colony-stimulating factor (GM-CSF). The RANK activation by TH 17 cell-expressed RANK ligand triggers the production of C-C motif chemokine ligand 20 - CCL20, triggering the recruitment of effector T cells in the CNS. In astrocytes, GM-CSF induces the expression of pro-inflammatory genes [61], creating a cytotoxic state mediated by the production of IL-1 β , IL-6, TNF- α , prostaglandins and vascular endothelial growth factor (VEGF) that migrate into the perivascular space through the destroyed BM [52]. Chronic overexposure of VEGF also increases the expression of intercellular adhesion molecule-1 (ICAM-1) and major histocompatibility complex (MHC) class I and II expression, modulating immune responses in the CNS through opening of the BBB and allowing contacts between CNS antigens and blood-borne immune mediators [62]. Activated microglia migrates to the injured area and release proinflammatory cytokines, NO, ROS, prostaglandins, and chemokines, resulting in the additional chemoattraction of circulating leukocytes [63]. Moreover, leptin leads to the activation of the mechanistic target of rapamycin (mTOR) and hypoxia-inducible factor 1 (HIF-1) in the endothelial cells of the CNS, leading to VEGF production. VEGF activates PKC- β and Rho-kinase (ROCK), exacerbating neuroinflammation. Activation of PKC- β is also due to increased diacylglycerol concentrations, typically observed in hyperglycemic conditions [64,65]. This pathway increases the activity of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, producing O₂⁻. O₂⁻ mediates the phosphorylation of the inhibitor of kappa β kinase (IKK) and induces downstream degradation of I κ B α , leading to the nuclear localization and transcriptional activation of NF- $\kappa\beta$ [66]. The activation of NF- $\kappa\beta$ regulates the synthesis, the release and the recruitment of various inflammatory mediators capable of disrupting the BBB through the reorganization of the actin cytoskeleton in brain microvascular endothelial cells, the disruption of TJs formation, the inhibition of the proliferative and migratory capacity of endothelial cells and astrocytes, and the apoptosis [67]. On the other hand, ROCK-mediated cellular pathway inhibits the expression of endothelial nitric oxide synthase (eNOS), which reduces the availability of NO, inducing endothelial dysfunction [68]. This is due to increased endothelial Na²⁺ channels (EnNaCs) activity, leading to polymerization of cortical actin fibers. Subsequently, it is possible to observe a reduction of eNOS activity and a decrease of nitric oxide (NO) production, resulting in increased vascular stiffness [39]. Mediators of obesity-induced endothelial dysfunction also include altered sirtuin 1 expression, oxidative stress, autophagy machinery and endoplasmic reticulum stress [68]. Inactivation of eNOS causes the activation of microglia, promoting a pro-inflammatory phenotype in the brain, downregulating the claudin-5 and occludin and increasing the BBB permeability caused by VEGF signaling from astrocytes [69]. Moreover, eNOS-deficient mice exhibit impaired cognitive performance, suggesting that loss of endothelial NO has a detrimental effect on the functions of neuronal cells [70]. At the same time, an increased NO production in the CNS is associated with the pathogenesis of neurodegenerative diseases, such as Parkinson's disease, and Alzheimer's disease (AD) [71]. In fact, the pathological manifestations of AD include not only the accumulation of amyloid-beta-protein (A β) and hyperphosphorylated tau (pTau) in the brain, but also microgliosis, astrocytosis, and

neurodegeneration mediated by metabolic dysregulation and neuroinflammation [72]. A β also increases ROCK-1 activity in neurons [73] and, in turn, ROCK-1 enhances cleavage of the amyloid precursor protein (APP), producing increased A β formation [74]. Neuroinflammation is characterized by a dysfunction of the influx transporters that impedes the supply of glucose and nutrient molecules, leading to hypometabolism that is detrimental to neuronal activity. Downregulation or decreased activity of efflux transporters fails to eliminate neurotoxic molecules, particularly A β , aggravating A β deposition in the parenchyma and brain [75]. Moreover, the downregulation of P-glycoprotein, amino acids and leptin transporters is observed [52]. In individuals with obesity, decreased leptin signalling in the CNS is also caused by downregulation of the leptin receptor (LepR) and by deficiency of leptin signalling at the LepR [76]. Leptin resistance is characterized by reduced satiety, over-consumption of foods, and increased total fat mass [77]. The leptin plasma levels may be protective against the development or progression of AD. Lower leptin plasma levels have a significant association with higher A β deposition in the brain, although there is not a significant association between leptin plasma levels and tau deposition [78]. High leptin levels were independently associated with a reduced risk of cognitive decline in elderly Italians [79]. In a cohort of older adults with mild cognitive impairment, plasma leptin levels were not associated with cognitive function, nor did they predict risk of dementia. Although leptin levels increase in obesity, leptin resistance prevents to leptin to exert its functions [80]. N-acetylaspartate (NAA) is synthesized by neurons and is involved in neuronal metabolism and axonal myelination. The concentration of NAA has been associated with cognitive dysfunction in neurodegenerative and metabolic diseases. NAA levels depend on age, BMI, and glucose levels [81]. In the study conducted by Coplan et al., higher BMI (≥ 25 kg/m²) has been associated with decreased levels of neural integrity and with neuronal injury, expressed by reduced concentrations of NAA in the hippocampus [82]. Irisin is an adipo-myokine hormone produced during physical exercise, through the expression of the peroxisome proliferative activated receptor- γ coactivator-1 α (PGC-1 α). Expressed PGC-1 α causes the production of the fibronectin type III domain containing 5 (FNDC5) protein, which is cleaved in skeletal muscle fibers by proteases to produce irisin [83]. Irisin binds to its integrin α V/ β 5 receptor with these consequences i) WAT browning; ii) improving of insulin sensitivity and metabolic balance, by enhancing mitochondrial functions and by reducing oxidative stress; iii) promoting osteogenesis and mitigating the bone loss; iv) attenuating the cognitive dysfunction, by decreasing A β toxicity, neuroinflammation, and oxidative stress and by improving brain-derived neurotrophic factor (BDNF) signaling, which rescues cognition and synaptic health; v) regulating dopamine pathways, alleviating neuropsychiatric symptoms like depression and apathy; and vi) mitigating cardiac injury [84,85]. The levels of irisin are significantly lower in patients with obesity, osteoporosis, sarcopenia, AD, and CVDs [85]. The dysfunctional phenotype caused by low levels of irisin is exacerbated in patients with SO. In fact, SO compromises mitochondrial oxidative capacity and lipid oxidation in skeletal muscle and suppresses sarcolipin-induced sarcoplasmic reticulum calcium ATPase (SERCA) activation, impairing the ability to switch between glucose and lipid metabolism in response to nutrients and physical exercise and resulting in reduced oxidative capacity, diminished energy expenditure, and increased adiposity [86]. SO patients display a smaller total gray matter volume [87] and show higher serum levels of IL-6, IL-18, TNF- α , TNF-like weak inducer of apoptosis (TWEAK) and leptin compared to non-sarcopenic patients; in contrast, the levels of insulin growth factor 1, insulin, and adiponectin are significantly lower [88]. For these reasons, Irisin may represent a therapeutic potential biomarker for metabolic diseases, osteoporosis, sarcopenia, and neurodegenerative diseases [84].

