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Skeletal Muscle PGC-1 α 1 and KAT Enzymes at the Intersection between Depression and Metabolic Disease

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Skeletal Muscle PGC1 α 1 and KAT Enzymes at the Intersection between Depression and Metabolic Disease

THESIS FOR DOCTORAL DEGREE (Ph.D.)

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*To my son,
Emil Agudelo Segerstolpe*

ABSTRACT

Depression and metabolic diseases are leading causes of disability and major contributors to socioeconomic burden worldwide. Physical activity exerts many beneficial effects that confer direct health improvement in individuals suffering from these disorders. However, the molecular mechanisms underlying the influence of different components of exercise interventions remain unknown. To isolate the impact of skeletal muscle conditioning on stress-induced depression, we used transgenic models that exhibit many of the chronic adaptations to aerobic exercise in skeletal muscle. Here, we show a mechanism by which skeletal muscle PGC-1 α 1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. PGC-1 α 1 acts in concert with PPAR α/δ transcription factors to induce the expression of kynurenine aminotransferases in skeletal muscle. The activity of this pathway diverts the metabolism of stress-induced kynurenine to kynurenic acid. Since kynurenic acid is unable to cross the blood brain barrier, this peripheral shift protects the brain from stress-induced accumulation of kynurenines. In addition, we further show that skeletal muscle PGC-1 α 1 and kynurenine aminotransferases are part of the physiological adaptations to aerobic exercise in both rodents and humans. Given that exercise-mediated activation of this pathway leads to peripheral accumulation of kynurenic acid, we evaluated the physiological role of this metabolite in modulating energy homeostasis. Here, we describe that kynurenic acid plays a role in systemic energy homeostasis through the regulation of adipose tissue function and inflammation. Kynurenic acid induces the expression of lipid metabolism, thermogenic and anti-inflammatory gene networks in the white adipose compartment. This reduces body-weight gain and improves glucose tolerance in animals fed a high-fat diet. Mechanistic studies in primary adipocytes show that kynurenic acid activates the G protein-coupled receptor 35. Downstream signaling of this activation is mediated through Ca²⁺, ERK, CREB and PGC-1 α 1 stabilization. Finally, activation of GPR35 by kynurenic acid induces the expression of RGS14, which sensitizes β -adrenergic response to specific agonists. In sum, this work uncovers a previously unknown function of PGC-1 α 1 in skeletal muscle and kynurenic acid in white adipose tissue. Targeting this metabolic node has great potential for the treatment of depression and metabolic diseases such as type-2 diabetes.

LIST OF SCIENTIFIC PAPERS

- I. **AGUDELO, L.Z.***, Femenia, T.*, Orhan, F., Porsmyr-Palmertz, M., Goiny, M., Martinez-Redondo, V., Correia, J.C., Izadi, M., Bhat, M., Schuppe-Koistinen, I., Pettersson, A.T., Ferreira, D.M.S., Krook, A., Barres, R., Zierath, J.R., Erhardt, S., Lindskog, M. and Ruas, J.L. (2014). Skeletal muscle PGC-1 α 1 modulates kynurenine metabolism and mediates resilience to stress-induced depression. *Cell* 159, 33-45.
- II. Schlittler, M., Goiny, M., **AGUDELO, L.Z.**, Venckunas, T., Brazaitis, M., Skurvydas, A., Kamandulis, S., Ruas, J.L., Erhardt, S., Westerblad, H., Andersson, D.C. (2016). Endurance exercise increases skeletal muscle kynurenine aminotransferases and plasma kynurenic acid in humans. *American journal of physiology Cell physiology* 310, C836-840.
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- II. Correia, J.C., Massart, J., de Boer, J.F., Porsmyr-Palmertz, M., Martínez-Redondo, V., **AGUDELO, L.Z.**, Sinha, I., Meierhofer, D., Ribeiro, V., Björnholm, M., Sauer, S., Dahlman-Wright, K., Zierath, J.R., Groen, A.K. and Ruas, J.L. (2015). Bioenergetic cues shift FXR splicing towards FXR α 2 to modulate hepatic lipolysis and fatty acid metabolism. *Mol Metab* 4(12), 891-902.

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LIST OF ABBREVIATIONS

3HAA	3-hydroxy anthranilic acid
3HAO	3-hydroxyanthranilate dioxygenases
3HK	3-hydroxykynurenine
5-HTP	5-hydroxytryptophan
5-TH	5-hydroxytryptamine
AA	Anthranilic acid
AAMs	Alternative activated macrophages
AHR	Aryl hydrocarbon receptor
AMPK	AMP-activated protein kinase
ANP, BNP	Atrial and Brain natriuretic peptides
APC	Antigen-presenting cells
BAIBA	β -Aminoisobutyric acid
BAT	Brown adipose tissue
BCG	Bacillus Calmette-Guerin
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
BMP-7	Bone morphogenic protein 7
CaMK	Ca ²⁺ /calmodulin-dependent protein kinases
CEBP α	CCAAT/enhancer-binding protein α
CEBP β	CCAAT/enhancer-binding protein β
CMS	Chronic mild stress
CNS	Central nervous system
COX	Cyclooxygenase
CPT1B	Carnitine O-palmitoyltransferase 1B
CXCL-1	Chemokine CXC motif ligand-1
DC	Dendritic cells
DDC	Dopa decarboxylase
ERK1/2, MAPK	Extracellular signal-regulated kinase 1/2, Mitogen-activated protein kinase
ER α	Estrogen receptor α
ERR α	Estrogen-related receptor alpha
eWAT	Epididymal white adipose tissue
FGF21	Fibroblast growth factor 21
FXR	Farnesoid X receptor
GATA-1	GATA-binding protein 1
GCN5	General control of amino acid synthesis 5-like 2
GIT	Gastrointestinal tract
GPCR	G protein-coupled receptor

HAT	Histone acetyltransferases
HFD	High-fat diet
HIF	Hypoxia-inducible factor
HIV	Human immunodeficiency virus
HPA	Hypothalamic-pituitary-adrenal axis
IDO	Indoleamine 2,3-dioxygenase
IFN- γ	Interferon gamma
IGF1	Insulin-like growth factor 1
IL-13	Interleukin 13
IL-4	Interleukin 4
IL-4R α	Interleukin 4 receptor alpha
IL-5	Interleukin 5
IL-6	Interleukin 6
IL-9	Interleukin 9
IL-17A	Interleukin 17A
IL-22	Interleukin 22
IL-33	Interleukin 33
ILC1s	Group 1 innate lymphoid cells
ILC2s	Group 2 innate lymphoid cells
ILC3s	Group 3 innate lymphoid cells
iNKTc	Invariant natural killer T cell
IRF4	Interferon regulatory factor 4
iWAT	Inguinal white adipose tissue
JNK	C-jun kinase
KAT	Kynurenine aminotransferase
KLF	Kruppel-like family
KMO	Kynurenine 3-monooxygenase
KP	Kynurenine pathway
KPM	Kynurenine pathway metabolites
KYN	Kynurenine
KYNA	Kynurenic acid
KYNU	Kynureninases
LPS	Lipopolysaccharide
MEF2	Myocyte enhancer factor 2
mTOR	Mammalian target of rapamycin
MRFs	Myogenic regulator factors
MyoD	Myoblast determination protein 1
NAD ⁺	Nicotinamide adenine dinucleotide
NAPRT	Nicotinate phosphoribosyltransferase

NEFA	Non-esterified fatty acids
NFE2L2	Nuclear factor erythroid 2-related factor 2
NF- κ B	Nuclear factor kappa-light-chain-enhancer of activated B cells
NMDAr	N-methyl-D-aspartate receptor
NRF1	Nuclear respiratory factor 1
PA	Picolinic acid
PENK	Proenkephalin
PGC-1 α	Peroxisome proliferator-activated receptor gamma (PPAR γ) coactivator 1 α
PGC-1 β	Peroxisome proliferator-activated receptor gamma (PPAR γ) coactivator 1 β
PKD4	Pyruvate dehydrogenase kinase isozyme 4
PPAR α	Peroxisome proliferator-activated receptor alpha
PPAR γ	Peroxisome proliferator-activated receptor gamma
PPAR δ	Peroxisome proliferator-activated receptor delta
PRC	PGC-1-related coactivator
QPRT	Quinolate phosphoribosyltransferase
QUIN	Quinolinic acid
RGS14	Regulator of G-protein signaling 14
ROR γ	RAR-related orphan receptor gamma
ROS	Reactive oxygen species
RRM	RNA recognition motif
RXRs	Retinoid X receptors
SIRT1	NAD-dependent protein deacetylase sirtuin-1
SSP1	Secreted phosphoprotein 1
SSRIs	Selective serotonin reuptake inhibitors
STAT6	Signal transducer and activator of transcription 6
T2D	Type-2 diabetes
TAG	Triacylglycerides
TDO	Tryptophan 2,3-dioxygenase
TNF- α	Tumor necrosis factor α
TPH	Trp-hydroxylase
Trp	Tryptophan
VEGF	Vascular endothelial growth factor
WHO	World Health Organization
XA	Xanthurenic acid
YY1	Yin Yang 1

1 INTRODUCTION

Understanding the molecular mediators of muscle health could have important applications in the development of new treatments for several diseases. With this work, we aimed at investigating the molecular mechanisms by which skeletal muscle conditioning contributes to overall health. The following sections summarize:

- Implications of muscle conditioning in different diseases.
- Molecular mediators of muscle conditioning, and crosstalk with other organs.
- How shifting metabolism of kynurenine towards kynurenic acid in skeletal muscle could have broad implications for health and disease.

1.1 BROAD CONSIDERATIONS

1.1.1 Skeletal Muscle Health

Skeletal muscle corresponds to up to 40% of body weight in a lean individual. At rest, it significantly contributes to basal metabolism, with up to 30% of calorie consumption (393). Upon insulin stimulation, it utilizes 75% of whole-body glucose (18). Moreover, skeletal muscle has the ability to adapt to energetic demands by using different fuel sources (330). This is particularly important in the case of physical activity or in cases of energy overload such as obesity. These physiological adaptations put skeletal muscle at the intersection between different metabolic diseases. This has led to suggestions that impaired insulin signaling in skeletal muscle might be implicated in the etiology of type-2 diabetes (T2D) (29). In addition, maintaining skeletal muscle health is important to counteract pathological processes associated with cancer, inflammatory conditions, neuromuscular disorders, neurodegeneration, ageing and mood disorders (163). In this sense, physical inactivity contributes directly to progressive loss of skeletal muscle function, which, in turn is coupled to the development of insulin resistance. The metabolic outcomes of the latter have been shown to exacerbate and promote the onset of aforementioned pathologies. Au contraire, physical activity entails positive molecular adaptations in skeletal muscle that decrease the risk and onset of several disorders (**Figure 1**) (137).

Physical activity

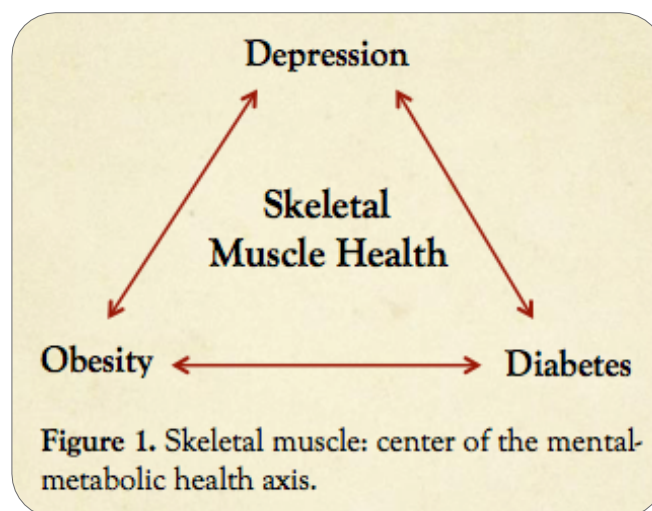
As defined by the World Health Organization (WHO), “*physical activity is any bodily movement produced by skeletal muscle that requires energy expenditure*”. Therefore, it is considered that any activity, ranging from moderate to vigorous, would aid overall health. Notably, it is estimated that around 1 in 4 adults does not engage in any physical activity (WHO, *Physical activity* [394]). Importantly, only 20% of the world’s adolescent population is physically active. Globally, lack of physical activity is one of the top risk factors of mortality due to associated diseases such as cardiovascular disease, cancer and diabetes. These estimations are expected to rise further if society fails to engage its population in educational programs about the benefits of physical activity (WHO, *Physical activity* [394]). Accordingly, it has been shown that regular physical activity improves cardiovascular function, weight control, and reduces the risk of cancer, obesity, diabetes and depression (40, 93, 114, 290).

1.1.2 Mental Health and Depression

Individuals with psychiatric disorders display a spectrum of symptoms that impair daily activities and functional life. Worldwide, the incidence of mental disorders is rising, which in addition to the profound deleterious effects on patients' lives, entails major socioeconomic consequences.

Depression

Individuals suffering from depression experience (on average for at least 2 weeks) a collection of symptoms including but not limited to loss of interest, reduced energy, sleep and appetite disturbances, anxiety symptoms and low self-esteem (WHO, *Depression* [395]). Although the precise etiology of this multifactorial disease remains elusive, it likely results from an interaction between environmental and genetic factors. Among the environmental factors, chronic stress has been strongly associated with depression. Moreover, when this psychobiological interaction leads to the onset of depressive symptoms, individuals are at risk of worsening overall health, with higher incidence of comorbid conditions.



According to the WHO, depression affects 350 million people worldwide. It is the leading cause of disability and a major contributor to socioeconomic burden of disease. More than 800,000 people commit suicide every year due to extensive periods of depression (WHO, *Depression* [395]). Similar to T2D, depression can go undetected due to inaccurate assessment and/or reluctance to seek professional help by affected individuals. This, in turn, deteriorates quality of life with detrimental consequences for overall health. For example, people with depression are at higher risk of developing diabetes and obesity (214, 248). Likewise, diabetes increases the risk of developing depression (8). When chronic stress contributes to the onset of depression and goes chronically undetected, its underlying molecular consequences will aggravate complications related to this affective disorder. Once

detected, psychological and pharmacological interventions can be used today to reduce symptomatology. However, as it is the case with other multifactorial disorders, relapse is often observed. To keep the disease at bay, more prevention programs should be established. These range from improving psychosocial environment to promoting regular physical activity (WHO, *Depression* [395]). The latter has gained interest as it improves overall health and substantially ameliorates depressive symptoms (**Figure 1**) (93).

1.1.3 Obesity

The term obesity is defined as excessive fat accumulation that might have a negative impact on overall health. It has also been shown that obesity increases the prevalence of other associated diseases. To quickly assess obesity in the population, health professionals use the body mass index (BMI). The BMI is calculated by dividing an individual's weight (in kilograms) by the square of height (in meters). Individuals with a BMI higher than 30 are considered obese, whereas those with a BMI between 25 and 30 are considered overweight (1).

According to the WHO, the number of individuals with a BMI greater than 25 has doubled since 1980 (102). It affects more than 1.9 billion adults, and 41 million children under the age of 5. Remarkably, there are currently more deaths associated with obesity than with malnutrition (WHO, *Obesity* [396]).

All things considered, an increase in the ratio between calories consumed and used, as well as an increase in sedentary lifestyles are main contributors to the development of obesity. Individuals with overweight or obesity have a higher incidence of developing chronic diseases, such as diabetes, cancer, cardiovascular diseases, musculoskeletal disorders and psychiatric diseases. On the other hand, evidence suggests that balanced and healthy food choices and regular physical activity can decrease the incidence of obesity in the population (WHO, *Obesity* [396]). Therefore, understanding the negative consequence of sedentary lifestyles could have broad implications for the prevention of metabolic disease.

1.1.4 Diabetes

Diabetes is a metabolic disorder with a heterogeneous etiology, defined by hyperglycemia, alterations in carbohydrate, fat and protein metabolism. This disorder arises from errors in insulin secretion and/or action. The consequences of this pathophysiological process have been associated with multi-organ failure. People with diabetes display characteristic symptoms such as polyuria, thirst and weight loss. Often, the absence of severe symptoms causes the disease to go undiagnosed (22). These long-term pathological changes lead to the development of complications such as retinopathy, nephropathy, foot ulcers, autonomic dysfunction and vasculopathy (4, 89, 236, 375). In addition, individuals with diabetes display a higher risk of developing neurodegenerative and psychiatric disorders (4, 8, 365).

