

Review

Neurotransmitters in Type 2 Diabetes and the Control of Systemic and Central Energy Balance

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Abstract: Efficient signal transduction is important in maintaining the function of the nervous system across tissues. An intact neurotransmission process can regulate energy balance through proper communication between neurons and peripheral organs. This ensures that the right neural circuits are activated in the brain to modulate cellular energy homeostasis and systemic metabolic function. Alterations in neurotransmitters secretion can lead to imbalances in appetite, glucose metabolism, sleep, and thermogenesis. Dysregulation in dietary intake is also associated with disruption in neurotransmission and can trigger the onset of type 2 diabetes (T2D) and obesity. In this review, we highlight the various roles of neurotransmitters in regulating energy balance at the systemic level and in the central nervous system. We also address the link between neurotransmission imbalance and the development of T2D as well as perspectives across the fields of neuroscience and metabolism research.

Keywords: neurotransmitters; energy balance; diabetes; metabolism; obesity



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1. Introduction

Diabetes mellitus is a chronic metabolic disease characterized by hyperglycemia that arises due to insufficient insulin production from the pancreas or from inadequate insulin utilization by the body, or a combination of both [1]. Approximately 5% of patients with diabetes suffer from Type 1 Diabetes (T1D), an autoimmune condition in which patients rely on exogenous insulin. The remaining majority have Type 2 Diabetes Mellitus (T2D), characterized by insulin resistance in its early stages. The mechanisms of disease progression in T2D, and other minor frequency forms of diabetes are under active investigation [2]. The International Diabetes Federation (IDF) indicated that 537 million adults globally were living with diabetes in 2021, with an expected 45.8% increase in the number of cases by 2045 [2].

T2D often goes undiagnosed until complications arise, and screening for the disease typically occurs only in obese patients [3]. The association between obesity and T2D is strong, yet some obese individuals maintain a healthy metabolism [3,4]. Therefore, only some mechanisms of insulin resistance are dependent on obesity. A chronic positive energy balance leads to obesity, which increases the risk of developing insulin resistance and T2D [5]. Positive energy balance results from either increased energy intake due to high calorie consumption or decreased energy expenditure due to a lack of physical activity, or a combination of the two. Readjusting energy balance to reduce body weight can improve diabetes. In fact, a 10% reduction in weight has been reported to reverse clinical diagnosis of T2D in some patients with obesity [6].

The basic mechanism for obesity is excess glucose and insulin; glucose stimulates insulin release allowing its utilization by the muscles and storage of the excess as fat. Multiple in vitro and in vivo studies have demonstrated that insulin resistance is part

of the pathogenesis of T2D as it compromises efficient use of glucose [7–10]. This also leads to elevated glucagon levels and glucose production by the liver [11,12]. Persistent high glucose levels are concomitant with the stimulation of fatty acid (FA) release from peripheral storage tissues (i.e., adipose tissue), attempting to provide an alternative energy substrate. However, as the disease progresses FAs fail to be utilized efficiently as an energy substrate, they are stored ectopically, and this prevents the compensatory mechanism of increased insulin production [13]. Moreover, associated with T2D are increased markers of chronic low-grade systemic inflammation as well as an altered gut microbiome and multi-organ pathologies [14,15].

Pioneering work by Claude Bernard in the 19th Century linked the brain to systemic glucose homeostasis in which a needle was used to stimulate a region of the brain in dogs, inducing a temporary diabetic state in the animal [16]. In the 1960s, insulin was found to be present in the Central Nervous System (CNS), and rather than being only of pancreatic origin, it was hypothesized and confirmed that the brain can synthesize its own insulin [17,18]. Insulin receptors were also found on neurons in many brain regions, with the highest density in the olfactory bulb and hypothalamus [19,20]. Functional insulin signaling in the brain via the PI3K/Akt and Ras/Raf/MAP pathways is metabolically protective, neuroprotective, and has a positive effect on neuroplasticity [21]. Disruption of insulin action in the brain alters neural and glial cell function at the synaptic level [22,23] and is associated with neurodegenerative and cognitive disorders as well as psychiatric diseases [24–26]. Experimentally, the selective disruption of insulin receptors in the brain also leads to reversible diet-induced obesity and peripheral insulin resistance [27–30]. Multiple studies have also reported an evident link between insulin-resistant peripheral tissues and the CNS (e.g., gut–brain axis, liver–brain axis, and central leptin resistance) [31,32]. Such phenomena are gaining attention for potential roles in systemic insulin resistance that is developed in obesity and T2D [32,33].