2.2. Obesity, Oxidative Stress and Osteoarthritis

In obese patients, many pro-inflammatory molecules and mediators are expressed during acute and chronic high-intensity loading [89], namely extracellular matrix (ECM) components and remodelers, joint cell- and AT cell-derived mediators (cytokines, adipokines), AGEs, and ROS [90]. Besides predisposing to OA for loading bio-mechanical reasons, obesity increases the risk of OA

development also in non-weight-bearing joints, such as hands, through the activity of systemic inflammatory mediators, such as adipokines, free fatty acids (FFAs), and ROS released by dysfunctional abdominal AT [91]. End-stage OA patients showed increased levels of ROS and decreased antioxidant capacity [92]. Many of these inflammatory mediators have been linked to cartilage matrix synthesis and degradation, and synovial tissue inflammation. For instance, leptin is a 16-kd polypeptide hormone secreted by adipocytes, regulating adipose mass and body weight. Impaired leptin signalling was related to protection against obesity-induced OA, even in absence of elevated body fat, thus corroborating the pro-inflammatory effects of leptin in OA [93]. Leptin secretion from the infrapatellar fat induces MMPs 1 and 13 gene expression in OA chondrocytes [94]. Recent literature supported the hypothesis that underlying mechanisms for OA go further than mechanical load and stress, since a correlation with CVDs, metabolic syndrome (MetS), and especially factors such as arterial hypertension, DM, dyslipidemia, has been observed [91], with a positive correlation with radiological OA severity [92]. In animal studies, omega-3 polyunsaturated fatty acids reduced the expression of inflammatory markers, cartilage degradation and oxidative stress in chondrocytes, while the opposite was true after omega-6 polyunsaturated fatty acid and saturated fatty acid administration, both in animals and in humans; hence, omega-3 polyunsaturated fatty acid supplementation may have a beneficial effect on pain and functionality through a reduction in structural damage [95].

2.3. Osteoarthritis

2.3.1. Osteoarthritis and Neuroinflammation

Chronic painful conditions, including OA, are accompanied and sustained by inflammatory responses in peripheral tissues, e.g. joints, as well as in the peripheral and central nervous system: such phenomena are described as “neuroinflammation”, and they rely on a bidirectional signalling between nervous structures and cells and the peripheral damaged tissues. Animal models of OA showed that joint neurons, especially high-threshold C and A δ afferents, undergo plastic changes [96] and develop an important sensitization, hence mechanical stimuli are perceived as painful in behavioural tests [97,98]. For instance, after induction of knee OA via intra-articular monosodium iodoacetate (MIA) injection, destabilization of the medial meniscus (DMM), or partial meniscectomy, animals display mechanical hyperalgesia, with pain evoked by simple gentle pressure or by normal-range joint mobilization [99]. Nociceptors that are initially considered as responsive to other stimuli, namely cold, heat, or chemicals, and silent to mechanical stimuli, become mechanosensitive too, taking on a polymodal phenotype [100]. Such peripheral findings are correlated with a higher response to the same stimuli in dorsal root ganglia (DRG) neurons, where nociceptors are activated via paracrine mechanisms [101]. Many mediators derived from degradation of inflamed cartilage are implicated in the sensitization and excitation of DRG neurons [102]. Under physiological conditions, several cytotypes in the joints, namely chondrocytes, fibroblast-like synoviocytes (FLS), synovial macrophages, and mast cells (MCs) are represented in a quiet state, as “sentinels” against pathogens and possible injuries [103,104]. When joint inflammation occurs, the disruption of the ECM allows for the release of damage-associated molecular patterns to the joint cavity, and consequent activation of pattern recognition receptors, namely Toll-like receptors (TLRs), on such sentinel cells. These phenomena lead to the production and release of inflammatory molecules, catabolic factors, and the activation of the complement cascade [105]. Particularly, MCs secrete granules containing proinflammatory substances, such as histamine, proteinases (tryptases and chymases) [106], as well as chemokines and cytokines (TNF- α , IL-1 β , IL-6, IL-8, CCL2, PG2, VEGF, and others), thus leading to vasodilatation, angiogenesis, as well as recruitment of other inflammatory cells from the bloodstream [107]. MCs also produce neurotrophin nerve growth factor (NGF) [108] which, after being secreted by MCs, binds to neurotrophin p75 and tropomyosin-related kinase (TRK)-A receptors on several inflammatory cells, including other MCs, promoting their degranulation. The increase of NGF has been correlated with sprouting of pain fibres in vitro [109], microglia activation

(e.g. “microgliosis”) in the dorsal horn [110], and other structural changes leading to neuroinflammation and pain chronification [111]. In the wake of this, clinical trials with humanized neutralizing monoclonal antibodies against NGF are ongoing for OA patients, as they have already been reported to have analgesic effects in animal models, both as prophylaxis and in therapeutic protocols. Accordingly, TRK-A inhibition showed analgesic results in animals [112,113]. Other immune cells, including circulating macrophages, infiltrate the DRG in OA rodent models [114], especially after HFDs administration, possibly hinting at a correlation between the latter and chronic pain [115]. Macrophage infiltration in the DRG in OA animals was positively correlated with persistence of pain [116]. Most of recent preclinical research has focused on the role of glial cells, such as microglia, in the DRG and the dorsal horn, which are activated during neuroinflammatory processes [117,118]. Microglia is actually the resident macrophages of the CNS: its activation in the DRG occurs in animal models after OA induction, with different timing based on the OA inducer: for instance, microglia activation is detectable as soon as one week after MIA injection, while it takes DMM models 8 to 16 weeks to display such activation [110]. These findings may correlate with the difficulty of treating OA in late stages, where drugs targeting the CNS are often necessary, such as opioids, while others, namely nonsteroidal anti-inflammatory drugs, are insufficient for pain control [100]. Microglial cells produce cytokines, such as TNF α , IL-1, and NGF, and release other molecules, namely substance P, which may further activate receptors expressed by macrophages in a paracrine manner, and sustain a shift in their phenotype to a M1 proinflammatory one [119]. Microglia activation seems to be accompanied by overexpression of stress markers in the DRG, and with allodynia; the latter is reversible via glia inhibition through minocycline and fluorocitrate [120]. For example, NF- κ B/p65 is overexpressed in astrocytes in the dorsal horn in rat MIA OA model, alongside cytokines like IL-1 β , TNF- α and IL-33; moreover, astrocytes themselves are heightened in number and mechanical hyperalgesia is advisable, albeit reversible through spinal inhibition of NF- κ B/p65 [121]. A predominant role for NF- κ B was also confirmed recently by Sun et al., who showed that inhibition of bromodomain-containing protein 4 (Brd4), a bromodomain and extra-terminal epigenetic reader protein that usually promotes gene transcription, attenuated MIA-induced pain behaviours in rats with OA through a reduced activation of inflammatory genes. Brd4 inhibition also promoted antioxidant responses in the DRG and in the spinal cord [122]. Oxidative stress has been linked to various inflammatory and degenerative conditions of the CNS [123] and may be a contributing factor for arthritic pain: overexpression of anti-inflammatory molecules, namely sestrin2 (Sesn2) [124], and inhibition of pro-inflammatory ones, such as GSK-3 β [125,126], reduced ROS and cytokines levels in the spinal cord in MIA- and complete Freund’s adjuvant (CFA)-induced OA, respectively, with analgesic effects on OA pain. Interestingly, OA symptom burden seems to be more severe in women than men in clinical practice [127,128], probably due to higher inflammatory responses in female than males [129,130], or, possibly, to differences in neuroimmune signalling. Kosek et al. showed that female subjects scheduled for total knee replacement displayed higher levels of IL-6 and IL-8 in synovial fluid (SF) and cartilage, correlated with more severe pain and higher pain sensitivity. Moreover, when considering the relative presence of different cytokines in the CSF, serum, SF, and cartilage, discrepancies between men and women were found, suggesting sex-related peculiarities in the cross-talk among peripheral damaged tissue and the CNS. Such communications rely, among other factors, on the presence of monocyte chemoattractant protein 1 (MCP1), which is responsible for increased BBB permeability, as well as spinal infiltration of monocytes and their eventual differentiation into activated microglial cells. Besides being produced by monocytes/macrophages, synovial fibroblasts, and chondrocytes, MCP1 is also detectable in nociceptive afferent fibers in peripheral tissues with possible implication in neuropathic manifestation, especially mechanical allodynia in animal models. Interestingly, higher concentrations of MCP1 and IL-8 in the CSF were correlated with lower pain levels, whereas their presence in joints led to higher pain sensitivity. Hence, presence of proinflammatory markers in the CNS may be part of a compensatory response against peripheral disease, such as OA [131]. This may be corroborated by the higher levels of both myo-inositol, a glial-derived neuroinflammation marker, and choline, a