According to the WHO, the global prevalence of diabetes has doubled since 1980 (294). In 2012, diabetes accounted for 1.5 million deaths and it is predicted to become the 7th cause of

death worldwide by 2030 (390). Diabetes can be classified in type-1, type-2, and gestational diabetes. Type-1 diabetes (previously known as childhood-onset) is characterized by deficient production of insulin by pancreatic beta cells. Its cause is currently unknown but is often attributed to autoimmune pathologic processes. Gestational diabetes is defined as high glucose levels during pregnancy. Finally, type-2 diabetes (T2D; formerly known as adult-onset) is the result of ineffective insulin action on target tissues (4).

Type-2 Diabetes

T2D accounts for the majority of people suffering from diabetes (33). Despite its complexity, the incidence of T2D increases in obese and sedentary individuals (67). According to the International Diabetes Foundation, other risk factors for developing T2D are: family history of diabetes, unhealthy food consumption, age, hypertension and gestational diabetes (67, 294)

T2D is usually diagnosed by fasting blood glucose levels higher than 7 mM or venous glucose levels higher than 11.1 mM after ingestion of 75 g oral glucose load (124). As mentioned before, undiagnosed cases, due to absence of symptomatology, promote silent pathological changes with devastating consequences. Chronic high glucose levels cause inflammation and tissue damage (118). The tissues most susceptible to these changes are kidneys, eyes, nerves and cardiovascular tissue. Notably, T2D has also been found to increase the risk of developing mood disorders, especially depression (5). T2D and its associated complications have significant costs and impact worldwide. In fact, it has been estimated that the healthcare system spends 12% of its funds to treat and prevent diabetes in particular T2D (319, 387). Similar to obesity, the incidence of T2D can be reduced (or, at least, its onset can be delayed) by adopting healthy and active lifestyles. This includes increased physical activity, healthy diets, and regular control of blood glucose level (294).

1.2 MOLECULAR MEDIATORS OF SKELETAL MUSCLE CONDITIONING

Both physical activity and exercise training impact positively whole body metabolism. Skeletal muscle is at the center of these physiological adaptations (137). During exercise, ATP is needed to support different cellular processes; for example, to support contraction skeletal muscle activates molecular adaptations that keep ATP production (112). This turnover is maintained via creatine phosphate and degradation of glycogen to lactate (110). During physical activity, skeletal muscle also needs to mobilize extramuscular substrates, such as glucose from the liver, long-chain non-esterified fatty acids from adipocytes and amino acids from blood (350, 358). The contribution of different substrates for fuel utilization is determined by the duration of exercise (295) and is impacted by different environmental and biological conditions (161). Factors such as sarcoplasmic calcium, level of ATP and byproducts, hormones and circulating metabolites (138), mediate acute adaptations to exercise, and regulate chronic molecular adaptations proper of conditioned skeletal muscle.

Physiological adaptations to muscle contraction lead to the activation of signaling pathways that modulate protein anabolism/catabolism and gene expression (85). These factors range from increased sarcoplasmic calcium, increased ADP/ATP ratio, high reactive oxygen species (ROS) levels, increased NAD^+/NADH ratio, to reduced creatine and glycogen levels (138).

Important signaling pathways that regulate transcription factors, coactivators and repressors, include calcineurin, Ca^{2+} /calmodulin-dependent protein kinases (CaMK), mitogen-activated protein kinases (ERK1/2, MAPK), mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK). Exercise increases intracellular calcium in muscle fibers, which leads to the activation of CaMKII and regulation of gene expression (296). In addition, exercise-dependent changes in AMP/ATP and ADP/ATP ratios lead to activation of AMPK (133, 139, 304). Increased activity of AMPK, upon metabolic challenges in skeletal muscle, regulates the activation of distinct gene programs that mediate chronic adaptations (220).

Repetitive activation of the aforementioned key signals, as in chronic exercise training, results in adaptations that are dependent on the transcriptional regulation of several gene networks. This regulation, in turn, is dependent on the activation of transcription factors and coregulators (196, 259, 357), alteration on DNA methylation (19), histone modifications (221) and microRNA modulation (381). The concerted action of transcriptional regulation of energy homeostasis in skeletal muscle depends upon key transcription factors and nuclear receptors. For example, during endurance exercise training, the coordination of several transcriptional events leads to the regulation of mitochondrial biogenesis. Major findings on the transcriptional control of mitochondrial adaptations have occurred since initial discoveries

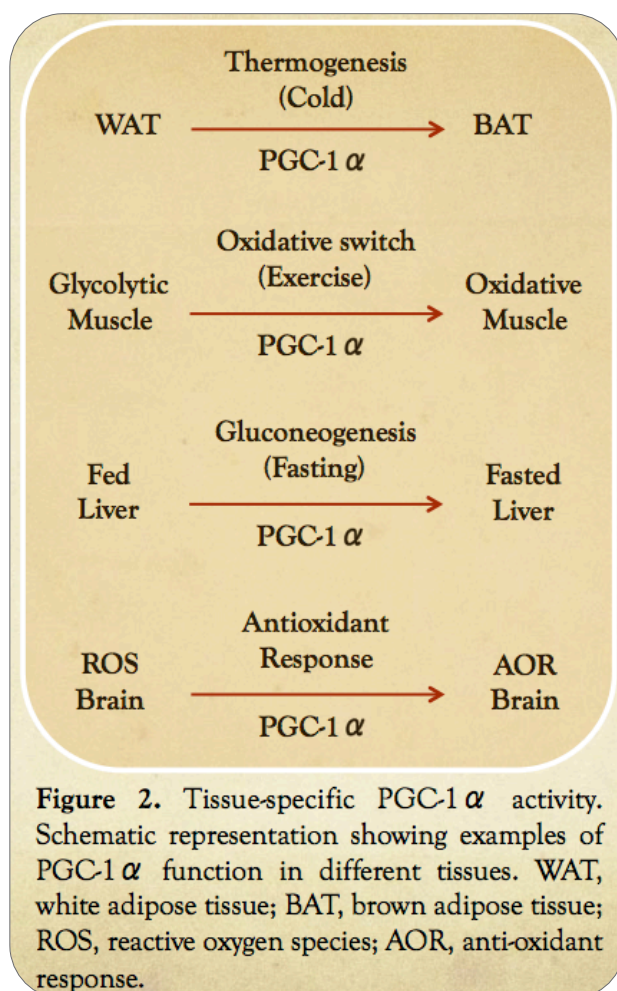
of exercise-mediated regulation of mitochondrial proteins by Holloszy in 1967 (149). Among them, it has been shown that nuclear respiratory factor 1 (NRF1) and nuclear factor erythroid 2-related factor 2 (NFE2L2 or NRF2) regulates the expression of nuclear-encoded mitochondrial proteins (94, 170, 219, 348). In addition, the estrogen-related receptor α (ERR α), initially identified due to its homology with the estrogen receptor α (ER α) (117), was found to modulate mitochondrial biogenesis (86, 154, 207, 310). Similarly, skeletal muscle Yin Yang 1 (YY1) transcription factor promotes the expression of nuclear-encoded mitochondrial genes, thereby regulating oxidative mitochondrial function (31). Other transcriptional regulators in skeletal muscle are the peroxisome proliferator-activated receptor (PPAR) subfamily of nuclear receptors composed of three members including PPAR α / δ and γ . PPAR α , for example, was initially discovered when searching for molecular targets of fibrates (156), whereas PPAR δ and γ were cloned based on sequence homology with PPAR α (174, 391). PPAR α / δ regulate lipid catabolism while PPAR γ is one of the main regulators of adipogenesis (91, 297, 340). PPAR δ is abundantly expressed in skeletal muscle (239) and regulates fiber-type determination, mitochondrial function and lipid catabolism (208, 357, 359). Skeletal muscle PPAR α , on the other hand, plays a role in the regulation of fatty acid oxidation (101). Contrary to PPAR δ , PPAR α does not modulate fiber-type switching (113). PPAR γ , in turn, has been shown to contribute to insulin sensitivity and glucose homeostasis in skeletal muscle (7, 141, 142). Mediating fiber-type switching, the transcription factor myocyte enhancer factor 2 (MEF2). This transcription factor together with PPAR γ coactivator-1 α (PGC-1 α) regulates the formation of slow-twitch muscle fibers (196). Additional regulators of muscle differentiation and function are the myogenic regulator factors (MRFs), among which myoblast determination protein 1 (MyoD) plays a crucial role in myogenesis (74). Indeed, the many adaptations of skeletal muscle to exercise training depend on a complex network of transcriptional regulators that are still not fully understood (99, 270, 310).

The PGC-1 α proteins regulate many of the transcriptional adaptations to exercise by interacting with several transcription factors, and constitute one of the main focuses of this work.

1.2.1 Skeletal Muscle PGC-1 α

PGC-1 α is the founding member of a group of transcriptional coactivators including PGC-1 β and PGC-1-related coactivator (PRC). Given its complex and tight regulation in several tissues and conditions, PGC-1 α remains the most studied and characterized member of the family. Indeed, we now know that although the mammalian genome has only one PGC-1 α gene, it can be transcribed from different promoters and differentially spliced to give rise to several PGC-1 α isoforms (217, 303). In many tissues, PGC-1 α coactivators transcriptionally orchestrate many biological responses to different metabolic challenges (**Figure 2**) (187, 196, 197, 280, 379). PGC-1 α was initially discovered in brown adipose tissue as a regulator of adaptive thermogenesis (280). Later, it was unraveled that PGC-1 α controls mitochondrial biogenesis and respiration in adipose tissue (372). PGC-1 α is characterized for being a highly regulated coactivator. It can interact with many transcription factors, allowing the regulation of several gene programs in different tissues (**Figure 2**) (195). PGC-1 α can also interact with

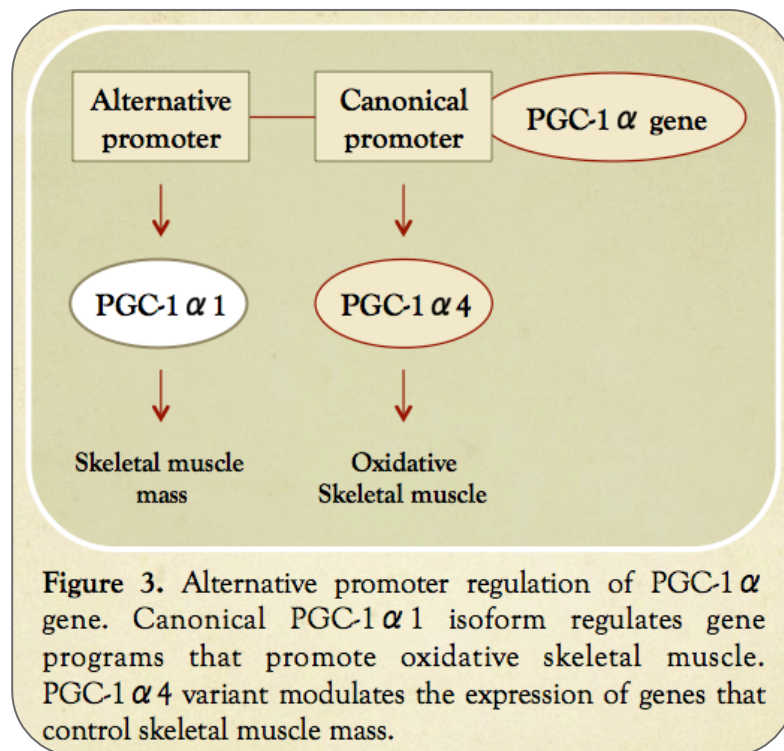
other coregulator proteins, such as histone acetyltransferases (HAT) including CREB-binding protein/p300 and steroid receptor coactivator 1 (SRC-1) (184, 279). In addition, it interacts with the mediator complex (353). Finally, PGC-1s possess a characteristic RNA recognition motif (RRM) (280) that has been suggested to participate in target gene splicing by interacting with nascent mRNA and/or the splicing machinery (216, 229).



Recently, it was demonstrated that alternative promoter usage of the PGC-1 α gene, leads to the expression of several isoforms such as PGC-1 α 2, PGC-1 α 3 and PGC-1 α 4 (303). PGC-1 α 4, for example is highly expressed in skeletal muscle, and regulates skeletal muscle mass. It does not regulate the same oxidative gene program as the canonical PGC-1 α (now known as PGC-1 α 1 or -a), but rather induces insulin-like growth factor 1 (IGF1; anabolic hormone) and represses myostatin (inhibitor of muscle growth; **Figure 3**) (303). PGC-1 α 2 and PGC-1 α 3, on the other hand, appear to regulate multiple splicing events on target genes (216). For clarity, we use PGC-1 α when referring to the gene and the collection of PGC-1 α variants, or we specify the isoform name when appropriate. Given that the PGC-1 α 1 variant is the most established regulator of oxidative metabolism and linked to endurance exercise training, which is suggested to be

relevant for mental health and depression, we focus on this isoform in this work.

PGC-1 α 1 is highly regulated by different stimuli in various tissues (**Figure 4**). For example, PGC-1 α 1 expression can be transcriptionally induced by physical exercise (271). This is modulated by different signaling pathways such as p38 MAPK (3), AMPK (160) and calcium signaling (368). In addition, it was shown that acute exercise training remodels PGC-1 α promoter methylation in human skeletal muscle (19). At the post-translational level, PGC-1 α activity is regulated by MAPK (98, 179), and AMPK phosphorylation (160). It is acetylated or deacetylated by general control of amino acid synthesis 5-like 2 (GCN5) (189) and NAD-dependent protein deacetylase sirtuin-1 (SIRT1), respectively (48). Moreover, the activity of PGC-1 α 1 is modulated by arginine methylation (336), O-linked N-acetylglucosamination (153) and by its degradation (258, 360).

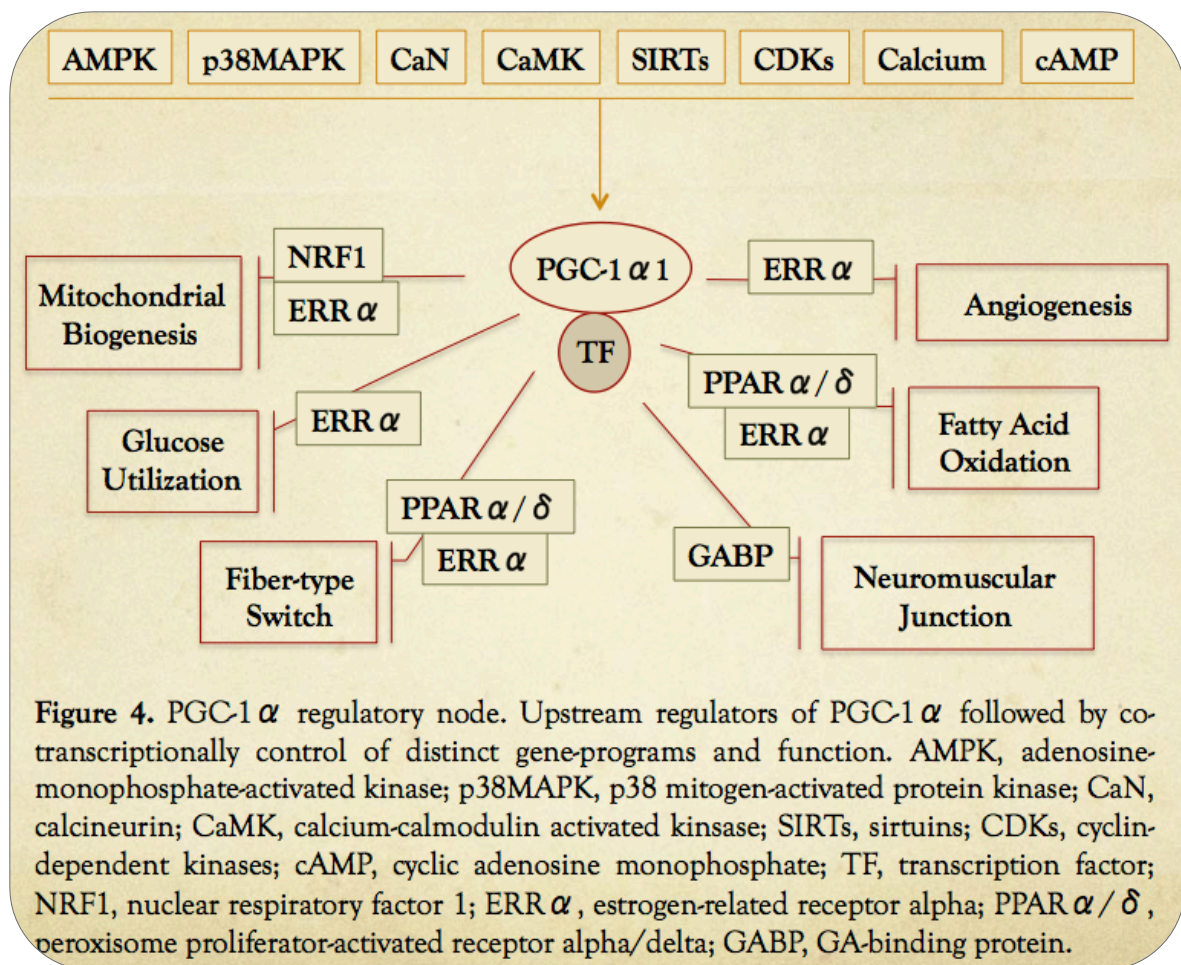


In skeletal muscle, PGC-1 α 1 modulates many of the oxidative adaptations to exercise. It has been shown to regulate mitochondrial biogenesis (196), to improve VO_2 max and to shift fuel utilization from carbohydrate to fat during endurance training (45). Mice with muscle-specific overexpression of PGC-1 α 1 activate gene programs distinctive of slow-type fibers (196). In addition, initial observations showed that PGC-1 α 1 regulates the expression of the angiogenic factor vascular endothelial growth factor (VEGF). This mechanism is independent of hypoxia-inducible factor (HIF) and relies on the transcription factor $\text{ERR}\alpha$ (11). Later studies showed that alternative promoter usage of the PGC-1 α gene in skeletal muscle is required for downstream expression of VEGF (60). In line with this, the skeletal muscle PGC-1 α 4 isoform was shown to regulate VEGF expression upon β 2-adrenergic stimulation (303, 337). Moreover, PGC-1 α 1, via the induction of secreted phosphoprotein 1 (SSP1) and subsequent activation of macrophages, modulates functional angiogenesis in skeletal muscle (301). Accordingly, mice with loss of PGC-1 α in skeletal muscle, where all PGC-1 α variants are absent, fail to induce angiogenesis in response to exercise (60).