In this review we discuss how metabolic disturbance, in the form of diabetes, affects neurological functions with a focus on energy balance and neurotransmission. Neurotransmitters are a class of communication molecules that ensure normal nervous system function, interacting systemically and with various tissue microenvironments. Reviewed below are the ways in which neurotransmitters and neurological functions are affected in metabolic disease. To our knowledge, no recent in-depth reviews have addressed how systemic dysmetabolism mechanistically alters neurotransmission and the ways this contributes to increased risk of neurodegenerative diseases in patients with diabetes.

2. Type 2 Diabetes and Neurological Complications

Several longitudinal studies show that patients with diabetes are more susceptible to cognitive impairment [34–36]. Altered brain function and metabolism is associated with insulin resistance and with vascular complications, dyslipidemia, and hypertension, which are all common in T2D [37,38]. A population-based study also showed that older patients with diabetes had higher risk of developing Alzheimer's disease (AD), linking diabetes to age-related neurodegeneration [39]. From the above studies and other mechanistic investigations, it is clear that impairment of glucose metabolism in the context of diabetes is a key element in the onset and progression of AD [40,41]. In cases of hyperglycemia, reactive oxygen species (ROS) production is elevated through stimulation of the polyol pathway. This leads to formation of advanced glycation end products (AGE) and causes considerable oxidative stress [42]. Accumulation of AGEs contributes to the pathological aspects of neurodegenerative diseases including AD, Parkinson's, and Huntington's diseases [43]. Kong et al., investigated the role of AGEs in AD and diabetes in vivo and found that mice injected with AGEs exhibited symptoms of AD with impaired memory and increased levels of amyloid precursor proteins (APPs) and tau [44]. Another study also highlighted that AGE receptor (RAGE) contributes to the decrease in locomotor activity and spatial memory in streptozotocin (STZ)-induced hyperglycemia in mice [45]. Another mechanism that links diabetes to cognitive decline is inflammation. It is well-established that diabetes and its complications and comorbidities occur on a background of low-grade chronic inflam-

mation, which participate in neurodegenerative processes that impair cognition, synaptic plasticity, and neurotransmission [38,46]. In particular, decline in executive functions and psychomotor speed in patients with T2D are associated with alterations in neurotransmitter release, neuronal dysfunction, and neurodegenerative damage [47].

3. Neurotransmitters

Neurotransmitters are a massive family of chemical messengers (>100 known neurotransmitters) involved in synaptic transmission; they regulate physiological functions in the central and peripheral nervous system [48]. They can be classified based on their physiological functions (excitatory or inhibitory), mode of action, molecular structure, or chemical group (Table 1) [49]. Neurotransmitters are generally stored in vesicles at the axon terminal of presynaptic neurons and can be released in response to action potentials, a rapid rise and fall in voltage, or membrane potential across the cellular membrane. Once released, they diffuse across the synaptic cleft to act on receptors on postsynaptic neurons to exert their effects (Figure 1A) [50]. This process creates neuronal circuits that facilitate communication between neurons through chemical synapses. Abnormal neurotransmitter levels reflect dysregulation of brain functions that manifest as physical, psychologic, and neurodegenerative diseases [51–55].