cell membrane metabolism and cellular turnover marker, in patients with knee OA, with positive correlation with pain, stiffness, and disability scores. On the other hand, concentrations of NAA, a marker for neuronal integrity, were reduced compared to healthy controls, but returned to normal-range levels after total knee arthroplasty, thus suggesting that surgical treatment may have a role in counteracting the maladaptive mechanisms leading to pain sensitization and chronification in subjects with OA. More specifically, since NAA is produced in oligodendrocytic and neuronal mitochondria, the restoration of its physiological levels after surgery may be the consequence of ameliorated mitochondrial function [132], further confirming the role of oxidative processes in neuroinflammation. Age, too, is correlated with higher levels of inflammatory markers in the DRG and the spinal cord, as well as peripherally, e.g. the sciatic nerve, in mice with MIA-induced OA: in particular, overexpression of CD68, CD11b, activating transcription factor 3, and TNF as neuroinflammatory markers were higher in old animals, and they were counteracted by subcutaneous morphine administration 7 days after OA induction [133]. Opioids are still pivotal in chronic pain management; however, they are burdened by important adverse effects, and tolerance may develop after long-term administration [134]. Research has focused on possible mechanisms and molecules involved in opioid tolerance, in order to counteract, or even prevent it. For instance, sigma-1 ($\sigma 1$) receptors are expressed in CNS areas implicated in pain perception, namely DRG, dorsal horns, and periaqueductal grey: given their cross-talk with the opioid system, their antagonism allowed for prevention of both pain sensitization and opioid tolerance in MIA-induced OA mice, hinting at a possible role for $\sigma 1$ receptors antagonists as analgesics [135].

A tight relationship between joint disease and CNS pathology is conveyed by the effect of collagen-derived AGEs on neuronal structure and functionality. AGEs derive from glycation of the ECM (ECMGC): this phenomenon is widely described in osteoarthritic joints, and recent data points out that it may hinder neuronal cell attachment and neurite formation, and elicit neuronal excitation, neuropeptide and neurotransmitters release, and eventually peripheral sensitization. Such effects are counteracted by morphine administration, thus suggesting that ECMGC may represent a new target for chronic pain treatment [136]. Moreover, a connection between peripheral damaged tissues and the CNS is suggested by the elevated levels of chemokines prokineticin (PK)-1 and PK-2, which act via interaction with two receptors, namely PK receptor (PKR)-1 and PKR2. This system was found to be upregulated in OA mice 28 days after MIA injection, with synovial fibroblasts and macrophages producing such chemokines, alongside elevated levels of several cytokines in the spinal cord. Concurrent development of allodynia, motor deficits, and fatigue was assessed, as well as mood disorders, particularly anxiety and depression. In fact, PK upregulation also occurred in brain areas that are typically related to mood control, such as the prefrontal cortex and the hippocampus. Administration of PK antagonist PC1 reverted such findings, possibly by both anti-inflammatory effects in damaged joints and in brain regions [137]. Similarly, heightened levels of proinflammatory cytokines and an anxio-depressive state were found in MIA-driven OA mice, with morphine administration contrasting both phenomena [138].

Preclinical research also pointed out that pain alters genetic expression [139], and genes expressed through early to chronic stages of pain are different [140]. A role may be played by long non-coding RNAs (lncRNAs), which act at transcriptional and post-transcriptional levels, via interaction with the DNA and regulation of mRNA translation into proteins, up to epigenetic modifications. lncRNAs play a role in neuronal functionality, immune responses, and inflammatory diseases, such as OA: in fact, different lncRNAs may be up- or downregulated, with modulating effects on inflammatory and apoptotic signalling pathways, and consequent impact on chondrocyte viability and functionality [141]. Among others, lncRNAs are responsible for the regulation and genetic expression of several inflammatory molecules, as is the case for member of the Krüppel-like transcription factors (KLFs) family, KLF4, which is implicated in inflammatory responses in various pathological condition, ranging from IBD, renal inflammation, pneumonia, neuroinflammatory conditions, and OA. In fact, KLF4 inhibits ECM-degrading enzymes in human chondrocytes,

synovial, and meniscus cells via an anti-inflammatory effect [142]. Hence, lncRNAs may represent a novel therapeutic target for OA management.

2.3.2. Osteoarthritis and Oxidative Stress

Besides being triggered and aggravated by biomechanical trauma, OA is known to be an inflammatory chronic condition, in which the oxidative stress probably plays a pivotal role in its pathogenesis and progression, as demonstrated by recent literature, both in vitro and in vivo [143]. Basically, an imbalance between the production of ROS and antioxidant defensive mechanisms occurs, with negative impact on joint structure and related pain [144]. Since OA pain is still largely undertreated, thus infecting functionality and QoL, the reduction of oxidative processes may be a new target for its treatment [145]. The role of inflammatory mediators, such as cytokines and chemokines, has been widely assessed in OA [146,147]. Such mediators may derive from lipid peroxidation processes, which are found to be enhanced in OA synovial cells compared to rheumatoid arthritis and healthy controls [148]. Many lipid peroxidation products, such as 8-isoprostane F_{2α} [149], malondialdehyde, 4-Hydroxy-2-nonenal [150], and so on, are in fact elevated in synovial biopsies from patients with OA compared to healthy subjects. The NO production by inducible nitric oxide synthase (NOS2) was also correlated with the pathogenesis of OA [151], and NO itself secreted by chondrocytes has been correlated with the induction of lipid peroxidation [152], as well as ECM degradation by MMPs [153] and inhibition of proteoglycans and collagen synthesis [154]. On the other hand, a growing body of evidence suggests a role for NO as an inhibitor of the NF-κB pathway [155] and a stimulator of collagen synthesis in vitro [156]. It is possible for NO to have pro-inflammatory effects only when in the form of redox derivative peroxynitrite, which is a known inducer of lipid peroxidation [157]. Mitochondria are key players in the oxidation pathways. Damaged mitochondria are continuously replaced by new ones, in order to preserve mitochondrial function: this process is known as mitochondrial biogenesis, and recent literature shows that it may be an indicator of OA [158]. Several transcription factors regulate mitochondrial renewal, namely PGC-1α [159] and nuclear respiratory factor (Nrf)-1 and Nrf-2, the latter further upregulating the expression of other factors, such as mitochondrial transcription factor A and nuclear-encoded mitochondrial proteins [160]. PGC-1α is deacetylated by NAD-dependent deacetylase sirtuin 1 (SIRT1), which is activated by AMP-activated protein kinase [161]. Nrf-2 was shown to positively modulate the expression of many endogenous antioxidants, namely NAD(P)H oxidoreductase 1 (NQO1), heme oxygenase-1 (HO-1), superoxide dismutase (SOD), glutathione (GSH), and glutathione peroxidase (GPx) [162,163]. Nrf-2 was also shown to inhibit pro-inflammatory pathways, such as NF-κB [164], hence reducing levels of inflammatory cytokines, namely IL-1β and TNF-α [165]. Nrf-2 promotes macrophage differentiation to M2 [166], it modulates osteoclastogenesis [167], and it inhibits the activation of inflammatory synovial fibroblasts [168]. The latter are responsible for the production of metabolic degradation factors, such as MMPs and disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS), resulting in synovial and ECM degradation [169,170]. Further, mitochondrial dynamics imply their continuous mixing with each other and dividing into daughters [171], alongside with removal of damaged ones through autophagy [172]. When such mechanisms are impaired, a reduction in ATP generation occurs, as well as augmented ROS production, mtDNA mutations, and mitochondrial membrane dysfunction [173]: such phenomena are linked to a wide range of degenerative and inflammatory diseases, including OA [174]. Dysfunctional mitochondrial activity has been increasingly linked to OA onset and progression [175], as assessed in animal models [176] and human chondrocytes [158]. Nrf2 induction in models of surgically-induced OA prevented OA progression via inhibition of NLR family pyrin domain containing 3 (NLRP3) inflammasome [177], a complex playing a pivotal in triggering inflammatory responses in several pathological conditions [178]. The latter is upregulated in the synovial tissue of mice with collagen-induced arthritis [179], as well as in sensory neurons in the DRG in MIA-induced OA. Accordingly, inhibition of NLRP3 inflammasome prevented the transition from an acute to a chronic painful condition in such animal models [180]. GSH is a well-known antioxidant that plays a