Other functions of PGC-1 α in skeletal muscle have been identified. For example, it was suggested that PGC-1 α activity in skeletal muscle is protective against low-grade inflammation (132) but required to maintain an acute lipopolysaccharide (LPS) response (257). In addition, mice with muscle-specific deletion of PGC-1 α have higher levels of interleukin 6 (IL-6) and display an exacerbated inflammatory response (129, 130). These anti-inflammatory effects in skeletal muscle have been attributed to PGC-1 α 1-mediated repression of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) (88).

Another function of PGC-1 α in skeletal muscle is regulating gene programs that participate in neuromuscular junction (NMJ) formation and signaling. It has been shown that PGC-1 α expression remodels both postsynaptic and presynaptic NMJ morphology (13, 55, 131).

In recent years, the evidence supporting a role for PGC-1 α coactivators in maintaining muscle mass has been growing (39, 146, 303, 307, 362). For example, skeletal muscle-specific PGC-1 α transgenic mice have been shown to be resistant to muscle atrophy by denervation and loss of muscle mass caused by aging (46, 307, 362). One of the mechanisms regulating these effects is mediated by PGC-1 α suppression of forkhead box O3 (FoxO3)-transcriptional induction of genes involved in protein degradation (46, 146, 307, 362) and decreased autophagy (46, 362). As mentioned before, the truncated isoform PGC-1 α 4 was shown to regulate skeletal muscle mass (**Figure 3**) (303). Interestingly, it was also observed that mice with transgenic expression of PGC-1 α 4 in skeletal muscle are resistant to cancer cachexia and metabolic dysfunction (303). Collectively, this evidence suggests that PGC-1 α coactivators are promising therapeutic targets in the context of metabolic and muscle-wasting disorders.



1.2.2 Skeletal Muscle and Interorgan Communication

Although the classical functions associated to skeletal muscle are related to contraction and movement, this tissue has more recently been shown to act as an endocrine organ under certain conditions. Molecules released from skeletal muscle are collectively called myokines (268). In this context, understanding how skeletal muscle communicates with other organs has helped explain some of the systemic effects of exercise. These systemic bioenergetic responses have been observed in adipose tissue, pancreas, liver, bone and brain. Even though myokines mediate the crosstalk with other organs, they might also act locally to regulate further adaptations to exercise. IL-6 was the first myokine found to be released after muscle contraction. IL-6 regulates muscle and systemic lipid oxidation and hepatic gluconeogenesis during exercise (169, 347).

To date, several myokines have been described. These include IL-8, IL-15, chemokine CXCL12 (CXCL-1), Fndc5/irisin, fibroblast growth factor-21 (FGF21) and meteorin-like (Metrl) (37, 269, 287, 366). PGC-1 α coactivators seem to play a central role in coordinating these systemic effects by controlling the expression of some of these molecules. For instance, PGC-1 α 1 induces the expression of FNDC5, whose cleaved and released product irisin regulates white adipose tissue (WAT) homeostasis (37). To clarify irisin regulation and action on different tissue further studies are warranted. In addition, the metabolite β -aminoisobutyric acid (BAIBA), is also under regulation of PGC-1 α 1. This factor targets adipose tissue and liver by activating WAT browning and hepatic fatty acid β -oxidation, respectively (293). Moreover, skeletal muscle PGC-1 α 4 regulates the expression of two other myokines IGF1 and myostatin, both with local functions in the modulation of muscle cell size (303). In addition, circulating myostatin has been implied in the regulation of energy homeostasis, as it has been shown to modulate adipose tissue function (194, 223). Later studies found that skeletal muscle PGC-1 α 4 drives the expression of Metrl (also known as glial differentiation regulator), which promotes WAT browning and glucose usage (287). This myokine does not appear to have an adipocyte cell-autonomous effect but instead an IL-4/IL-13-mediated enhancement of adaptive thermogenesis (287). Recently, it was demonstrated that skeletal muscle PGC-1 α 1 regulates kynurenine metabolism, thereby mediating resilience to stress-induced depression (2). Together with PPAR α/δ , PGC-1 α 1 drives the expression of muscle kynurenine aminotransferases (KAT), which shift peripheral metabolism of kynurenine to kynurenic acid (KYNA). This mechanism decreases kynurenine-mediated changes in synaptic function and behavior (2). Taken together, current evidence places PGC-1 α coactivators as important players regulating skeletal muscle communication and systemic effects of physical exercise. Whether these myokines can be used as potential therapeutic targets to treat obesity and other diseases exacerbated by physical inactivity, remains to be established.

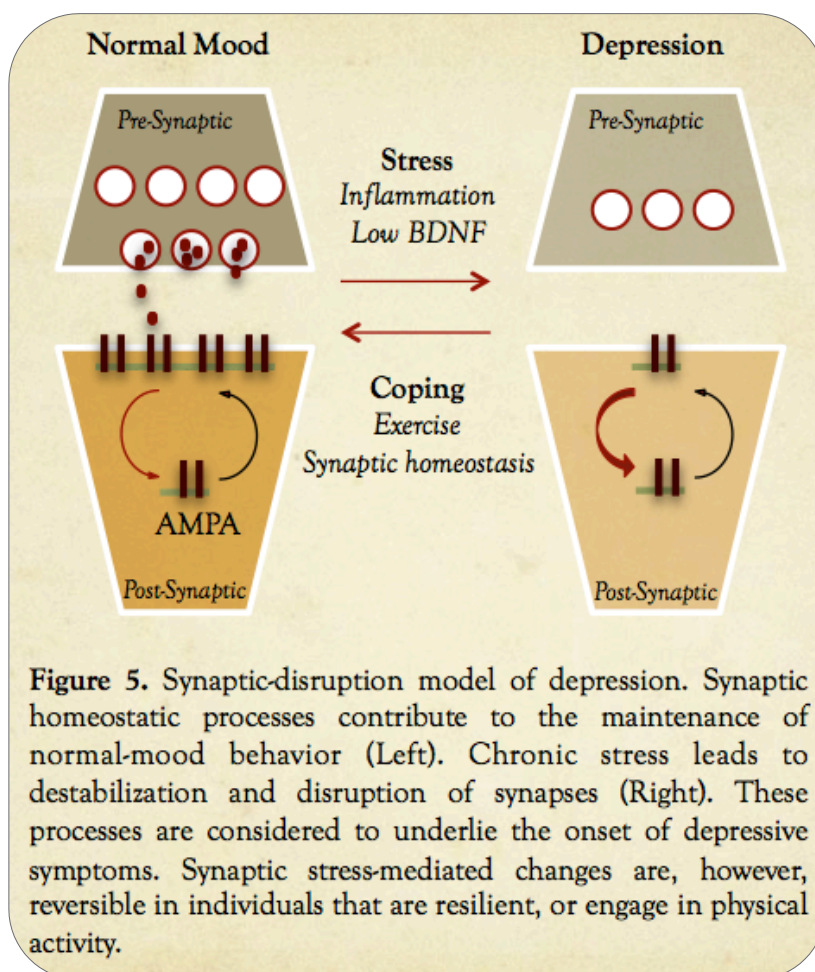
1.3 MOLECULAR ASPECTS OF DEPRESSION

Despite recent advances in our understanding of depression, the clear biological mechanism underlying its pathophysiology remains unknown. Nevertheless, cross-disciplinary studies suggest that molecular changes observed in depression can be grouped in two categories: firstly, molecular perturbations that lead to morphological synaptic dysfunction. Among these changes, imbalanced glutamate transmission (305), alterations in neurotransmitter levels (147), and defective neurogenesis (172) are among the most studied. Secondly, molecular changes associated with brain or systemic inflammatory processes.

In terms of synaptic dysfunction, it has been proposed that depression is caused by an abnormal regulation of different mechanisms governing synaptic plasticity (80). This results in loss of synaptic stability in the limbic circuitry. Accordingly, neuronal atrophy has been observed in brain imaging studies (211) and functional imaging of patients with depression (276). Studies in mice have also unveiled detailed observations of neuronal loss and altered glutamatergic synapses in models of stress-induced depression (202). The use of chronic mild stress (CMS; also known as chronic unpredictable stress) protocol to induce depressive-like behavior in rodents (145) has also revealed that the phenotype is accompanied by neuronal atrophy, loss of synaptic homeostasis and impaired neurogenesis (87, 272). The hypothalamic-pituitary-adrenal (HPA) axis has been proposed to be a mediator of stress-induced damage to the central nervous system (CNS). Similar to chronic-stress exposure, glucocorticoid treatment leads to neuronal atrophy in limbic circuitry (202, 234). Moreover, stress-mediated overactivity of the HPA axis has been shown to affect neurotrophic factors, especially brain-derived neurotrophic factor (BDNF) (81, 182). Similarly, BDNF levels have been found to be reduced in postmortem brain samples from patients with depression (81, 182). Taken together, this suggests that stress-mediated disruption of homeostatic processes that impact synaptic stability and maturation can lead to depression (68, 148, 324).

It is well established that antidepressant treatment increases neurotrophic factors and ameliorates synaptic plasticity. Typical antidepressants such as selective serotonin reuptake inhibitors (SSRIs) improve synaptic function, spine density and neuroplasticity (21, 167, 363). Despite being highly prescribed, SSRIs (as well as other antidepressants currently used) take weeks or months to generate therapeutic effects. The lack of better therapeutic alternatives leaves 30% of depressed patients on the verge of suicide attempts (343). Recently, studies have shown that ketamine, a N-methyl-D-aspartate receptor (NMDAr) antagonist, promotes a rapid and potent antidepressant action in severely depressed patients (28, 382). Ketamine-mediated improvement of depressive symptoms has been attributed to its effect on synaptic function and plasticity (191). This also suggests that loss of synaptic homeostasis might underlie behavioral disturbances (**Figure 5**). Despite advances in our

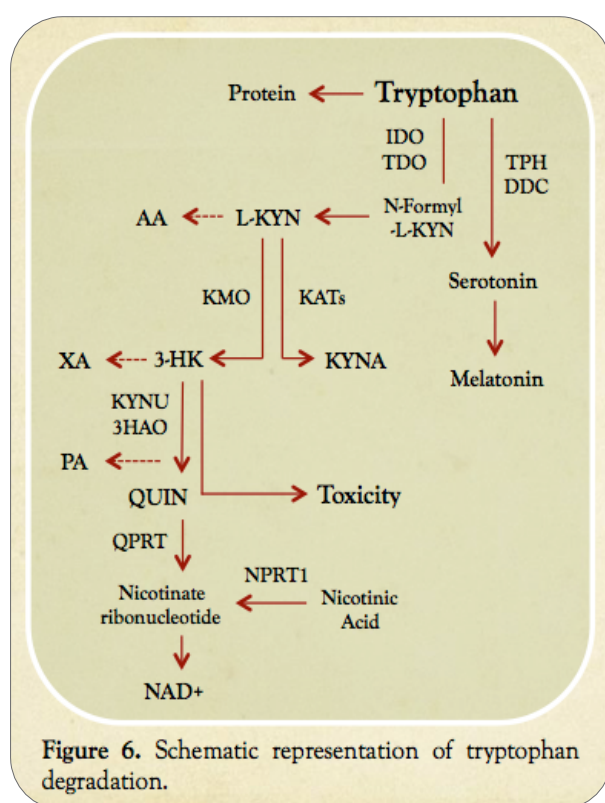
understanding of the molecular underpinnings of depression, causality - regarding the pathophysiological events that lead to synaptic dysfunction - remains elusive.



Several lines of evidence indicate that inflammatory processes play a crucial role in synaptic disruption. This idea has been gaining interest since inflammation exists in comorbid diseases associated with depression, such as metabolic syndrome, diabetes, stroke and autoimmune disorders (9, 284). Initial observations showed that depressed patients display elevated inflammatory factors in circulation. In rodents, treatment with LPS provokes depressive-like behavior (9, 140). In humans, low doses of bacterial endotoxin leads to elevated levels of IL-6 and TNF- α , as well as mood perturbations (155, 289). Further support for the deleterious role of inflammation in mood disorders came from cancer and hepatitis C patients receiving interferon gamma (IFN- γ). Half of the patients developed depression that went into remission after antidepressant treatment (283). In mice, combining pro-inflammatory treatments with CMS exacerbated depressive-like behavior and increased the HPA-response (10, 116). Furthermore, administration of IL-6, IL-1 β or TNF- α decreases neurogenesis and BDNF levels (376). Recently, it has been proposed that inflammation mediates synaptic dysfunction through microglia activation (377). Comprising about 10% of all brain cells, they regulate neurogenesis, synaptic function and behavior (342, 351). Inflammation leads to microglia

activation and to NF- κ B-mediated changes that further prolong the inflammatory state (377). This cascade seems to be mediated by microglial release of inflammatory signals that have long-lasting effects on synaptic plasticity (121, 180). However, it has been proposed that type-1 or pro-inflammatory cytokines activate a feed-forward loop in microglia. This loop further promotes the formation of neurotoxic metabolites with the ability to affect synaptic function (377). It is precisely at the intersection between synaptic dysfunction and brain inflammation that the kynurenine pathway (KP) of tryptophan degradation plays an important role in mental health (237, 377).