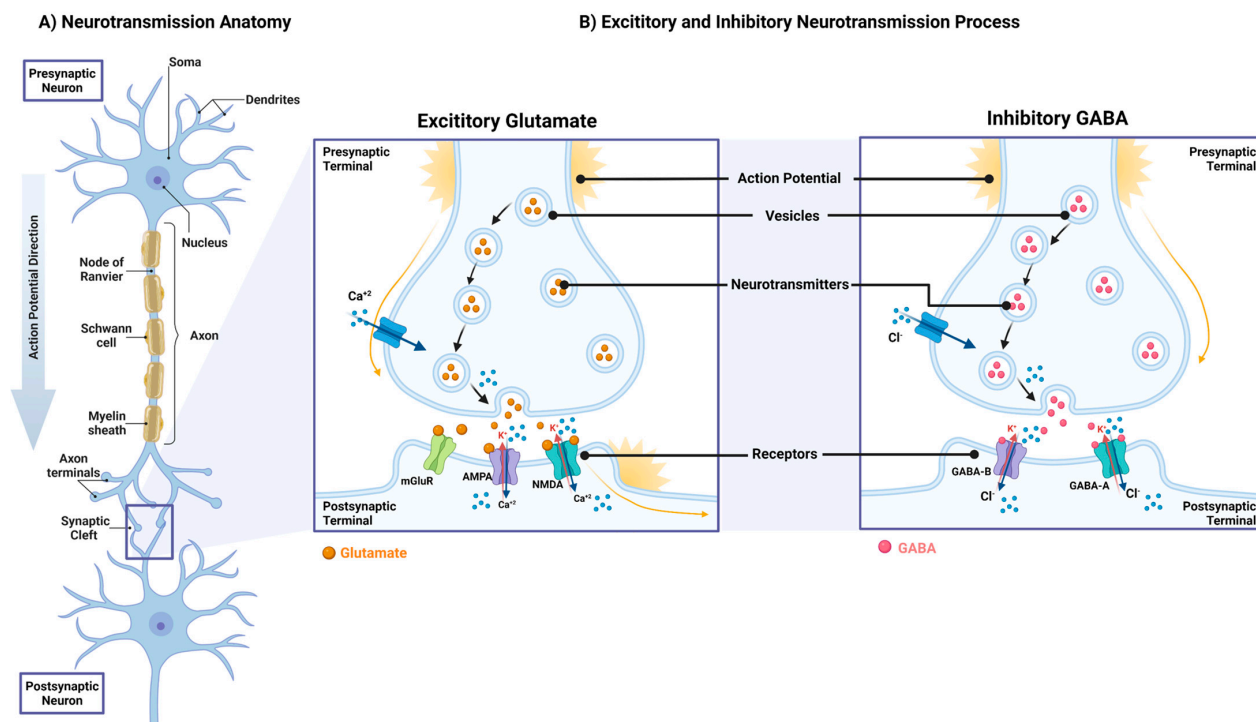


Figure 1. Neurotransmission anatomy and process. (A) Neurotransmission anatomy: An action potential moves along the axon of the presynaptic neuron to interact with the dendrites of the postsynaptic neuron creating a synaptic cleft in which the neurotransmission process occurs. (B) Excitatory and inhibitory neurotransmission process: Neurotransmitters are stored in vesicles in the presynaptic terminal and are released upon the receipt of an action potential that triggers the release of different ions (i.e., Ca^{2+} , Cl^- , K^+) and neurotransmitters (i.e., excitatory glutamate and inhibitory GABA) which activates different receptors depending on the synaptic activity. Abbreviations: Ca^{2+} : calcium ions; K^+ : potassium ions; mGluR: metabotropic glutamate receptor; AMPA: α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; NMDA: N-methyl-D-aspartate receptor; Cl^- : Chloride ions; GABA_A and GABA_B: γ -Aminobutyric acid receptors (A,B), respectively. Created with [BioRender.com](https://www.biorender.com).

Glutamate, Gamma-aminobutyric acid (GABA), dopamine, serotonin, norepinephrine, and acetylcholine are of clinical relevance and are the most studied neurotransmitters. Most of the synaptic activity and intracellular signaling in the brain is accounted for by

glutamate (excitatory) and GABA (inhibitory) [56]. Healthy function of neurotransmission requires a balance between excitatory and inhibitory (E/I) signals that is crucial for proper neuronal firing and synaptic transmission. This is mediated by glutamate through the activation of the ionotropic receptors N-methyl-D-aspartate (NMDA), α -amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), and the metabotropic glutamate receptors (mGluRs); and by GABA through GABA_A and GABA_B receptors (Figure 1B). Appropriate activation of these receptors ensures that the right neuronal excitability level is translated to different brain regions [57]. Thus, a balanced interaction between glutamate and GABA ensures physiological homeostasis, and alterations in E/I balance leads to disorders such as epilepsy and AD [58–60]. A similar concept also applies to the development of other chronic conditions such as Parkinson’s (acetylcholine/dopamine) and Huntington’s (glutamate/dopamine) diseases [61,62].