key role against oxidative stress, with pleiotropic effects, including activation of Nrf2 [181]. Reduced GSH and its precursor molecule, N-acetylcysteine, have demonstrated a specific role in oxidative stress resistance [182], and efficacy in reducing inflammation markers and cartilage degradation, as well as significant amelioration in pain control and functionality [183]. One of the ways to increase GSH levels is through hydrogen sulfide [184]. Administration of slow-releasing hydrogen sulfide donors phenyl isothiocyanate [185], allyl isothiocyanate [186], diallyl disulfide [187] and morpholin-4-ium 4-methoxyphenyl(morpholino) phosphinodithioate dichloromethane complex (GYY4137) [188] alleviated the mechanical allodynia, the grip strength and memory deficits, as well as the depressive-like behaviors accompanying OA through inhibition of activated microglia, downregulation of NOS2, CD11b/c, phosphatidylinositol-3-kinase-PI3K, and phosphorylated Akt- p-Akt all while maintaining high levels of antioxidant/detoxicant molecules in central regions such as the hippocampus, the amygdala, periaqueductal gray matter, and infralimbic cortex, thus demonstrating the antinociceptive potential of NOS2 inhibition [189].

3. Therapeutic Perspectives

3.1. Palmitoylethanolamide

Palmitoylethanolamide (PEA, N-hexadecanoylethanolamide) is a N-acylethanolamine (NAE), and it was first discovered in the late 1950's in soybean, peanut oil, and egg yolk [190]; later on, it was also identified in mammalian tissues [191]. PEA is a highly lipophilic molecule, which may hinder its absorption: in fact, the micronization was found to be useful, since this process makes the original compound smaller [192,193]. After absorption, PEA is hydrolysed to ethanolamine and palmitic acid by fatty acid amide hydrolase (FAAH), which is a membrane-bound enzyme with a heterodimeric structure. It is located in the endoplasmic reticulum and it acts on multiple substrates, including N-acylamines, NAEs, and N-acyltaurines [194]. PEA is also metabolized by FAAH-2, which is localised in lipid droplets [195], and by lysosomal enzyme NAE acid amidase [196]. Such enzymes act on either endogenous [197–199] or exogenous [200,201] PEA, and are found in different tissues and cytotypes, ranging from the gastrointestinal tract [199] [202], to joints [203], to the brain [204–206]. Various attempts to bypass its presystemic metabolism were made, either using prodrugs [207,208] or PEA analogues [209–212] however, such compounds need further investigation and regulation. Since it is almost insoluble in water, the bioavailability of PEA *per se* is poor [213]. Data on its distribution is overall quite scarce. Nonetheless, given its lipophilic nature, the volume of distribution for PEA is high [214], and way greater than its plasma volume [214]. As shown by early studies in rats, after intraperitoneal administration PEA tends to distribute in several organs and tissues, according to the following order: adrenal > diaphragm > spleen > kidney > testis > lung > liver > heart > brain > plasma > erythrocytes [215]. When orally administered, PEA is able to cross the BBB, albeit in small amounts [216]. PEA is now recognized as a lipid mediator, with anti-inflammatory properties [217] via interaction with several receptors and mediators. Among the latter, peroxisome proliferator-activated receptor (PPAR) is a nuclear transcription factor, with several ligands [218], including arachidonic acid and fibrates, the latter being used to treat dyslipidaemias [219]. In fact, PPAR activation leads to the transcription of genes involved in lipid metabolism [220], as well as inflammatory responses [221], with consequent enhanced expression of pro-inflammatory molecules, such as NF-κB. In fact, highly bioavailable formulations of PEA, e.g. micronized (m-PEA) and ultramicronized (um-PEA), were found to promote white-to-beige AT conversion [222], reducing fat mass; and counteracting lipid and glucose dysmetabolism [223]. Recently, comicronized PEA with rutin (m-PEA– rutin), a plant-derived polyphenol compound, well-known for its antioxidant and anti-inflammatory properties, have been investigated in a murine model of obesity-induced metabolic alterations, supporting their effect in counteracting glucose and lipid dysmetabolism associated with diabetes [223]. Clinical results against adiposopathy have been found when m-PEA– rutin and hydroxytyrosol (HTyr), a phenolic compound found in olive leaves, fruits and extra-virgin olive oil, have been added to the Mediterranean diet as a potential conservative treatment for patients

with MetS. HTyr has been shown to reduce oxidative stress, and modulate inflammatory pathways [224].

3.1.1. Palmitoylethanolamide and Osteoarthritis

PEA is present in high concentrations in healthy joints and acts as a MCs modulator [225]. Physiologically, MCs, alongside macrophages, represent about 3% of resident cellular cell population and act as sentinels for possible pathogens and injuries. In arthritic joints, the number of MCs increases via maturation and proliferation of resident cells, as well as recruitment of progenitors from the blood stream, via paracrine mechanisms [107]. PEA reduces the degranulation of MCs in vitro [226] and in vivo [227].

3.1.2. Palmitoylethanolamide and Neuroinflammation

PEA is also among the many substances produced, released, and hydrolyzed by microglia [228]. The involvement of PEA in neuroinflammatory processes was thoroughly studied, and it may be mediated by its direct and indirect interaction with various receptors, namely PPAR [229], cannabinoid receptors (CB)-1 and CB2 [230], as well as non-CB1 and non-CB2 [231], with paracrine effects on microglia itself, furtherly boosting neuroinflammation [232], even more so considering that recent literature has highlighted the existing link between MCs and glial activation [225]. Neuroinflammatory responses may be driven by the effects of PEA on TRPV1 channels [233], which are knowingly implicated in such processes [234], possible via modulation of cannabinoid pathways [235]. Such cross-communications between these systems may give reason to the possible role for PEA in modulating intestinal inflammatory conditions [236,237]. PEA levels increase in several animal models of neurological disorders, and in human models, e.g. of migraine [238]. Administration of exogenous PEA was found to be efficacious in experimental models of mast cell-mediated acute and neurogenic inflammation [239].