1.4 KYNURENINE METABOLISM



The KP of tryptophan (Trp) degradation represents a major metabolic route for the catabolism of this essential amino acid (**Figure 6**). Importantly, Trp is not only used for protein synthesis but also for the generation of several metabolites with biological activity. On one hand, Trp can be converted to serotonin and melatonin, important for neurotransmission in limbic circuitry, and for regulation of circadian rhythms. On the other hand, 95% of Trp is degraded towards the KP. This branch generates metabolically active metabolites involved in neurotransmission, inflammation and immune tolerance. Moreover, degradation of Trp towards kynurenine (KYN) can ultimately end with the generation of nicotinamide adenine dinucleotide (NAD⁺), a cellular cofactor that plays a crucial role in energy

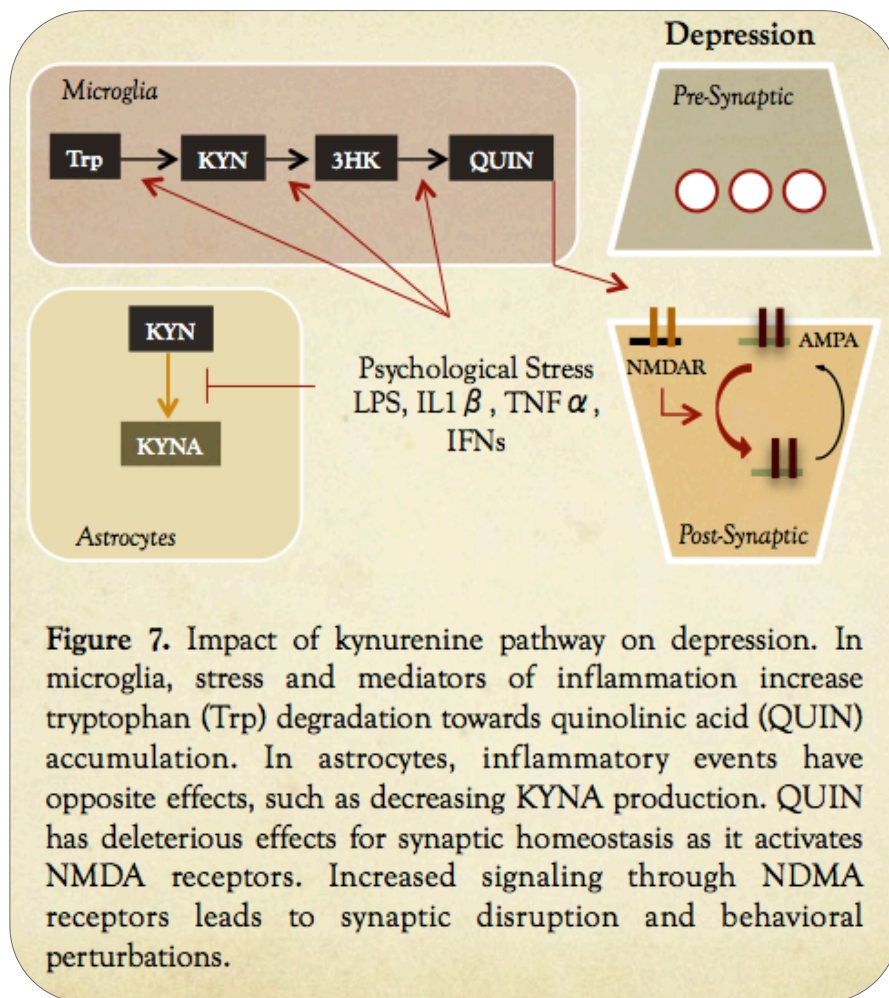
metabolism (48). KP metabolites were initially described in the CNS, where they were proposed to contribute to pathophysiological processes in mood disorders such as schizophrenia and depression (237). About 60% of peripheral KYN contributes to the kynurenine-pool in the CNS (109, 111). There, KYN is metabolized in astrocytes to produce KYNA and in microglia to generate quinolinic acid (QUIN). KYNA is an NMDA and $\alpha 7$ NACH receptor antagonist, and has been described as neuroprotective at physiological levels. QUIN, on the other hand, is an NMDAR agonist, with neurotoxic properties. KYNA is also an agonist for G protein-coupled receptor (GPCR) 35 and, as well as KYN, an agonist for the aryl hydrocarbon receptor (AhR). 3-hydroxykynurenine (3HK), in turn, has been shown to contribute to QUIN formation and to generate oxidative stress. Both centrally and in the periphery, the KP seems to play a role in the regulation of immune response. Evidence is consistent, however, that chronic accumulation of its bioactive metabolites can be deleterious for the organism.

Briefing on Tryptophan Degradation

Approximately 1% of Trp is used for protein synthesis. Trp hydroxylase (TPH) and 5-OH-Trp decarboxylase (DDC) convert Trp to serotonin, which can be further converted to melatonin. Trp catabolism towards KYN is regulated by the activity of Trp 2,3-dioxygenase (TDO) and the highly inducible indoleamine 2,3-dioxygenase (IDO). Most of KYN is destined to renal excretion. However, and when renal clearance is saturated, kynurenine 3-monooxygenase (KMO) hydroxylates KYN to 3HK. In addition, KYN can also be converted to KYNA by KAT enzymes, or to anthranilic acid (AA) by kynureninases (KYNU). KATs can further metabolize 3HK to xanthurenic acid (XA), which has been shown to be elevated upon Trp loading. If not converted to XA, 3HK is converted to metabolites that can produce either picolinic acid (PA) or QUIN. This step is catalyzed by KYNU and 3-hydroxyanthranilate dioxygenases (3HAO). Once QUIN is formed, quinolinate phosphoribosyltransferase (QPRT) together with nicotinate phosphoribosyltransferase (NAPRT and in the presence of nicotinic acid) catabolize the formation of intermediates (nicotinate ribonucleotide) that will be further metabolized to NAD⁺ (**Figure 6**).

1.4.1 CNS Kynurenine Metabolism: *Focus on Depression*

The implication of the KP in the neurobiological changes observed in depression is well documented. It has been proposed that KP is at the transition between the effects of stress-induced inflammation and the onset of depressive-like behavior (72, 275). For example, pro-inflammatory conditions seen upon treatment with IFN- γ , IL-6, TNF- α , IL-1 β , LPS, HIV Tat protein and Bacillus Calmette-Guerin (BCG) induce microglia IDO activity (73, 250, 352). The same was observed by psychological stress (173). Moreover, IFN- γ immunotherapy produces accumulation of KP metabolites both centrally and in the periphery, which correlates with the severity of depressive symptoms (34, 51, 52). Postmortem studies have further revealed increased numbers of QUIN-positive microglia in the cortex of depressed patients (327). Studies in rodents have confirmed that inflammation promotes microglial-dependent KP activation and subsequent depressive-like behavior. Namely, administration of low doses of LPS leads to anhedonia, which is decreased upon IDO antagonist treatment. In addition, exogenous kynurenine administration induces depressive-like behavior in rodents (79, 250, 251). Similar behavioral findings were seen after exposure to CMS protocols (173). Interestingly, blockade of NMDAr using ketamine abolishes depressive-like behavior induced by LPS (352). Collectively, these findings suggest that the limbic system is susceptible to deleterious effects of KP-metabolites, which accumulates upon inflammation (**Figure 7**).



1.4.2 Peripheral Kynurenine Metabolism

Peripheral metabolism of KYN depends upon Trp absorption and availability (**Figure 8**). This essential amino acid is enriched in fish, eggs, vegetables and meat. Most of Trp consumed is absorbed in the gut, followed by its entry into liver metabolism. Trp can also reach other tissues such as immune cells, brain, skeletal muscle and heart tissue. Furthermore, a small portion of Trp is metabolized by the microbiota in the gastrointestinal tract (GIT) (162). Interestingly, Trp can be converted to serotonin in the gut where 85-90% of serotonin production takes place (192). Of note, microbiota metabolism of Trp impacts its availability and regulates local inflammation through the production of indole compounds (384). These compounds have immunomodulatory effects, which further highlights the systemic implications of peripheral Trp and kynurenine metabolism. Interestingly indole compounds are used in inter-species communication as they signal between bacteria but also to the host.

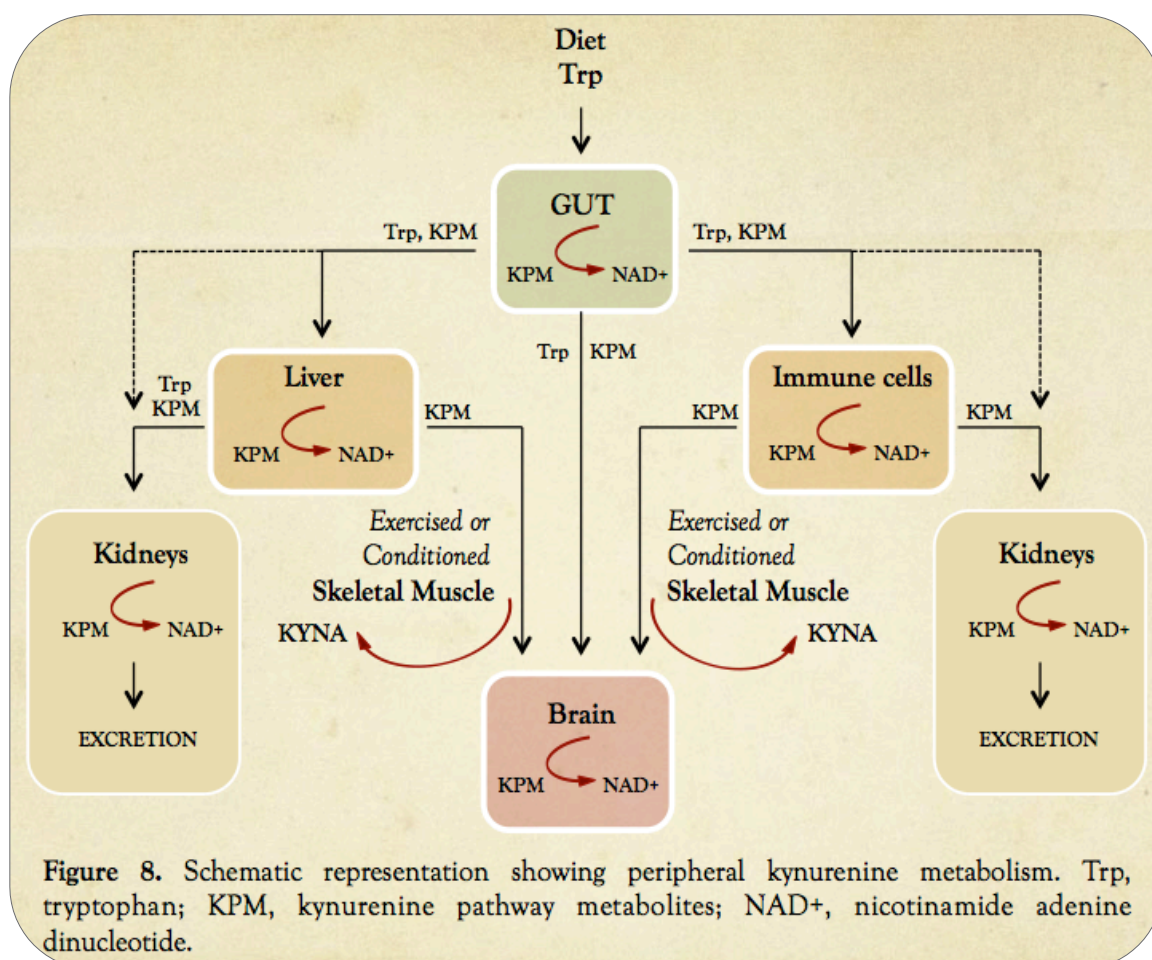
Liver Kynurenine Metabolism

It is well established that the liver and in particular hepatocytes, express all the enzymes required for Trp catabolism (227). Of note, TDO expression in mammals (the first rate limiting enzyme in tryptophan degradation) is mainly restricted to the liver (355). In the periphery, TDO appears to control systemic Trp levels by regulating its entry into the KP (274, 308, 309). TDO activity is increased by Trp (175), glucagon, estrogens and glucocorticoids (176, 315). Under normal conditions, the liver metabolizes Trp to NAD^+ . It can also oxidize KP metabolites via the glutarate pathway (355). When Trp availability is low, the liver will degrade circulating Trp to NAD^+ for energy demands (227). Notably, if there is constant Trp supply to the liver and TDO activity is increased by glucocorticoids, accumulation of KP-metabolites locally will lead to leakage of some of its metabolites such as KYN. Interestingly, social stress elevates glucocorticoid levels (202, 234), which, in turn, increase TDO activity and KYN in circulation. Consequently, liver-mediated KYN metabolism will contribute to elevate KP metabolites levels in the CNS. As mentioned before, under inflammatory conditions, the accumulation of some of these metabolites in the brain will bring negative consequences for mental health (237). In sum, the liver exerts its metabolic regulation on Trp degradation by promoting the KP. Notably, under inflammatory conditions, TDO activity is reduced and extrahepatic Trp metabolism will occur (335).

Kynurenine Metabolism in the Immune System

The enzyme IDO catalyzes the initial step of extrahepatic Trp to KYN metabolism. IDO is expressed in most tissues and also has affinity for 5-hydroxytryptophan (5-HTP) and 5-hydroxytryptamine (5-HT or serotonin). In the immune system, IFN- γ , TNF- α , virus and bacteria induce the expression and activity of IDO (73, 241, 250, 314, 334, 352). It was initially suggested that degradation of Trp in the microenvironment surrounding parasites, virus and bacteria was a way to control proliferation of pathogens (273). Evidence that IDO has a broader spectrum of immune regulation came from observations of immune cell Trp degradation during non-pathogenic inflammation (313). In order to control the immune system, cells have evolved metabolic systems to restrain inflammatory processes in case of over-activation (115, 164). It has therefore been proposed that metabolic immune regulation relies upon IDO-mediated Trp degradation. Accordingly, Type-1 or pro-inflammatory cytokines induce IDO activity (63, 119, 135) while type-2 or anti-inflammatory cytokines restrains it (59, 242). This suggests that immune regulation prompts the generation of metabolites with immunologic activity such as KYN and KYNA (213). In agreement with this, it has been shown that KYN decreases the activity of natural killer cells (108) and antigen-presenting cells (APC) including dendritic cells (DC), monocytes and macrophages (96, 261). Subsequent studies on T-cells described the ability of KYN to block T cell proliferation (26, 119). Furthermore, KYN derived from DC promotes proliferation of regulatory T cells (Tregs) (97, 144). Supporting this, it was later shown that KYN and KYNA are ligands for AhR (224, 260). This transcription factor controls xenobiotic responses to foreign substances. AhR has been shown to have anti-inflammatory activity upon ligand activation in both innate and adaptive immune system (23, 370). In addition, activation of AhR by KYN promotes Treg cell proliferation (224, 246), while suppressing innate immune

responses (224, 246, 260). Notably, regulating KYN/AhR responses has gained therapeutic interest in cancer, given that pharmacologic blockade of this axis could increase immune surveillance (17). Therefore, KYN/AhR has been proposed to be a crucial transitional link between chronic inflammation and carcinogenesis. Finally, KYNA was also found to be an agonist for AhR at low concentrations (78). It remains to be clarified if this activation has physiological relevance in terms of immune system regulation.



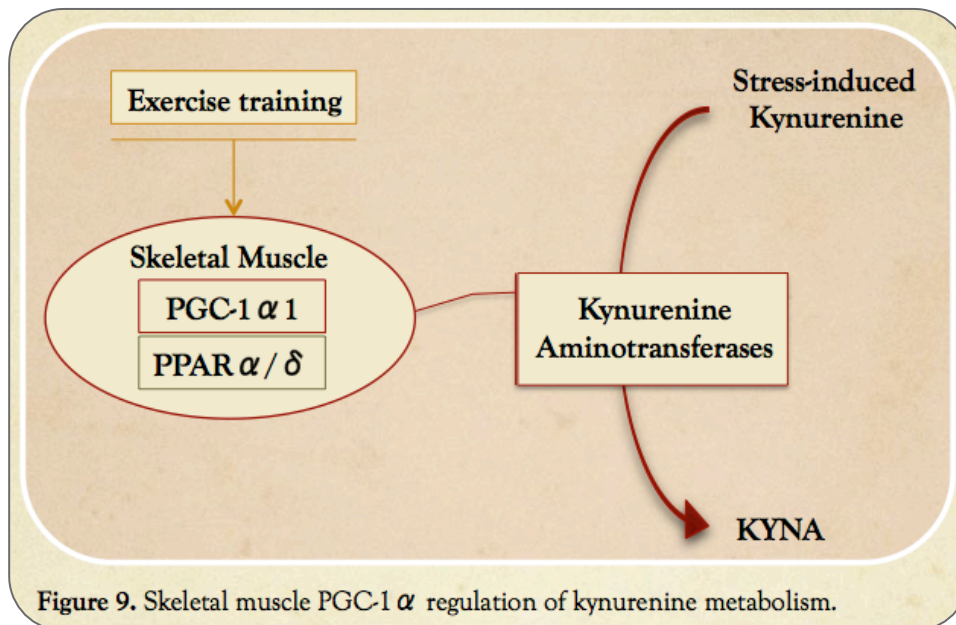
The discovery that KYNA is an agonist of the GPR35 increased the interest on this KP metabolite with potential immunomodulatory properties (354). In addition to the GIT, GPR35 is also expressed in immune subpopulations including human CD14⁺ monocytes, T cells, neutrophils, DCs, eosinophils, basophils and invariant natural killer T cells (iNKTc) (95, 354). Interestingly, it has been shown that binding of KYNA to GPR35 promotes monocyte extravasation (20), reduces LPS-inflammatory response in monocytes and macrophages (339), and controls cytokine release in human iNKT cells (95). Collectively, the immunomodulatory effects of KYNA further reinforce the immunosuppressant function of Trp catabolism. Accordingly, other KP-metabolites such as 3-hydroxyanthranilic acid (3HAA) and QUIN promote apoptosis of Th1 cells (96). Under normal tissue homeostasis,

the immunosuppressant effect caused by KP metabolites regulates the deleterious effect of uncontrolled immune activation.

During inflammation, immune cells promote NAD^+ synthesis due to energetic demands (122, 227). This suggests that Trp catabolism could replenish NAD^+ levels for immune cellular function. Accordingly, inflammatory processes and in particular $\text{IFN-}\gamma$, increase the expression of enzymes leading to NAD^+ production from Trp (213, 377). Notably, LPS-treatment causes QUIN-accumulation in the immune compartment (227). Similarly, it was found that Trp-derived NAD^+ could be synthesized in macrophages (122). Of note, if immune cells fail to meet NAD^+ demands during chronic inflammation kynurenines will be accumulated. These metabolites, as described before, will lead to type-2 immune responses that favor cell survival. However, their unbalanced accumulation could potentially harm different tissues. Therefore, it becomes important to understand the physiological processes governing kynurenine metabolism in the periphery. These molecular events would decrease the burden of KP metabolites on the CNS, without impacting the immune-tolerant function of Trp degradation.

Kynurenine Metabolism in Skeletal Muscle

Skeletal muscle can metabolize amino acids for protein synthesis and energy supply (350, 358). During metabolic challenges such as physical exercise catabolism of amino acids such as leucine, valine and Trp will supply ATP. Skeletal muscle needs thus to maintain constant redox reactions to have the NAD^+ required for ATP production. As mentioned before, initial fuel sources come from glucose and, as they are depleted during continuous exercise, skeletal muscle will shift to other sources such as fatty acids and amino acids. Trp catabolism could then contribute to NAD^+ supply for energy requirements. Accordingly, endurance exercise training decreases circulating Trp levels (331). Therefore, it could be argued that skeletal muscle Trp depletion would lead to ATP- NAD^+ supply, or that skeletal muscle has a specialized function along the KP. Interestingly, endurance exercise training increases the levels of circulating kynurenines (331), especially KYNA (190, 312). Further supporting a skeletal muscle-specialized function in KYN metabolism, it was demonstrated that aerobic exercise training increases the mRNA and protein levels of KAT enzymes in both mouse and human skeletal muscle (2, 312). KAT gene regulation by exercise training is under control of skeletal muscle PGC-1 α 1 and PPAR α/δ (2). As mentioned before, this coactivator modulates many of the adaptations to exercise, especially aerobic training (196). This supports the notion that skeletal muscle might have a specialized function in Trp catabolism towards KYNA production. This physiological shift in the KP, observed in exercised skeletal muscle, could have broad implications for mood and metabolic disorders. In fact, it was shown that mice with transgenic expression of PGC-1 α 1 in skeletal muscle have high skeletal muscle KAT levels and are resilient to the effects of stress-induced KYN or exogenous KYN administration (**Figure 9**) (2). Moreover, accumulation of KYNA in the periphery regulates systemic energy homeostasis and adipose tissue inflammation (Agudelo et al., unpublished; Study III).



1.4.3 Peripheral Kynurenine Metabolism: *Focus on Diabetes*

Diabetes is a multifactorial disorder also associated with disturbed Trp metabolism, where the often underlying inflammatory state contributes to the accumulation of KP metabolites (265). It has been shown in both mouse models and diabetic patients that low-grade chronic inflammation leads to increased IDO activity (265). Moreover, obese and T2D patients show elevated KYN:Trp ratio and KYNA levels (265). This has led to the suggestion that KP-metabolites could be considered biomarkers of diabetes and metabolic disease. In addition, insulin synthesis and insulin release from the pancreas are inhibited by KP metabolites such as QUIN and 3HK (265, 329). Another KP metabolite, XA, has been shown to prevent insulin action on target tissue (136, 181). These observations suggest that diabetes is characterized by abnormal levels of different KP metabolites. Whether these contribute directly to the pathophysiological process remains to be clarified. Moreover, it is not known if any end-product of the KP has a specific function that would ease the disease process.

1.5 MOLECULAR ASPECTS OF ADIPOSE TISSUE AND METABOLIC DISEASE

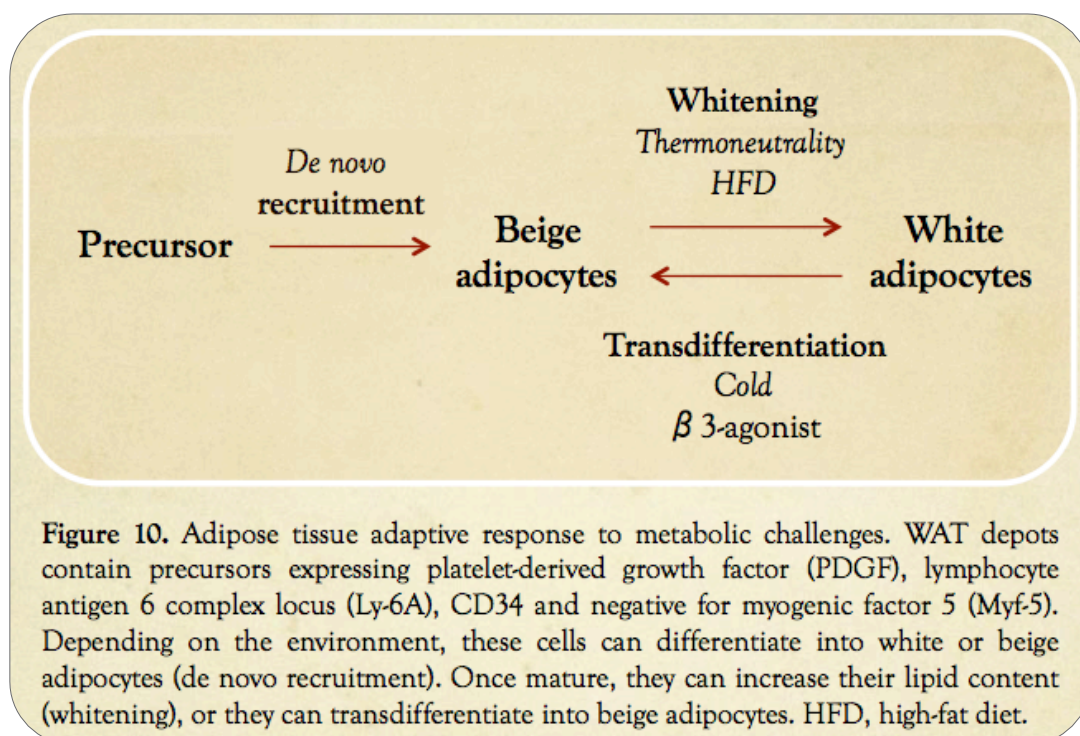
Throughout evolution, different adipose tissue depots have developed mechanisms to adapt to variations in temperature and food supply. WAT, for example, insulates the body and stores energy sources as lipids that can later be transformed and released as fatty acids (383, 392). Brown adipose tissue (BAT), on the other hand, stores lipids and dissipates their energy through thermogenesis (47, 70).

Brown adipocytes have multilocular lipid droplets, large number of mitochondria and are positive for uncoupling-protein 1 (UCP1). Sympathetic tone activates brown adipocytes, which, through UCP1, dissipate chemical energy in the form of heat. This energy comes from routing triglycerides to β -oxidation (218, 278) while UCP1 uncouples proton gradient from ATP production, thus terminating the electrochemical gradient. For this reason, BAT metabolism is mainly considered as a source of heat used to preserve core body temperature. In humans, low temperatures lead to the activation of these processes in BAT, which correlate with energy expenditure induced by adaptive thermogenesis (346, 378). On the other hand, white adipocytes are UCP1 negative and store energy in the form of triacylglycerides (TAG). During fasting or strenuous exercise, TAGs can be converted into non-esterified fatty acids (NEFA) that are released into circulation. These NEFAs are cleared from blood by other tissues such as skeletal muscle and liver, where they serve as energy sources. Moreover, it has been shown that adipocytes can regulate systemic energy homeostasis by secreting adipokines (12, 107, 152, 264, 388).

Both WAT and BAT display plasticity under different metabolic adaptations such as fasting, overfeeding or cold exposure (65). These changes involve the coordinated regulation of several gene networks, which result in tissue remodeling and modified function. Particularly relevant for metabolic disease, WAT contains another cell type able of undergoing dynamic adaptations. This cell-type has been termed beige adipocyte (also known as brite or recruitable adipocytes) and can induce UCP1 expression and proliferate upon different stimuli such as exercise and cold exposure. It has been suggested that they contribute to heat dissipation and might have a crucial role in counteracting obesity (134). Excessive WAT increases the risk of developing T2D (126). It remains unclear however, why not all obese individuals develop metabolic disease. Therefore, understanding the mechanisms that promote the recruitment and stimulation of beige adipocytes could potentially lead to new treatments for weight loss and metabolic disorders.

1.5.1 The Developmental Origins of Brown and Beige Adipocytes

Brown adipocytes develop during embryogenesis and are composed of a uniform population. In rodents, BAT depots are located in the interscapular region. In humans, infants have been shown to have a similar BAT depot that disappears in adults (193). In adults, BAT appears to be located around the neck region close to the vascular compartment (70, 349). Moreover, it has been shown that both skeletal muscle and BAT share the same precursor cell during development (306, 317). Additional findings confirmed that both tissues display similar mitochondrial proteome (104). Beige adipocytes, on the other hand, were initially shown to derive from perivascular and endothelial cells (127, 341). By lineage tracing studies, it was shown that beige adipocytes could derive from white adipocytes. The latter came from observations in subcutaneous WAT, where it was described that some adipocytes responsive to cold exposure have an intrinsic ability to become either white or beige adipocytes. This process was called trans-differentiation (299). Finally, another study in 2012 identified the gene expression pattern of beige adipocytes from WAT (371). By comparing gene specific signatures between murine beige cells and brown-fat depots in adult humans, Wu and colleagues showed that human brown fat is in fact composed of beige fat cells (**Figure 10**) (371).



1.5.2 Transcriptional Regulation of Adipogenesis

PPAR γ and CCAAT/enhancer-binding protein α (CEBP α) are the master regulators of adipocyte formation. While PPAR γ is required for adipogenesis (297, 340), CEBP α is not fundamental for brown/beige differentiation (200). PPAR γ and CEBP α modulate pro-adipogenic transcription factors, including kruppel-like family (KLF), GATA transcription factors, liver X receptors (LXR) and sterol regulatory element-binding protein 1c (SREBP1C). There are however transcription factors essential for brown adipocyte differentiation (325). Despite this, their contribution to WAT browning/beiging is still unclear. The discovery of the zinc-finger protein PRDM16 as a regulator and driver of brown adipocytes opened new avenues for our understanding of WAT browning/beiging (317). PRDM16 induces UCP1 expression, by modulating the activity of other transcription regulators such as CCAAT/enhancer-binding protein β (CEBP β), PPAR γ , PPAR α and PGC-1 α 1 (317). Later, it was demonstrated that PRDM16 expression is higher in inguinal WAT depots, which are more prone to beiging when compared to visceral (318). In addition, PRDM16 expression promotes the recruitment of beige adipocytes in WAT and counteracts the deleterious effects of diet-induced obesity (318).

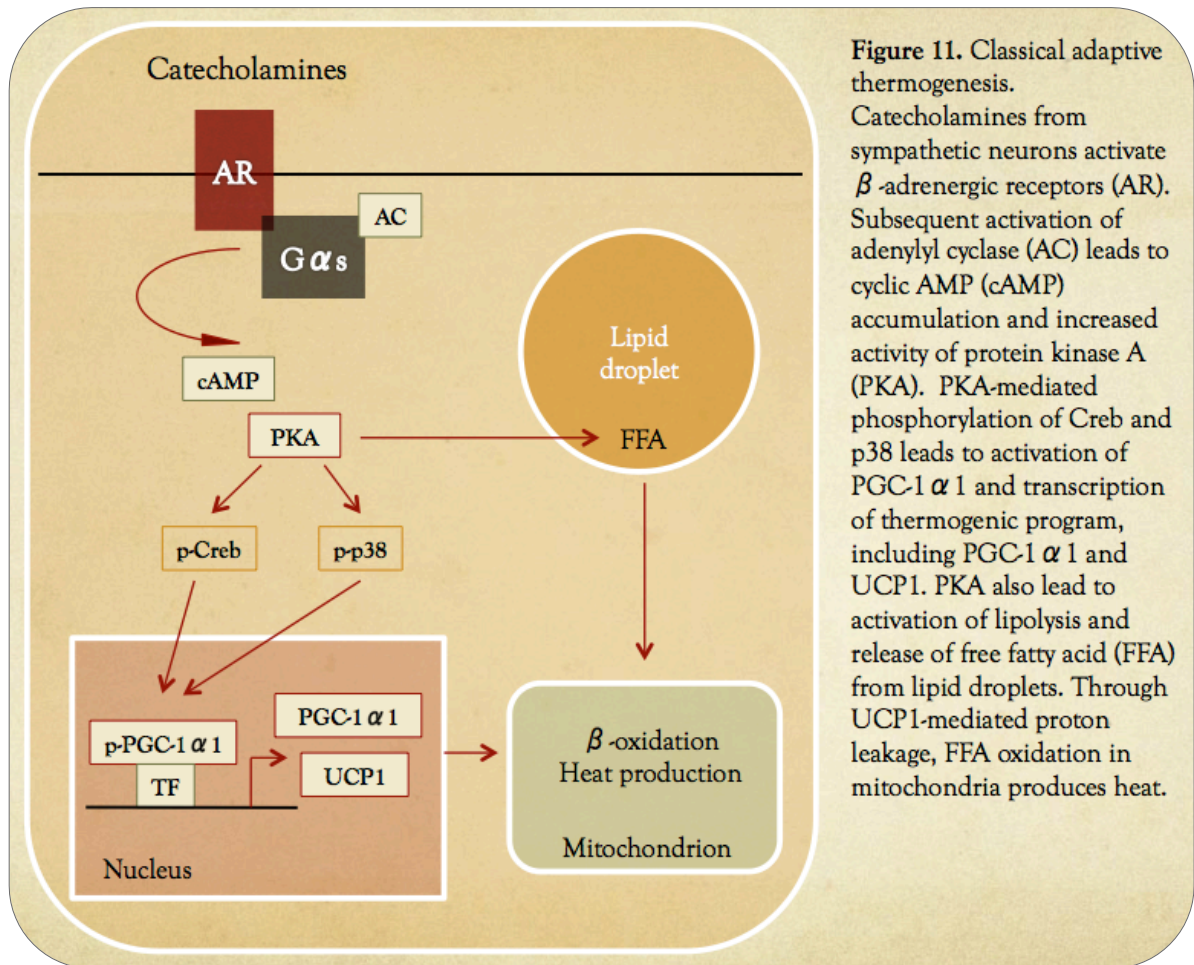
1.5.3 Thermogenesis through UCP1 Regulation

In adipose tissue, the regulation of UCP1 expression and activity is thought to underlie functional browning/beiging and change the metabolic profile of adipocytes (35, 158, 159). In BAT, β -adrenergic and cAMP signaling are the main regulators of thermogenesis (**Figure 11**) (43, 389). In fact, protein kinase A (PKA) senses cellular cAMP cellular variations and leads to activation of p38MAPK and CREB transcription factors (49, 50, 320, 338). This leads to the activation of PGC-1 α 1 and subsequent increased expression of thermogenic genes including UCP1. Of note, PKA also leads to the activation of lipolysis, which will release free fatty acids to mitochondria for oxidation and heat dissipation (392). PGC-1 α 1 regulates gene expression in response to cold temperatures, by binding transcription factors such as PPAR α , PPAR γ , retinoid X receptors (RXRs), NRF1 and thyroid receptors (178, 279, 280, 348, 372). Moreover, some of these transcription factors are nuclear receptors. Thus, using specific agonist induces the expression of UCP1 in adipose tissue (150). For example, rosiglitazone, a PPAR γ agonist induces PGC-1 α 1 and promotes PRDM16-mediated browning (255). In addition to controlling brown adipocyte fate, PRDM16 is necessary for WAT browning/beiging by β 3-adrenergic receptor downstream signaling (318). Finally, another mechanism that contributes to adaptive thermogenesis is the induction of PPAR α / δ -mediated signaling cascades by lipolytic products (235).