Moreover, it showed promising results in reverting amyloid β -peptide-induced astrogliosis [240,241] and consequent learning and memory impairment in mice [242], hinting at a possible role for PEA as adjuvant and add-on therapy for human neurodegenerative disorders, such as Parkinson's and Alzheimer's diseases [243–245].

PEA was found to reverse histopathological changes, reduce joint swelling, and reduce serum levels of NO, IL-1 β , leukotriene B4, TNF- α , and prostaglandin E2, as well as cartilage-degrading MMPs in MIA-induced knee OA rats, hence preserving cartilage structure [246]. PEA administration decreased neuropathic pain, especially mechanical hyperalgesia, in Sprague-Dawley rats that were injured via L5 and L6 spinal nerves transection: interestingly, intrarticular injection of PEA was effective at lower doses compared to intraperitoneal PEA [247]. PEA administration had beneficial effects in dogs with chronic OA and lameness, with the latter having significant improvement, alongside better functioning and pain control [248].

3.1.3. Palmitoylethanolamide and Low Back Pain

m-PEA administration was found to be useful for pain control in patients with LBP, with efficacy against neuropathic features. Although m-PEA may not have a role on functional improvement when administrated alone at low doses (600 mg/die) [249], um-PEA showed promising results when administrated at higher dosage (600 mg twice a day), at least in an early stage, as a support therapy during rehabilitation, with improvement in mental and physical components of QoL, as well as disability scores [250]. Moreover, add-on therapy with um-PEA was correlated with reduced intake of opioids in patients with chronic LBP, with a significant reduction in pain perception and neuropathic manifestations, overall maintaining a good tolerability and safety profile [251,252], which makes um-PEA a good option even in older patients [253]. In addition, um-PEA was found to ameliorate pain control in patients with failed back surgery syndrome as an add-on therapy, together with dual opioid tapentadol and anticonvulsant pregabalin [254]. The modulatory properties of PEA

on neuropathic pain are potentially driven by both its effects on CB1, Transient Receptor Potential Vanilloid 1- TRPV1, and PPAR- γ , and a reduction of proinflammatory cytokines, namely NGF and TNF- α [255].

3.1.4. Palmitoylethanolamide and Gut Dysbiosis

Gut microbiota exerts a significant influence on both human physical and mental health [256]. The bidirectional communication between the gastrointestinal tract and the CNS, defined as “gut microbiota-brain axis”, occurs through the neuroendocrine system, the activation of immune system and the production of bacterial metabolites by the gut microbiota (Figure 1) [257]. In detail, the neuroendocrine system refers to the hypothalamus-pituitary-adrenal- HPA axis, while the immune system to microbial- and pathogen-associated molecular patterns (such as lipopolysaccharide-LPS pathway), and finally the bacterial metabolites to the production of short-chain fatty acids (SCFAs), neurotransmitters (dopamine, norepinephrine, serotonin- 5-HT, histamine and gamma-aminobutyric acid- GABA) and tryptophan (Trp) [257]. The communication between the gut microbiota and the HPA axis is closely interconnected with the immune system, microbial metabolites, gut hormones, BBB, and sensory and autonomic nervous system [258]. Gut dysbiosis is defined as an alteration in the gut microbiota composition, detected by an increase in the number of pathobionts and a decrease in symbionts [259], a consequence of high-fat diets (HFDs) and Western diet [260], drugs, immune system dysfunction, stress conditions [261] and diseases (including those inflammatory, autoimmune, metabolic, neoplastic, neurodegenerative and CKD) [262–267]. In chronic pain patients, gut microbiota may be affected by opioid administration [268] and drugs used for managing opioid induced constipation [269]. The HPA axis is part of the limbic system and is the main regulator of the stress response [270]. Signals generated by the hypothalamus reach the pituitary and adrenal glands and communicate with entero-epithelial cells via the HPA axis. The signals influence the gut microbiota through the enteric nervous system (ENS), located in the submucosa and myenteric plexus of the gut wall [271]. However, the relationship between the gut dysbiosis and the HPA axis is bidirectional [272]. In fact, stress conditions can alter the gut microbiota composition [273]. Gut microbiota dysbiosis, in turn, influence HPA axis activity, resulting in excess circulating cortisol production through the synthesis of corticotropin-releasing hormone (CRH) by the hypothalamus [274]. CRH stimulates the anterior pituitary gland to produce adrenocorticotrophic hormone- ACTH, resulting in the release of an excess cortisol by the adrenal cortex [275]. Cortisol overproduction is implicated in neuroinflammation and impairments of the hippocampus and prefrontal cortex, namely brain regions involved in emotional regulation and memory [276]. While cortisol is necessary for an adaptive stress response, its chronic and excessive production can have neurotoxic effects [277], manifesting with depressive symptoms, cognitive deficits, neuropsychiatric disorders and impaired adaptation to stress, and exacerbating gut dysbiosis [278]. In fact, impairment of the hippocampus and prefrontal cortex, in response to cortisol overproduction, damages the CNS, inducing a reduced neuronal plasticity, a decreased level of BDNF, and atrophy of hippocampus and prefrontal cortex [279]. The overactivity of the HPA axis contributes to the alteration of the composition of the gut microbiota, with an increase in the abundance of *Firmicutes* phyla and a decrease in *Bacteroidetes* one [280]. Both phyla are responsible for the production of SCFAs (acetate, propionate and butyrate). The latter are metabolites produced by bacterial fermentation from indigestible carbohydrates (dietary fibre) in the gastrointestinal tract [281]. They perform beneficial functions for the gut microbiota, regulating positively its composition, increasing the amount of TJs proteins and improving the function of intestinal epithelial barrier. SCFAs produced adhere to FFA receptors on the surface of intestinal epithelial cells and interact with neurons or enter the bloodstream [271]. SCFAs modulate TJs protein expression also in the BBB. Indeed, fecal transfer of gut microbiota to germ-free mice decreases BBB permeability and regulates the expression of claudin-5 and ZO-1 in the CNS, reducing BBB permeability [282]. The reduction of SCFAs is closely associated with the onset and development of metabolic and inflammatory diseases (such as type 2 DM, obesity, CKD, arterial hypertension, inflammatory bowel disease-IBD and colorectal cancer) [283]. *Firmicutes*