1.5.4 Hormonal Regulation of Adipose Tissue Browning/Beiging

Metabolic challenges regulate adipose tissue homeostasis through activation of different mechanisms, among which browning/beiging is thought to reduce the risk of developing metabolic disease (134). This network of systemic energy adaptations includes local molecules or molecules synthesized by other organs such as liver, brain and skeletal muscle. Situated in close proximity to BAT and WAT, sympathetic nerve terminals release catecholamines upon stimulation. These, in turn, are required for rapid activation of the browning/beiging machinery (47). Alternatively activated macrophages (AAMs) have been also shown to be a source of catecholamines in WAT (245). Conversely, pro-inflammatory macrophages (also known as M1) counteract catecholamine production in obesity (205). Among the lipid-derived hormones, prostaglandins have been shown to promote browning/beiging. These cyclooxygenase (COX)-dependent molecules activate PGC-1 α 1 in WAT thereby regulating systemic energy homeostasis (212). Moreover, thermogenesis is induced by fatty acid derivatives in a PPAR γ -dependent manner (204). Among peptides hormones, FGF21 has been shown to induce browning/beiging in WAT through stabilization of PGC-1 α 1 protein (103). While other studies have confirmed this, one report showed that in the fed-state FGF21 could promote PPAR γ -mediated WAT adipogenesis (82). Therefore, a physiological model of how local or systemic FGF21 regulates adipose tissue is missing. Another secreted molecule shown to induce brown adipocyte differentiation through PRDM16 and PGC-1 α 1 is bone morphogenic protein 7 (BMP-7) (345). BMP-4, on the other hand, promotes commitment of mesenchymal precursors to beige adipocytes (281).

Early studies demonstrated that cold exposure increases sympathetic tone, promoting catecholamine-mediated browning/beiging of adipose tissue. Acute cold exposure increases heart rate and promotes muscle-mediated shivering thermogenesis (32, 38, 168). This would suggest that heart and skeletal muscle are implicated in physiological responses that regulate body temperature and heat production. For example, upon cold exposure cardiomyocytes release atrial and brain natriuretic peptides (ANP, BNP), which promote browning/beiging of WAT (36, 226). In line with this, it has been proposed that this mechanism entails evolutionary advantages as it protects from cardiac hypertrophy during chronic cold exposure (333). Interestingly, aerobic exercise and cold-induced shivering are implicated in browning/beiging of WAT. As mentioned before, skeletal muscle PGC-1 α 1 and PGC-1 α 4 lead to the release of circulating factors that impact adipocyte biology (37, 287, 293). Whether these myokines display a physiological role in regulating human systemic energy homeostasis through browning/beiging of adipose tissue needs to be further elucidated.



1.5.5 Immune Regulation of Adipose Tissue Homeostasis

Numerous studies have found a role for different immune cell populations on metabolic health and disease (252, 263). Initial findings demonstrated that TNF- α negatively regulates glucose uptake in murine obesity (152). Similar findings in obese individuals confirmed that TNF- α production is higher in obesity and is inversely correlated with weight loss (151, 171). Later, macrophages were found to be the main source of TNF- α production in adipose tissue of obese mice (361, 373). These seminal studies suggested that low-grade inflammation could be associated with obesity and metabolic disease. Of all the organs affected by chronic inflammatory processes during obesity, WAT is the most investigated regarding the role of different immune populations (64). Immune cells in WAT integrate local and systemic signals to modulate metabolic homeostasis (253). It is now accepted that dysfunction of this immunological network in WAT can have deleterious effects for metabolic health (92, 206). Different examples including, but not limited to, transcription factors such as NF- κ B, c-jun kinase (JNK) and interferon regulatory factor 4 (IRF4), as well as metabolite-sensing receptors PPAR γ , farnesoid X receptor (FXR), liver X receptor and GPR120, have been described as regulators of immune-metabolic responses (206, 263). These observations have highlighted the importance of understanding in detail the interactions between the immune system and adipose tissue in lean and obese states. This will bring numerous insights of great therapeutic value for metabolic disease.

Immune Cell Populations in Healthy White Adipose Tissue

Observations in WAT of lean individuals have revealed that resident immune cell populations seem to be associated with anti-inflammatory type-2 immune responses (**Figure 12**). It appears that the crosstalk between this specific immune adaptation and adipocytes results in an integrated regulation of energy homeostasis. Recently, AAMs have been associated with metabolic homeostasis in WAT (143, 252, 256). To keep their alternative state, these cells are dependent on IL-4, IL-13 and signal transducer and activator of transcription 6 (STAT6) (120, 252, 256). Initial studies demonstrated that specific deletion of PPAR γ in AAMs decreases their number and worsens the metabolic outcomes imposed by HFD (254). Later, it was observed that exogenous administration of IL-4 improves AAMs response during diet-induced obesity (57, 292). In addition to their anti-inflammatory profile, AAMs improve glucose homeostasis and mitochondrial dysfunction by handling iron excess in WAT (262). As mentioned before, AAMs were shown to release catecholamines in adipose compartments, which then act on β 3-adrenergic receptor to induce lipolysis and browning/beiging (201, 245, 282, 287). Again, this mechanism was shown to be dependent on IL-4/IL-13, IL-4R α and STAT6 (282, 287). Other studies identified eosinophils as the principal source of IL-4 in lean WAT (367). These cells are dependent on IL-5 and the transcription factor GATA-binding protein 1 (GATA-1) (298, 300). Moreover, eosinophils largely contribute to type-2 immune responses, and their absence aggravates obesity and insulin resistance (298, 367). In agreement, mice with overrepresentation of this cell population in WAT were preserved from the negative consequences of diet-induced obesity (367, 374). It is still not known, however, if these cells have any other function in WAT.

Another source of IL-4 in WAT are iNKT cells (128, 209). In WAT, iNKT cells seem to have a specific phenotype distinct from that observed in spleen and liver (209). They are in an alternative activated state and have the ability to produce IL-4 and IL-10. Moreover, they can be activated by lipid derivatives coming from adipocytes (165, 209, 286). It was observed that in both rodents and humans obesity decreases the relative numbers of iNKT cells in WAT. In addition, mice lacking this cell population display severe glucose intolerance and a type-1 immune response (209). Taken together, this evidence suggests that eosinophils and iNKT cells are the main source of IL-4, an important cytokine driving an anti-inflammatory immune profile.

Another important immune cell population present in the steady state of WAT is composed of group 2 innate lymphoid cells (ILC2s) (232, 244). These cells were found to regulate the activity of eosinophils and AAMs (228, 249). Belonging to the innate immune responses, this group of cells is comprised by three subpopulations: ILC1s produce IFN- γ ; ILC2s are GATA-3-dependent and produce IL-4, IL-13, IL-5 and IL-9; and ILC3s, ROR γ -dependent and producing IL-17A and IL-22 (231, 326). Recent studies demonstrated that ILC2 in WAT are required to maintain eosinophils and AAMs via IL-5 and IL-13 (228). Moreover, it was shown that ILC2 numbers decrease in WAT during obesity, whereas antibody-depletion of

ILC2 aggravates insulin resistance and weight gain upon HFD feeding (128). In 2015, two different studies showed that ILC2 could directly regulate adipocyte function through the release of enkephalin peptides and IL-13 (42, 185). Brestoff and colleagues showed that ILC2-derived enkephalin peptides promote UCP1 expression to drive the formation of beige adipocytes (42). On the other hand, Lee and colleagues demonstrated that ILC2-derived IL-13 induces the recruitment and proliferation of beige adipocytes (185).

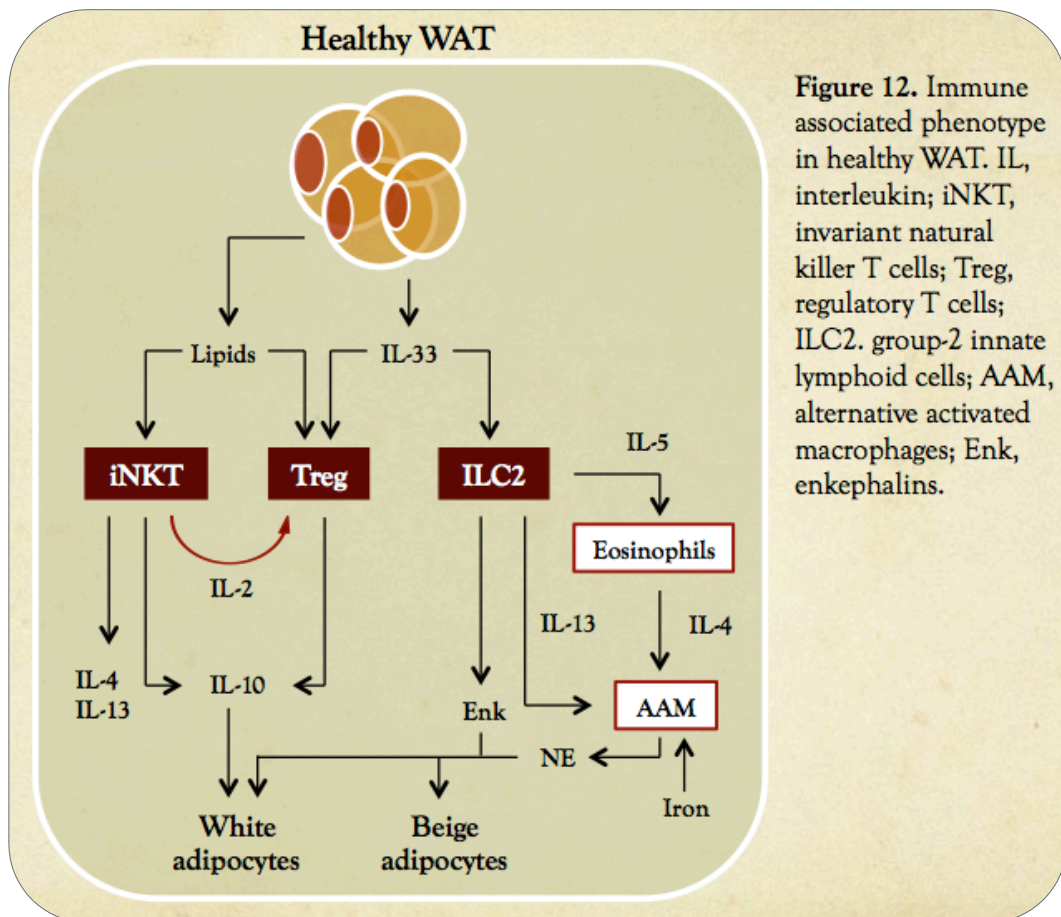


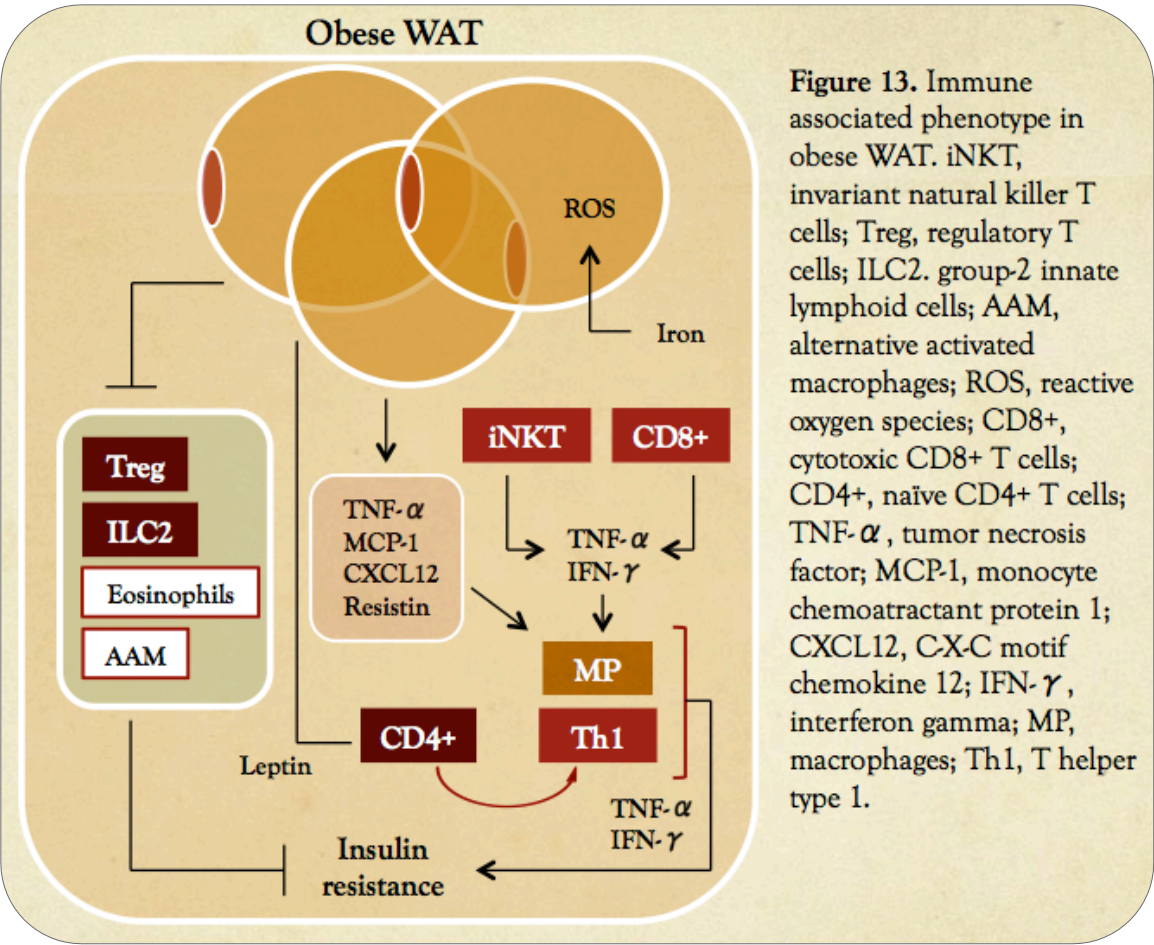
Figure 12. Immune associated phenotype in healthy WAT. IL, interleukin; iNKT, invariant natural killer T cells; Treg, regulatory T cells; ILC2, group-2 innate lymphoid cells; AAM, alternative activated macrophages; Enk, enkephalins.

The cytokine IL-33 has been shown to contribute to the initial steps of type-2 immune regulation in lean WAT, and to induce the proliferation of ILC2 (230, 232, 244). IL-33 was later shown to be crucial to counteract diet-induced obesity (42, 225). Genetic deletion studies further confirmed that IL-33 and its receptor are required to prevent alterations in glucose metabolism during HFD (42, 225). In addition to IL33-mediated effects on innate immunity, this cytokine was found to regulate adaptive immune response in Th2 cells (228) and Tregs (311). Tregs are specialized cells on type-2 immune adaptations (44, 125). In WAT, evidence suggests that Tregs display a unique profile dependent on PPAR γ , Foxp3 and IL-10 (66, 75, 100). It was further shown that Tregs contribute to insulin sensitivity via IL-10 secretion (66, 100). Notably, in obese mice and humans, decreased Treg numbers have been observed (66, 100). This phenotype was reverted by exogenous administration of PPAR γ -

agonist (thiazolidinediones), showing that improvements in insulin resistance were due to Treg-mediated effects on adipose tissue (66). In sum, it appears that type-2 immune-metabolic adaptations in lean WAT mediated by IL-33, ILC2s, ILC2-derived enkephalins, Tregs, IL-4/-13, IL-10, AAMs and AAM-derived catecholamines cooperate to regulate and preserve metabolic homeostasis during several physiological challenges.

Immune Cell Adaptations in White Adipose Tissue during Obesity

During the course of obesity WAT can suffer the effect of underlying inflammatory processes. If imposed chronically, inflammation can contribute significantly to the development of insulin resistance and associated complications. The constant accumulation of triglycerides drives hypertrophy of white adipocytes. These morphological changes could then lead to cellular hypoxia, oxidative stress (69, 266), and to the production of pro-inflammatory signals such as leptin and resistin (14, 222, 263). This array of pro-inflammatory mediators starts a cascade of signaling pathways that result in the proliferation of type-1 immune populations (**Figure 13**).