are responsible for the production of butyrate, while *Bacteroidetes* of acetate and propionate. However, decreased *Bacteroidetes* abundance results in reduced acetate and propionate production. Rats treated with HFD are associated with increased *Firmicutes* phyla and decreased *Bacteroidetes* phyla abundance. This leads to a change in SCFAs production, with an increase in butyrate levels and a decrease in propionate levels. The globally decrease in SCFAs production induces to a loss of enteric neurons and thus a weakening of the ENS [271]. Gut dysbiosis is also associated with increased Gram-negative bacteria, which activate the immune system and neuroendocrine system via LPS [257,260], the major component of the outer membrane of Gram-negative bacteria [284]. The increase of Gram-negative bacteria in the gastrointestinal tract allows LPS to act locally and systemically, after crossing the impaired gut barrier and entering in the systemic circulation. In fact, the LPS can enter in the bloodstream thanks to increased gut permeability, as pointed out by decreased levels of TJ proteins, zonulin-1 and occluding [285]. High concentrations of circulating LPS are defined as metabolic endotoxemia, which is responsible for triggering chronic-metabolic diseases [286]. Therefore, once LPS has crossed the intestinal barrier to enter in the systemic circulation, it binds to TLR4 and leads to systemic inflammation by stimulating the production of pro-inflammatory cytokines and activating the innate immune system response [287]. Pro-inflammatory cytokines, such as IL-6 and TNF- α , further activate HPA axis, stimulating the release of cortisol [288], exacerbating depression and contributing to symptoms such as apathy, demotivation, and fatigue [274]. Restoring the eubiosis of gut microbiota could be beneficial to nervous peripheral and central disorders related to gut dysbiosis [289]. Over the years, the role of PEA on the gut microbiota has been studied in the literature. For the first time, Couch and co-Authors have investigated the effects of PEA on the permeability of the human gastrointestinal tract in vitro, ex vivo and in vivo. In *vitro* and ex vivo studies, PEA prevented inflammation-induced permeability of dextran. In the in *vivo* study, the aspirin-induced increase in intestinal permeability, detected by an increase in urinary lactulose-to-mannitol ratio, was rescued by PEA administration at the dose of 600 mg. These data suggest how PEA is able to reduce the permeability in the human colon [290]. The effects of um-PEA on the gut microbiota have been better elucidated by Pirozzi and co-Authors on HFD-fed mice. The Authors showed, in this animal model, that um-PEA, administered at the dose of 30 mg/kg/die per os for 7 weeks, has been able to reduce the inflammatory response in the gut, restore Trp metabolism and remodel the gut microbiota of mice. The reduction of the inflammatory response is supported by the immunomodulatory effects exerted by um-PEA. Indeed, its administration was able to limit immune cell recruitment and activation of intestinal MCs and macrophages, leading to a reduction in the expression of intestinal pro-inflammatory factors, namely IL-1 β , TNF- α , cyclooxygenase-2, and NOS2. The effects on Trp metabolism were evidenced by the ability of the um-PEA to restore 5-HT/kynurenine (KYN) levels in the mice colon, rescuing altered 5-HT turnover, decreasing gastrointestinal indoleamine-2,3-dioxygenase (IDO) expression and resulting in reduced Trp oxidation in KYN [291]. Trp metabolism connects the gut to the CNS, as the enzyme IDO oxidizes Trp in KYN, decreasing circulating levels of 5-HT. KYN reaches the systemic circulation, crosses the BBB and acts at the CNS level, causing depression, anhedonia, anxiety, and metabolic dysfunction related to obesity and insulin resistance [292]. The same Authors pointed out that the administration of um-PEA in HFD-fed mice was able to reduce the *Firmicutes/Bacteroidetes* ratio and to increase the *Bifidobacterium* genera and the *Oscillospiraceae* family, both butyrate producers. Confirming this, the Authors have highlighted an increased expression of monocarboxylate transporters-1- MCT-1, a gene related to butyrate activity that mediates its transport in the colon mucosa, and of G-protein-coupled receptors-43- GPR43, which is involved in the control of the gut inflammation. Finally, the increase of SCFAs-producing bacterial species, such as the genera *Turicibacter sanguinis*, has been highlighted in the gut [291]. To date, only a randomized, placebo controlled, double-blind study conducted by Batacan and co-Authors has investigated the role of PEA on the gut microbiome of overweight adults (BMI 30-40 kg/m²), at the dose of 700 mg/day for 12 weeks. At the end of the study, the Authors demonstrated the ability of PEA in reducing triglycerides and IL-2 levels. The in vivo effects of PEA remain unclear. In fact, no significant

differences in overall microbiota composition were found after PEA administration. Moreover, the microbiota richness and diversity remained constant for both groups [293]. In light of this, further studies are needed to better determine the action of PEA on gut dysbiosis.

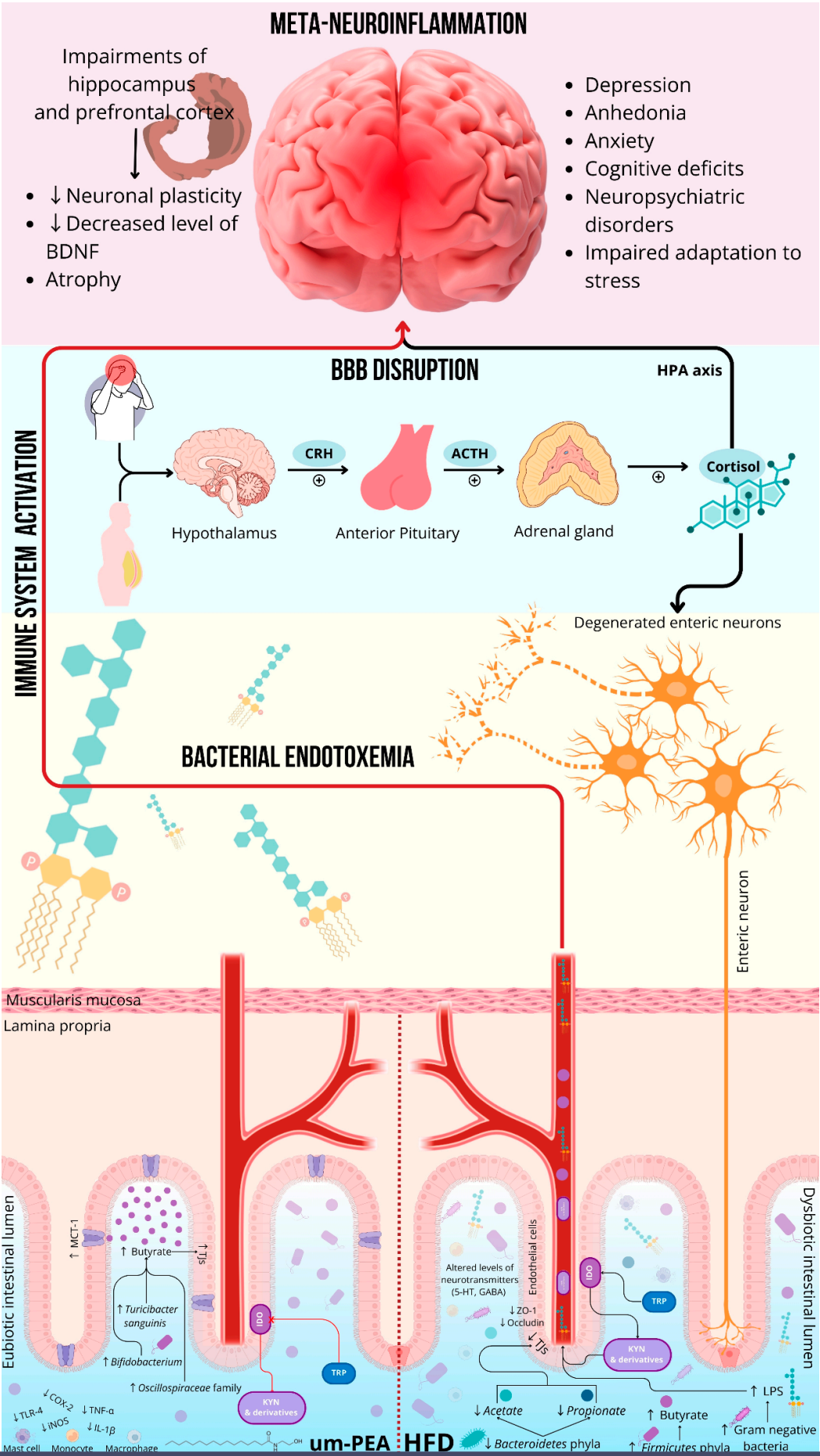


Figure 1. Meta-neuroinflammation and gut-brain axis. The communication between central nervous system and gut occurs through the hypothalamus-pituitary-adrenal axis, the activation of immune system that involved the lipopolysaccharide (LPS) pathway, and through the production of bacterial metabolites by the gut microbiota, such as short-chain fatty acids (SCFAs) and neurotransmitters. The hyperactivation of HPA axis, as consequence of stress conditions and metabolic diseases leads to an overproduction of cortisol, influencing the gut microbiota composition by the enteric nervous system, located in the submucosa and in the myenteric plexus of the gut wall. This HPA axis hyperactivation is implicated in neuroinflammation, impairments of the hippocampus and prefrontal cortex and gut eubiosis. In the dysbiotic gut microbiota, the lower production of SCFAs, contributes to increase the permeability of the intestinal barrier, as shown by a reduction in zonula occludens-1 and occludin. Moreover, the translocation of LPS in the bloodstream is responsible of bacterial endotoxemia, that dysregulates the immune system. The ultramicronized-palmitoylethanolamine (um-PEA) can restore the eubiosis of the gut microbiota, through the SCFAs-producing bacterial species, such as *Turicibacter sanguinis*, *Bifidobacterium*, *Oscillospiraceae* family. In fact, the enhancement release of butyrate increases the production of tight junctions and the expression of monocarboxylate transporters-1. Finally, um-PEA is able to limit immune cells recruitment and activation of intestinal mast cells and macrophages and to restore serotonin/kynurenine levels. Abbreviations: ACTH, adrenocorticotrophic hormone; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; COX-2, cyclooxygenase-2; CRH, corticotropin-releasing hormone; GABA, gamma-aminobutyric acid; HFD, high-fat diet; HPA, hypothalamus-pituitary-adrenal axis; IDO, indoleamine-2,3-dioxygenase; IL-1 β , Interleukin-1 β ; iNOS, inducible nitric oxide synthase; KYN, kynurenine; LPS, lipopolysaccharide; MCT-1, monocarboxylate transporters-1; TJs, tight junctions; TLR-4, toll-like receptors-4; TNF- α , tumor necrosis factor- α ; TRP, tryptophan; um-PEA, ultramicronized palmitoylethanolamide; ZO-1, zonula occludens-1; 5-HT, serotonin.

3.2. Adelmidrol

Adelmidrol (ADM) is a synthetic derivate of azelaic acid and a member of the Autacoid Local Injury Antagonist Amides (ALIAMides) family, with both amphipathic and amphiphilic properties, which make it particularly suitable for topical and intra-articular administration [294]. A gel combining 2% ADM with 0.1% hyaluronic acid (HA) showed antioxidant effects in the inflamed gut in a mouse model of colitis after intrarectal administration, with protective effects on the epithelial barrier [295]. Moreover, aerosol administration of 2% ADM reduced inflammatory damage in a LPS-induced mice model of acute lung injury, particularly through a reduction in MC activation [296]. Topical ADM (mucoadhesive gel) showed anti-inflammatory effects in small animals with inflammatory pathologies [297–299]. A combination of 2% ADM with 1% high molecular weight HA has been approved for intra-articular injections in knee OA, with a significant improvement in analgesia and functionality [300]. In OA joints, ADM acts as a PEA enhancer, leading to higher PEA levels [301]. Moreover, ADM leads to a reduction in inflammatory cytokines and cartilage degradation, through its effects on MCs [211]. Activated MCs release lytic enzymes that accelerate degradation of HA in the joints. Therefore, ADM, by normalizing MCs activity, increase the bioavailability of HA. Moreover, it supports the phenotypical switch of MCs, from an hyperactivated to a physiological state, with consequent restoration of their function of heparin secretion. Since heparin is a precursor of HA, ADM displayed a visco-inductive effect in OA joints in preclinical models [300]. The maintenance of results at follow-up after intra-articular administration of ADM-HA 2%/1% were affected mainly by the BMI of patients and dysmetabolic disorders [300]. Finally, a clinical investigation comparing ADM-HA 2%/1% versus HA alone, showed that at 2-years follow-up, ADM improved all components of the WOMAC scale in the treatment of knee OA [302]. These data suggest a possible combined used of Adelmidrol-HA in obese patients, together with other systemic strategies for targeting meta-neuroinflammations, such as um-PEA and the association m-PEA– rutin and HTyr, with the aim of optimizing body mass index, reducing inflammation biomarkers, and preventing pain chronification (Figure 2).

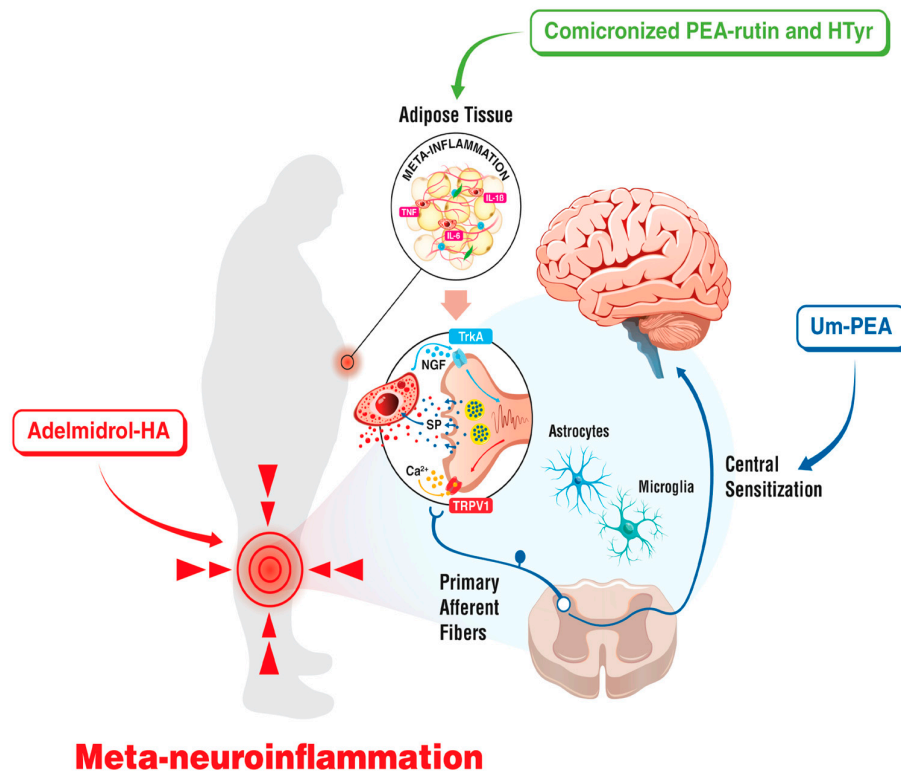


Figure 2. Mechanisms of meta-neuroinflammation underlying OA. Possible targets of treatment for managing meta-neuroinflammation in obese patients suffering from OA-related chronic pain include: the pro-inflammatory state sustained by the adipose tissue, the microglial activation in the CNS, and peripheral hyperactivation of mast cells in the peripheral joints. The association m-PEA– rutin and HTyr has been shown to restore the eubiosis of the gut microbiota and to reduce body weight, body mass index, fat mass, and inflammation biomarkers. Um-PEA is proven to restore physiological role of microglia and to prevent central sensitization, which is a critical factor for pain chronification. Adelmidrol, a PEA congener, facilitates the switch of mast cells from the hyperactivated to the physiological state, therefore it reduces the degranulation of lytic enzymes and prevent HA degradation. Moreover, by normalizing mast cells production of heparin, it further increases the bioavailability of HA, supporting a visco-induction in the overloaded joints of obese patients. Abbreviations: HA, hyaluronic acid; HTyr, hydroxytyrosol; IL-1 β , interleukin-1 β ; IL-6, interleukin-6; SP, substance P; TGF, transforming growth factor; TNF- α , tumor necrosis factor- α ; TRKA, tropomyosin receptor kinase A; TRPV-1, transient receptor potential vanilloid; um-PEA, ultramicronized palmitoylethanolamide.