In the last decade it has been demonstrated that adipocyte-derived mediators including monocyte chemotactic protein (MCP-1), C-X-C motif chemokine 12, leukotrienes and prostaglandins, are potent activators of pro-inflammatory macrophages in WAT (6, 243, 361). The initial response of these macrophages is to scavenge cellular debris (e.g. toxic lipids) from dying adipocytes (240). They also release IL-1 β , TNF- α and IL-6 (205, 386), which can act locally or reach other organs where they can impair insulin sensitivity (123). It has also been shown that during HFD feeding and before pro-inflammatory macrophage infiltration, there is recruitment of adaptive immune cells such as CD8 $^{+}$ T cells (247, 288). In this setting, CD8 $^{+}$ T cells were also found to release IFN- γ (291), which induces CD4 $^{+}$ T cells polarization to Th1 pro-inflammatory responses and exacerbation of insulin resistance (62, 233, 328). Adipocytes also contribute to the onset of this Th1 response. They try to preserve energy homeostasis during excessive calorie intake by releasing leptin, which induces collaterally CD4 $^{+}$ T cell-dependent Th1 polarization (77). Collectively, this suggests that WAT-type-1 inflammatory responses are orchestrated by adipocytes, CD8 $^{+}$ T cells, CD4 $^{+}$ T cells and macrophages. This inflammatory loop will impose detrimental effects on WAT that subsequently lead to impaired insulin sensitivity.

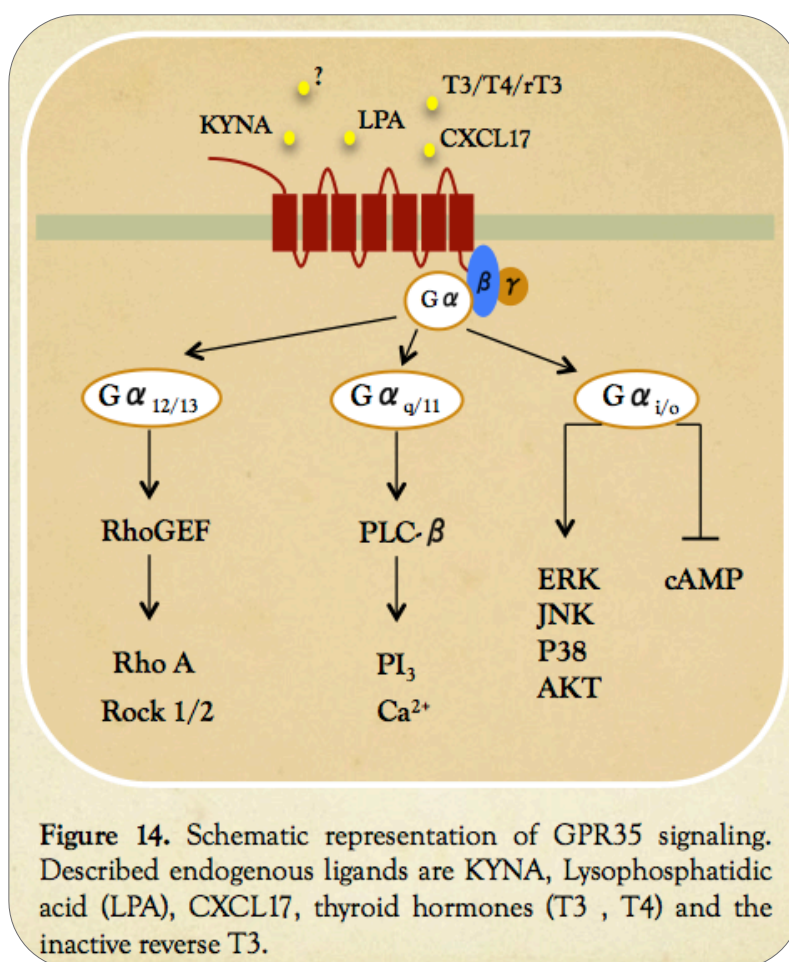
1.5.6 Nutrient Sensing by G Protein-coupled Receptors

Although it is currently appreciated that one of the main contributing factors to obesity is an excessive caloric intake accompanied by decreased energy expenditure, it is still not well understood why obesity does not always mean glucose intolerance and insulin resistance (277). This has led to the suggestion that obesity alone does not cause metabolic disease (25). Instead, lifestyle factors such as diet composition might directly impact metabolic homeostasis. In fact, nutrients and their metabolites can serve as important signaling factors that transduce yet another environmental influence (84).

GPCRs are membrane receptors that transduce information from local or systemic signals to the intracellular environment. These signaling pathways regulate diverse physiological processes such as those that mediate metabolic adaptations to our environment. In fact, many GPCRs and their ligands have been identified as crucial players in metabolism (30). As mentioned before, β -adrenergic receptors modulate environmental adaptations to cold exposure by altering adipose tissue metabolism (344). Likewise, GPR40 in pancreatic β -cells regulates insulin secretion by sensing fatty acids (157), whereas in intestinal enteroendocrine cells, mediates incretin release (83).

Changes in diet-derived nutrients and metabolites have been proposed to influence systemic energy homeostasis (84). Living organisms have evolved molecular ways to transduce diet-derived signals in an intricate network of organ communication. Moreover, organ-specific catabolism of nutrient-derived molecules will subsequently produce metabolites that carry downstream messages. From diet-derived Trp consumption to QUIN accumulation, KP-metabolites are good candidates to be integrators of metabolism due to their interaction with different organ-networks. In agreement, KYN metabolite levels are associated with diet-derived Trp ingestion, and seem to respond to physiological challenges. For instance, KYNA could be considered a message-carrier able to integrate environmental challenges as it is

produced under aerobic exercise (2, 312), and is a GPR35 agonist (354). The KYNA-GPR35 interaction suggests they could be a molecular node relevant to metabolic function and disease. Indeed, specific agonists confirmed that GPR35-downstream signaling modulates glucose homeostasis in metabolic tissues (188). In addition, GPR35 appears to be activated by several endogenous ligands and to be mainly coupled to G-alpha subunits (**Figure 14**) (76, 210). It was also shown that, in addition to GPR35-mediated regulation of inflammatory processes (95, 339), this receptor is activated endogenously by chemokine (C-X-C-motif) ligand 17 (CXCL17) at nM concentrations (215). This cytokine has anti-inflammatory properties and regulates angiogenesis (186), which further highlights the potential immune-metabolic functions of this GPCR. Collectively, these observations suggest that GPR35 and KYNA could be a relevant cluster for the regulation and integration of systemic metabolic homeostasis.



2 AIMS

The overall focus of the work presented in this thesis was to investigate the systemic impact of skeletal muscle conditioning through PGC-1 α 1 in the context of depressive and metabolic disease.

Specific aims:

- To understand and isolate the molecular effects of skeletal muscle conditioning on depression.
- To investigate the molecular mechanisms by which physical exercise, through conditioned skeletal muscle, exerts beneficial effects on the progression of stress-induced depression.
- To investigate the behavioral response of skeletal muscle-specific PGC-1 α 1 transgenic mice to stress-induced depression.
- To identify novel pathways that mediate the effects of skeletal muscle PGC-1 α 1 on the central nervous system, especially in stress-induced depression.
- To investigate which transcription factors act in concert with skeletal muscle PGC-1 α 1 to regulate gene programs relevant to stress-induced depression.
- To verify in both rodent and humans if novel pathways modulated by skeletal muscle PGC-1 α 1 and relevant to stress-induced depression are part of the physiological adaptations to exercise training.
- To examine the effect of exercise training on kynurenine metabolism. In particular, the effect of skeletal muscle PGC-1 α 1 and KAT enzymes on KYNA production during aerobic exercise.
- To investigate the role of KYNA on systemic energy homeostasis and peripheral metabolism.
- To investigate the role of KYNA-GPR35 in adipose tissue function and inflammation.

3 RESULTS AND DISCUSSION

Study I: Skeletal Muscle PGC-1 α 1 Modulates Kynurenine Metabolism and Mediates Resilience to Stress-Induced Depression

Exercise interventions benefit human health and are used as a therapeutic strategy for the prevention and treatment of several disorders. These range from diabetes, obesity, cardiovascular, to even psychiatric diseases such as depression (56). For example, different components of exercise – skeletal muscle conditioning, central and immunological compartments, social effects among others – confer therapeutic value in the case of depression. However, the molecular mechanisms underlying the beneficial effects of individual compartments during exercise remain elusive. As mentioned before, skeletal muscle PGC-1 α coactivators regulate many of the physiological adaptations to physical activity (303, 321). In fact, several findings have described that aerobic exercise increases the activity of PGC-1 α 1, which subsequently regulates mitochondrial biogenesis, fatty acid oxidation and angiogenesis (11). Exhibiting many of the chronic adaptations to aerobic exercise, transgenic mice with skeletal muscle-specific PGC-1 α 1 overexpression (mck-PGC-1 α 1) (196), are a great tool to isolate the impact of skeletal muscle conditioning on diseases such as depression.

The socioeconomic burden of depression stems from the fact that it is a highly debilitating disease, causing 35% of years lived with disability worldwide (WHO, *Depression* [395]). Depression has a heterogeneous etiology with underlying molecular mechanisms that remain elusive. Nevertheless, chronic stress has been proposed to drive pathophysiological processes that lead to disease progression (106). Emerging evidence suggests that stress-induced inflammatory changes in the brain affect neurotransmission and synaptic plasticity (203, 380). Hence, we use one of the most validated models to induce depressive-like behavior in rodents (364), the chronic unpredictable mild stress (CMS) protocol.

Given the different etiologies of depression, a clear understanding of its cause has made its treatment and complete remission difficult. Neurotransmitter levels (147), neuroinflammation (285), glutamate alterations (305) and synaptic homeostasis (54) are among the molecular mechanisms whose disturbance seems to heavily impact the development of this disorder. Interestingly, physical activity and exercise have been shown to positively influence most of

these disease-contributors (40, 93). Using a muscle-specific PGC-1 α 1 transgenic model that shows many of the chronic adaptations to endurance-type exercise (196), we have aimed to isolate the physiologic impact of skeletal muscle conditioning in the progression of stress-induced depression. In this study, we describe how skeletal muscle PGC-1 α 1 regulates peripheral KYN metabolism and prevents the development of stress-induced depression. When induced by exercise, PGC-1 α 1 acts in concert with the transcription factors PPAR α / δ to induce the expression of KAT enzymes in skeletal muscle. This muscle-specific function on KYN metabolism diverts stress-induced KYN elevation in circulation towards the production of KYNA. This peripheral shift reduces central levels of kynurenines associated with disruption of synaptic homeostasis and depression (237).

During chronic stress and inflammation peripheral Trp degradation towards the KP has been associated with neuroinflammation and the development of depression (316). In this study, circulating KYN levels increase after chronic stress and correlate well with its downstream toxic metabolite 3HK in the CNS. As mentioned before, during stress or inflammation KYN and 3HK can be further degraded towards QUIN in microglia (377). As an NMDA α agonist, this metabolite is known to cause excitotoxicity and lead to synaptic disruption. In agreement, under our experimental conditions we observe a clear association between circulating KYN and the expression of hippocampal synaptic proteins. Given that KYNA has been shown to be unable to cross the blood-brain barrier (109), switching peripheral KYN metabolism towards KYNA would ease centrally pathophysiological processes caused by stress-induced inflammation. In fact, we observe that skeletal muscle PGC-1 α 1-mediated conversion of KYN to KYNA confers protective effects in the brain after chronic-stress exposure. Compared to wild-type mice, neuroinflammation and synaptic markers in mck-PGC-1 α 1 animals are unaffected by chronic stress. Of interest, stressed-transgenic animals show reduced body weight gain similar to stressed wild-type mice and higher expression of inflammatory markers in skeletal muscle. Collectively, this suggests that mck-PGC-1 α 1 is resilient to stress-induced depression by specific mechanisms related to decreased kynurenine-derived toxic metabolites in limbic circuitry as opposed to overall stress-protection.

Increased peripheral Trp catabolism and elevation of KYN contribute to the development of depressed-like behavior in mice (250). In fact, peripheral exogenous administration alone is able to induce the same behavioral responses (251). In line with this, mck-PGC-1 α 1 mice are protected from developing depressive-like behavior by intraperitoneal administration of KYN. On the other hand, mice with skeletal muscle-specific deletion of PGC-1 α 1 display a more pronounced behavioral response to exogenous KYN administration. In agreement, we observed a clear relationship between KYN administration and the expression of inflammatory markers in the hippocampus. Taken together, skeletal muscle PGC-1 α 1 and KAT enzymes harness peripheral stress-induced accumulation and central response of KYN.

Furthermore, we observed that synaptic proteins are dysregulated by chronic stress in wild-type mice. This suggests that synaptic homeostatic mechanisms might underlie depressive-

like behavior. Despite these observations, the cause of depression remains unknown. Given that stress-induced inflammation mediates significant changes in astrocytic and microglial markers only in wild-type mice, this supports the idea that altering homeostatic processes regulated by other cell types in brain might directly contribute to synaptic disruption (15, 16, 24, 71). Nevertheless, it is still unknown how these processes are timely regulated and compartmentalized. Interestingly, some regions of the limbic circuitry in mck-PGC-1 α 1 display different expression levels at baseline of some synaptic and astrocytic markers. This argues for other muscle-to-brain signaling molecules that are regulated by PGC-1 α 1. As recently published (37), skeletal muscle PGC-1 α 1 regulates the expression of FNDC5, cleaved as Irisin, with effects on systemic energy homeostasis (37). This myokine was also found to regulate BDNF expression in CNS (366). In our study, we observe that the expression levels of BDNF are unchanged in mck-PGC-1 α 1, which suggests this pathway is unlikely to mediate resilience to stress-induced depression. Whether there are other contributing factors regulated by PGC-1 α 1 in skeletal muscle and relevant to stress-induced depression remains to be clarified.

Emerging evidence suggests the presence of an underlying molecular association between insulin resistance and inflammation. In addition, alterations in the KP have been postulated to be the link between both conditions (265). Interestingly, skeletal muscle PGC-1 α 1 is reduced in diabetes and obesity, which suggests that KYN could contribute to disease progression. The same molecular mechanism could offer new avenues of research to clarify why individuals suffering from T2D display higher incidence of depression (302, 332).

There are many components of exercise training with broad health benefits. In order to isolate the skeletal muscle compartment we used transgenic models of skeletal muscle conditioning. After identifying a mechanism in the skeletal muscle compartment that is relevant to stress-induced depression, we next aimed at understanding whether this also was part of the physiological adaptations to exercise. Indeed, endurance exercise interventions in both humans and mice induce PGC-1 α , PPAR α/δ and KAT enzymes in skeletal muscle. This is accompanied by the elevation in circulating KYNA levels in mice. The same findings have been shown in humans, where circulating KYNA levels were found to robustly increase after extensive aerobic training (190). However, more interventional studies will be needed to confirm the role of skeletal muscle PGC-1 α /KAT during exercise, especially in depressed individuals. In sum, our work has uncovered a physiological role for skeletal muscle, mediated through PGC-1 α 1 and PPAR α/δ transcription factors, in the regulation of KYN metabolism. Dampening the stress-induced accumulation of toxic metabolites offers great therapeutic advantages for depression (316, 369) and other metabolic diseases (265).

Study II: Endurance Exercise Increases Skeletal Muscle Kynurenine Aminotransferases and Plasma Kynurenic Acid in Humans

In this study, we show that aerobic exercise training in humans leads to the regulation of KYN metabolism. Endurance exercise elevates circulating KYNA levels and decreases QUIN/KYNA ratio. Furthermore, we observed that individuals with long-term adaptations to endurance exercise training display higher KAT enzyme gene and protein expression in skeletal muscle. In line with this, skeletal muscle PGC-1 α 1 and PPAR α exhibit elevated expression levels in the same subjects. These results are consistent with our previous findings showing that a 3-week endurance exercise protocol in human volunteers induces skeletal muscle KAT enzymes. Moreover, we have shown in our previous study that the mechanism for KAT gene regulation is mediated by PGC-1 α 1 and PPAR α / δ . In this study, we observe a clear relationship between KAT gene expression and PGC-1 α 1/PPAR α , but not PPAR δ . Supporting an exercise-induced transcriptional activity of PGC-1 α 1, we observe elevated expression of some of its downstream target genes including carnitine O-palmitoyltransferase 1B (CPT1B), VEGFA and pyruvate dehydrogenase kinase isozyme 4 (PDK4).

This study confirms a specialized skeletal muscle function on KYN metabolism, in particular in the context of endurance-exercise training. We show that the regulation of mRNA and protein levels of KAT enzymes in human skeletal muscle is part of the physiological adaptations to aerobic exercise. Moreover, this is accompanied by an elevation in circulating KYNA levels and a reduction of the QUIN/KYNA ratio. This suggests that during aerobic exercise there is a shift within Trp-kynurenine degradation pathway towards KYNA production. Interestingly, decreased plasma KYNA levels and high QUIN/KYNA ratio have been observed in depressed patients. Collectively, these observations highlight the great therapeutic potential of exercise-mimetics in modulating KYN metabolism in the periphery.