4. Conclusions

Globally, obesity is a serious public health problem associated with increased morbidity and mortality from all causes, leading to a reduction in patients' quality of life and life expectancy. Suffering from obesity, the adipocyte hypertrophy, visceral and ectopic adiposity predispose the organism to the meta-inflammation. The dysbiosis of the gut microbiota is typically of obesity, contributing to the meta-neuroinflammation. In fact, the gut microbiota and the CNS are in close communication, defining the gut microbiota-brain axis. Moreover, the integrity of the BBB is compromised in obesity. In light of this innovative point of view, the um-PEA and the m-PEA– rutin and HTyr seem to be able to restore the eubiosis of the gut microbiota and to reduce body weight, body mass index, fat mass, and inflammation biomarkers, to such an extent that they are considered a new adjuvant therapy against adiposopathy. This evidence supports a modern and innovative approach to many comorbidities associated with obesity, particularly for chronic pain syndromes. Osteoarthritis is the most commonly observed painful disease in obese patients and targeting meta-

neuroinflammation is the challenge of the next future. Clinicians should be aware that a modern approach to OA in obese patients require the ability to “think outside the box”, by focusing not only on the single organ or disease, but on the close interconnection between systems, sustained by meta-neuroinflammation. Nowadays, in clinical practice, both central and peripheral mechanisms of neuroinflammation can be managed by using natural bioactive compounds with antioxidant and anti-neuroinflammatory properties. In particular, clinical evidence is available for um-PEA, through systemic administration, and for adelmidrol, as intra-articular injections for knee OA. Further studies are warranted to support these data and open new perspectives for the future of obese patients suffering from chronic pain in OA.

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Abbreviations

The following abbreviations are used in this manuscript:

AD	Alzheimer’s disease
ADAMTS	Disintegrin and Metalloproteinase with Thrombospondin Motifs
ADM	Adelmidrol
AGEs	Advanced glycation end-products
APP	Amyloid Precursor Protein
AT	Adipose tissue
Aβ	Amyloidbeta-protein
BAT	Beige adipose tissue
BBB	Blood–brain barrier
BDNF	Brain-Derived Neurotrophic Factor
BM	Basement membrane
BMI	Body Mass Index
Brd4	Bromodomain-containing protein 4
CB	Cannabinoid Receptors
CFA	Complete Freund’s Adjuvant
CKD	Chronic kidney disease
CNS	Central nervous system
CRH	Corticotropin-Releasing Hormone
CVDs	Cardiovascular diseases
DALYs	Disability-Adjusted Life-Years
DM	Diabetes mellitus
DMM	Medial meniscus
DRG	Dorsal root ganglia
ECM	Extracellular matrix
ECMGC	Glycation of the extracellular matrix
EnNaCs	Endothelial Na2+ Channels
eNOS	Endothelial Nitric Oxide Synthase
ENS	Enteric nervous system
FAAH	Fatty Acid Amide Hydrolase
FFAs	Free fatty acids
FLS	Fibroblast-Like Synoviocytes
FNDC5	Fibronectin type III domain containing 5
GM-CSF	Granulocyte-Macrophage Colony-Stimulating Factor
GPx	Glutathione Peroxidase

GSH	Glutathione
HA	Hyaluronic acid
HFDs	High-fat diets
HIF-1	Hypoxia-Inducible Factor 1
HO-1	Heme Oxygenase-1
HTyr	Hydroxytyrosol
ICAM-1	Intercellular Adhesion Molecule-1
IDO	Indoleamine-2,3-Dioxygenase
IKK	Inhibitor of Kappa β Kinase
IL	Interleukin
JAM-A	Junctional Adhesion Molecule-A
KLFs	Krüppel-Like Transcription Factors
KYN	Kynurenine
LBP	low back pain
LepR	Leptin receptor
lncRNAs	Long non-coding RNAs
LPS	Lipopolysaccharide
m-PEA	Micronized palmitoylethanolamide
M1	Pro-inflammatory macrophages
M2	Anti-inflammatory macrophages
MCP1	Monocyte Chemoattractant Protein 1
MCs	Mast cells
MetS	Metabolic syndrome
MHC	Major Histocompatibility Complex
MIA	Monosodium iodoacetate
MMPs	Matrix metalloproteinases
m-PEA– rutin	Comicronized palmitoylethanolamide with rutin
mTOR	Mechanistic Target of Rapamycin
NAA	N-acetylaspartate
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NAE	N-acylethanolamine
NF- $\kappa\beta$	Nuclear Factor kappa β
NGF	Neurotrophin Nerve Growth Factor
NLRP3	NLR Family Pyrin Domain Containing 3
NO	Nitric oxide
NOS2	Inducible nitric oxide synthase
NQO1	NAD(P)H Oxidoreductase 1
Nrf	Nuclear Respiratory Factor
OA	Osteoarthritis
PEA	Palmitoylethanolamide
PECAM	Platelet Endothelial Cell Adhesion Molecule
PGC-1 α	Peroxisome Proliferative Activated Receptor- γ Coactivator-1 α
PK	Prokineticin
PKC	Protein Kinase C
PKR	Prokineticin receptor
PPAR	Peroxisome Proliferator-Activated Receptor
PSGL-1	P-selectin glycoprotein ligand-1
pTau	Hyperphosphorylated Tau
QoL	Quality of Life
RAGE	Advanced glycation end-products receptor
RANK	Receptor Activator of Nuclear Factor-kappa β
ROCK	Rho-kinase
ROS	Reactive Oxygen Species
SCFAs	Short-Chain Fatty Acids
SERCA	Sarcoplasmic Reticulum Calcium ATPase
Sesn2	Sestrin2
SF	Synovial fluid
SIRT1	NAD-Dependent Deacetylase Sirtuin 1
SO	Sarcopenic obesity

SOD	Superoxide Dismutase
TGF-β	Transforming Growth Factor-β
TIMPs	Tissue Inhibitor of Metalloproteinases
TJs	Tight junctions
TLRs	Toll-Like Receptors
TNF-α	Tumor Necrosis Factor-α
TRK	Tropomyosin-Related Kinase
Trp	Tryptophan
TWEAK	Tumour Necrosis Factor-Like Weak Inducer of Apoptosis
um-PEA	Ultramicronized palmitoylethanolamide
VEGF	Vascular Endothelial Growth Factor
WAT	White adipose tissue
WHO	World Health Organization
ZO-1	Zonula occludens-1
σ1	Sigma-1

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