To further investigate whether other type of exercise training influences KYN metabolism in humans, circulating KYNA and QUIN/KYNA ratio were determined after an eccentric exercise protocol. The latter consists of 100-drop jumps, which leads to skeletal muscle soreness and stress (166). In this experimental condition, we observed that KYNA levels and QUIN/KYNA ratio were unaffected. This suggests that KYN metabolism is regulated during more energy demanding exercise such as endurance-type. This has been previously shown by a study performed by Lewis and colleagues, in which circulating KYNA levels were substantially elevated in humans after running a marathon (190). In this study, we obtained similar results in human subjects that run half-marathon. Altogether, these findings suggest that production of KYNA is related to aerobic exercise training. The fact that skeletal muscle PGC-1 α 1 – a mediator of many of the chronic adaptations to endurance exercise including

expression of KAT enzymes – modulates this fate set aside skeletal muscle as one of the main regulators of KYN metabolism in the periphery.

The increase in circulating KYNA levels after extensive endurance exercise might be correlated with availability of free Trp in plasma. At steady state, Trp is bound to albumin. However, in the course of endurance training FFAs are released into circulation, and competitively bind albumin (58). This mechanism suggests that skeletal muscle clears plasma free Trp for KYNA production. Despite these compelling observations, more studies are needed to clarify whether stress-induced accumulation of KYN could lead to higher availability of free-Trp or if conditioned skeletal muscle displays higher KYN clearance.

In this study we further highlighted the effects of exercise on KYN metabolism in humans, especially a specialized skeletal muscle function on KYNA production during this metabolic challenge. Interestingly, KYNA kinetics after endurance exercise interventions show that KYNA rises transiently (1 hour) and is cleared from circulation after 5 hours. Whether KYNA is only excreted by the kidneys, as previously proposed (90), or whether it is partly used by other organs in the periphery to accomplish a metabolic role remains unknown. With this in mind, we wanted to investigate in our next study a possible role for KYNA in regulating organ-crosstalk adaptations to energy homeostasis.

Study III: Kynurenic Acid and GPR35 Regulate Adipose Tissue Energy Homeostasis and Inflammation

In the CNS, KYN metabolites have been associated with numerous processes including neuroinflammation and synaptic homeostasis (316). Moreover, the diverse actions of KYN metabolites appear to contribute to pathophysiological disturbances observed in psychiatric disorders such as schizophrenia and depression (316). It has been shown that many of these disorders display an inflammatory component considered today as one of the main drivers of disease progression (316). This concept has gained interest as an explanatory argument for the increased incidence of metabolic disease in subjects affected by mood disorders (214, 248). At the intersection between synaptic and metabolic disturbances dysregulation of the KP appears to be a contributing factor to disease onset (265, 329). Given that KYN metabolism occurs initially in the periphery and that it contributes to its central regulation, understanding the molecular function of its metabolites could provide important therapeutic tools and targets. Accordingly, recent findings have observed aberrant levels of these metabolites in obesity and T2D (136, 181, 329). Despite this, more functional studies on the role of these metabolites in the periphery are still missing. In this study, we investigated the biological role of KYNA, an end metabolite of the KP induced by exercise and with anti-

inflammatory properties (2, 105, 213, 312). Here we show that chronic elevation of KYNA (by exogenous administration) lead to regulation of systemic energy homeostasis. We observe that the systemic effects of KYNA are mainly mediated by the WAT compartment where it induces browning/beiging and an anti-inflammatory immune profile. Other molecules involved in mediating skeletal muscle to adipose tissue crosstalk have been described before and include Irisin (37), Metnl (287), BAIBA (293), IL-6 (177) and lactate (53). In addition, we observe that KYNA-specific actions on WAT correlate well with the expression of GPR35 (expressed higher in WAT than BAT). With knockdown experiments in inguinal primary adipocytes, we further confirmed that KYNA-mediated effects depend upon GPR35-signaling.

KYNA and GPR35 signal through elevation of intracellular Ca^{2+} , ERK1/2 phosphorylation and increased PGC-1 α 1 stability. All of which regulate adipose function via adaptive thermogenesis and browning/beiging (199, 280, 356, 385). GPR35 association to Gai/o has been shown to inhibit Gas-dependent cAMP accumulation and mediate ERK1/2 phosphorylation (210). In line with this, we observed that KYNA potentiates the effects of propranolol on β -adrenergic receptors and promotes ERK1/2 phosphorylation. GPR35 has also been shown to regulate Ca^{2+} signaling through interaction with Gq/11 subunits (210). Accordingly, we observe that in inguinal primary cultures KYNA increases intracellular Ca^{2+} , in a GPR35-dependent manner. Moreover, we could confirm that some KYNA downstream target genes are dependent on the presence of GPR35 (for instance, PGC-1 α 1 and NRF1), while others seem to be mediated due to enhanced β -adrenergic activity when GPR35 is silenced. These results suggest that silencing GPR35 in inguinal primary adipocytes abrogates some of the acute effects mediated by KYNA while losing the dampening effect of GPR35 on β -adrenergic activity. Given this observation, we assessed whether chronic KYNA treatment sensitizes to a β -adrenergic receptors agonist. Indeed, we observed that a much lower dose of isoproterenol was required to elicit functional changes in adipocytes. This evidence suggested that KYNA and GPR35 crosstalk with β -adrenergic receptors. To evaluate this, we re-analyzed global gene expression profiles in inguinal primary adipocytes treated with KYNA. We found that one of the top-regulated genes was indeed a component of GPCR signaling, the regulator of G-protein signaling 14 (RGS14). RGS14, whose gene expression is dependent on GPR35, has been shown to bind GTP-G α complexes promoting their dissociation to form inactive G $\alpha\beta\gamma$ heterodimers (27, 61). We observed that RGS14 silencing blunts the KYNA-sensitizing effect on isoproterenol induction of β -adrenergic activity. Interestingly, RGS14 has been previously shown to have high expression in brain where it regulates spatial learning (322, 323). Here we found that, in addition to the brain and spleen, RGS14 is highly expressed in WAT, in particular in subcutaneous WAT. Previous reports on *Drosophila melanogaster* have shown that lacking the RGS14 fly homologue leads to increased fat mass and low Gas-cAMP signaling (198). Taken together, the KYNA-GPR35-RGS14 axis offers great therapeutic value as it sensitizes β -adrenergic responses in adipocytes. This could substitute therapeutic interventions for metabolic disorders where direct β -adrenergic agonists confer undesired effects.

Seminal studies have demonstrated the role of the KP on immune regulation (213). Thus, production of KYN metabolites has been suggested to play a crucial role in breaking an overactive immune system (238). KYN and KYNA, in particular, dissipate inflammatory process by activating cellular populations specialized in type-2 immune responses. KYNA, for instance, dampens pro-inflammatory cytokine release in iNKT cells and mononuclear cells (95, 354). In this study, we show that exogenous chronic elevation of KYNA (at physiological levels) induces the expression of cytokines that mediate type-2 immune adaptations. By analyzing a panel of specific immune cell markers, we could observe that KYNA associates with AAMs, ILC2s and Tregs cellular markers. Importantly, these cell populations have been shown to reduce adipose tissue inflammation and improve insulin sensitivity (41, 183). In addition, we found that KYNA induces IL-33. This cytokine regulates the proliferation of Tregs and ILC2s, and induces browning/beiging of WAT (185). Moreover, IL-33 enhances ILC2-proenkephalin expression and is considered to play a crucial role in maintaining anti-inflammatory immune adaptations in WAT. We observed that KYNA induces a similar profile in both visceral and subcutaneous adipose depots. Collectively, these findings are in line with previous results indicating an anti-inflammatory role for KYNA. Hence, having a specialized immune function in WAT opens new avenues for KYNA-dependent modulation of the immune-metabolic interaction. This could offer alternative therapeutic interventions for insulin resistance and T2D.

Given the KYNA-induced effects including regulation of systemic energy homeostasis, functional changes in adipocyte function, and immune regulation in WAT depots, we next investigated whether chronic KYNA administration could modulate similar processes in mice fed a HFD. Indeed, we observed that mice on a HFD and receiving exogenous KYNA reduce weight gain, ameliorate glucose tolerance and decrease triglycerides levels in plasma. In addition, KYNA rescues the HFD-mediated reduction in the expression of thermogenic and lipolytic genes. Moreover, we observed a KYNA-mediated anti-inflammatory immune profile in WAT of mice on a HFD.

Interestingly, elevating KYNA levels both acute and chronically decreases circulating levels of some metabolites of the KP such as QUIN, 3HK and PA. Among these, QUIN and 3HK have been shown to be toxic in numerous tissues if they are accumulated. Furthermore, we observed that KYNA elevates circulating levels of nicotinic acid, which suggests that KYNA can regulate the levels of other metabolites from the KP and metabolites from other pathways that influence Trp catabolism. Understanding this mechanism could be of physiologic relevance, as KYNA accumulation would preserve the immune-tolerant effect of Trp-degradation while avoiding accumulation of toxic metabolites. Of note, KYNA induces changes in PGC-1 α 1 and PPAR α in WAT. These transcriptional regulators modulate the expression of KAT enzymes in skeletal muscle (2). In agreement, as KYNA modifies WAT-depots towards a beige phenotype, it also increases the expression of KAT enzymes. This could possibly explain the observed circulating levels of KP metabolites. Collectively, these observations suggest that KYNA-mediated changes in adipose tissue function are

accompanied by modulation of KYN metabolism in the same organ. This overall metabolic regulation could have implications not only for metabolic disorders but also for depression.

4 CONCLUSIONS & FUTURE PERSPECTIVES

The general aim of this thesis was to investigate molecular mechanisms in conditioned or exercised skeletal muscle that contribute to overall health. Using murine genetic models that mimic many of the chronic adaptations to aerobic exercise, we wanted to isolate the skeletal muscle compartment from other exercise components in the context of stress-induced depression. Our studies indicate that skeletal muscle PGC-1 α 1, together with PPAR α / δ , regulate peripheral KYN metabolism via the expression of KAT enzymes. This mechanism shifts KYN degradation towards KYNA production. In addition, we verified in both rodent and humans that this axis is part of the physiological adaptations to endurance exercise. Since this exercised-mediated mechanism leads to accumulation of KYNA in the periphery, we investigated the role of this metabolite in regulating systemic energy homeostasis. Our results indicate that KYNA plays a role in peripheral energy metabolism as it contributes to the regulation of adipose tissue function and inflammation. These previously unknown functions of PGC-1 α 1 in skeletal muscle and KYNA in white adipose tissue offer promising therapeutic value for the treatment of depression and metabolic diseases such as T2D. The results can be summarized as follows:

Study I

- Mck-PGC-1 α 1 transgenic animals are resilient to chronic mild stress-induced depression.
- Skeletal muscle PGC-1 α 1 induces the expression of kynurenine aminotransferases (KATs), and enhances peripheral metabolism of KYN to KYNA.
- Mck-PGC-1 α 1 mice are resilient to depressive-like behavior induced by exogenous KYN administration. Whereas skeletal muscle-specific deletion of PGC-1 α 1 sensitizes to KYN-induced depressive-like behavior.
- PGC-1 α 1, together with PPAR α / δ regulate myotube KAT enzyme expression.
- Aerobic exercise training increases murine and human KAT expression in skeletal muscle.

Study II

- In humans, the PGC-1 α 1-PPAR α -KAT axis is part of the physiological adaptations to aerobic exercise.

- Both mRNA and protein levels of skeletal muscle KAT enzymes increase after endurance-exercised training.
- Endurance-training leads to the elevation of circulating KYNA 1 hour after the exercise intervention.

Study III

- KYNA regulates systemic energy expenditure and induces a brown/beige transcriptional signature in subcutaneous and visceral adipose depots.
- Adipose depots of KYNA-treated mice reveal a gene expression profile of anti-inflammatory immune cells.
- Specific visceral WAT Tregs and ILC2 gene signatures are among the KYNA-induced genes.
- KYNA has cell-autonomous actions in inguinal primary adipocytes. The adipocyte gene expression signature generated by KYNA partially overlaps with that of other known thermogenic agents.
- Activation of adipocyte GPR35 by KYNA activates Ca^{2+} / ERK / CREB / PGC-1 α 1 signaling.
- A crosstalk between KYNA-GPR35 and β -adrenergic receptor is mediated by RGS14
- KYNA administration induces weight and adiposity loss and prevents high-fat diet-induced weight-gain.
- Brown/beige adipose tissue expresses high KAT levels.

Skeletal muscle PGC-1 α 1 orchestrates many physiological states where cells try to regain control of energy homeostasis. Therefore, the observation that this transcriptional coactivator modulates KYN metabolism may have relevant implications for several diseases. It would be interesting to evaluate if KYNA has an autocrine function in skeletal muscle, regulating either energy adaptations or different immune populations. This could have potential implications in the context of muscle-related diseases.

Interestingly, PPAR α / δ are transcriptionally regulating the expression of KAT enzymes in skeletal muscle. PPAR α / δ are ligand-regulated transcription factors, which implies that their pharmacological manipulation could offer an alternative therapeutic intervention to modulate KYN metabolism. It would be interesting to assess whether such approach could be used in stress-induced depression as well as metabolic diseases.

Skeletal muscle PGC-1 α 1-PPAR α / δ -KAT enzymes with subsequent production of KYNA are part of the physiological adaptations to endurance exercise in both rodents and humans. It would be interesting to evaluate whether manipulation of this specific axis could increase exercise performance or enhance the molecular adaptations to exercise.

Peripheral shifting of KYN metabolism to KYNA can have broad applications for immune and metabolic disorders. It would be interesting to better understand which immune populations are being directly influenced by KYNA in other organs such as liver and pancreas. Likewise, what are the molecular downstream signalling events governing such regulations.

KYNA appears to influence other metabolites from the KP. It would be interesting to understand how exactly KYNA regulates the levels of metabolites from the other branch of the pathway (3HK and QUIN), while increasing circulating levels of nicotinic acid. Of interest, the KYNA-nicotinic acid regulation could be further investigated as it could open new areas of research for understanding the possible KYNA-mediated regulation of NAD⁺ levels.

The KYNA-GPR35 interaction seems to be a relevant molecular node for energy homeostasis. It would be compelling to assess what is the molecular mechanism controlling GPR35 expression. As this physiological interaction seems to integrate molecular responses to environmental challenges, its transcriptional regulation could offer a therapeutic window where activity of downstream signaling could be pharmacologically manipulated.

The KYNA-GPR35-RGS14 axis seems to mediate crosstalk with β -adrenergic receptors. It would be interesting to find potent molecular activators of RGS14. This could offer open novel avenues for treatment of metabolic diseases where combined therapeutic interventions would reduce the side effects of β -adrenergic agonist.

Exercise training promotes many molecular adaptations that are not limited to one specific organ or cell type. These widespread events are likely to impact many pathophysiological processes that silently drive disease progress. More than mimicking the entire plethora of adaptations to physical activity, understanding individual components in different disease context becomes important. This would allow us to manipulate exercise-mediated networks that are relevant to specific disorders. As the field progresses, it becomes evident that the physiological adaptations to exercise happen ubiquitously. This fact entails many challenges for future research that could be addressed with an integrative approach to study inter-organ communication. Finally, this will help us to understand the behaviour of specialized molecular nodes in the regulation of energy homeostasis and other physiological adaptations.

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“Lorem ipsum dolor sit amet, consectetur adipiscing elit. Etiam in tortor ac ante varius vestibulum vel sit amet mauris. Pellentesque tempus nunc in nulla ornare ultricies. Proin non dictum diam, ac rhoncus ante. Nullam ligula magna, aliquam eu nibh eget, dapibus malesuada risus. Morbi euismod augue at diam accumsan ullamcorper. Suspendisse vitae augue enim. Etiam vestibulum ipsum sed elit congue pellentesque. Nullam dignissim tempus egestas. Suspendisse potenti. Duis elit tortor, facilisis sed purus ut, ullamcorper tempus neque. Nunc sit amet lei lacinia, cursus felis vestibulum, posuere nunc. Nam at turpis viverra, aliquam lacus id, euismod nibh”... **Don’t translate it!** It does not mean anything. You just skipped the hard-core part to get into this section. So, I felt the right to have a little fun at your expense 😊

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