Table 1. Neurotransmitter classification by chemical group.

| Category | Neurotransmitter | Function |
|----------------|--------------------------------|--|
| Amino Acids | Gamma-aminobutyric acid (GABA) | Learning, memory, locomotion, metabolism mediators, appetite regulation [63,64] |
| | Glutamate (Glu) | Memory, learning, cognition, appetite regulation [48,64] |
| | Glycine (Gly) | Motor control, sensory and auditory processing, cardiovascular, and respiratory functions [65] |
| Amines | Dopamine (DA) | Motivation, memory, attention, locomotion control [66] |
| | Norepinephrine (NE) | Emotional arousal, regulating blood pressure, mood, appetite [49] |
| | Epinephrine | Boosts oxygen and glucose supply to brain and muscles, increases awareness [48] |
| | Serotonin (5-HT) | Regulate sleep–wake cycle, mood, appetite and digestion [65] |
| | Histamine | Regulate sleep–wake cycle, stress response, appetite and memory [67] |
| Acetyl Choline | Acetylcholine (Ach) | Cognition, learning, memory, modulation of electrical, and mechanical functions of the heart [51,68] |
| Other | Nitric Oxide (NO) | Learning, memory, homeostatic functions [69] |
| | Hydrogen Sulfide (HS) | Neuromodulator, smooth muscle relaxation [48] |
| | Purines (ATP) | Controls intracellular energy homeostasis, autonomic control, sensory transduction [70,71] |

Neurotransmission also occurs through electrical synapses that contain intercellular aggregate channels known as gap junctions (GJs) allowing electrical and metabolic communication between adjacent neurons. GJs are formed by hemichannels from each side of the synapse which are composed of transmembrane proteins called connexins that allow the transfer of ions and small molecules between neurons [72,73]. Cx36 is the most abundant connexin type in neurons and it forms most of the electrical synapses in the CNS [74]. Connexin GJs play a homeostatic role in CNS physiology. This includes synaptogenesis, neuronal differentiation and circuit formation and maturation [73]. GJs also regulate neural activity oscillations (i.e., maintaining a synchronized excitatory and inhibitory electrical activity) that allow robust communication between neuronal assemblies. Alterations in connexin GJ activities can impact their expression and function leading to the progression of neurodegenerative diseases, including AD and Parkinson’s disease and epilepsy [75–78].

4. Effect of Metabolic Dysregulation on Neurotransmitters Functions

T2D often exists with other factors that disrupt homeostasis and worsen metabolic dysregulation. For example, obesity is the result of chronic energy imbalance and is associated with low-grade chronic inflammation that strongly influences the diabetic state and susceptibility to complications and comorbidities, such as cardiovascular or liver disease [37,79]. Recent evidence suggests that cognitive impairment and dementia are

emerging complications of T2D and obesity, and that this outcome is associated with alterations in neurotransmitter homeostasis and synaptic activity [80–82]. Peripherally, glutotoxicity has been reported to increase glutamate levels, inducing β -cell dysfunction and neuronal injury through the activation of pancreatic NMDA receptors; and blocking these receptors improved β -cell function in vitro and in vivo [83]. D’Almeida and colleagues reported that metabolic alterations in T2D dysregulate the E/I balance between glutamate and GABA causing cognitive impairment [84]. Changes in amino acid neurotransmitter homeostasis was also observed in obese and diabetic rats as a result of impaired brain glucose metabolism [81]. Furthermore, hyperglycemic conditions lead to GJ impairment that disrupts astrocyte–neuron communication leading to changes in brain function [85]. Head et al. reported that loss of Cx36 GJs disrupted glucose homeostasis through the alteration of oscillating insulin levels in mice [86]. This was further confirmed in patients with diabetes, as they exhibited disruption in Cx36 GJ permeability and Ca^{2+} electrical activity. Treatment with Modafinil restored Cx36 GJ function, maintained cell viability, and protected against β -cell dysfunction [87].

In obesity, excessive intake of macronutrients such as carbohydrates and fats lead to failure in homeostatic mechanisms that are involved in regulating energy balance, especially in the hypothalamus [88]. Exposure to obesogenic diets leads to early hypothalamic alterations indicating a causal role of central dysregulation in the onset of obesity [37]. Functional dysregulation of neurotransmitters such as dopamine disrupts the hypothalamic circuitry controlling satiety, leading to uncontrolled weight gain [89,90]. These studies highlighted that hyperglycemia and/or dyslipidemia significantly impact hypothalamic neurotransmitter function and the neurotransmission process, affecting systemic energy balance and metabolism.

5. Role of The Hypothalamus in Controlling Energy Balance

Located in the base of the brain, the hypothalamus plays an essential role in regulating energy balance through the integration of neural circuits and humoral factors (e.g., hormones) in response to food intake and energy expenditure [91]. It consists of several nuclei with different functions that communicate systemically with one another through neurotransmitters and neuropeptides (Table 2, Figure 2) [92]. In particular, the Arcuate Nucleus (ARN) is a major contributor in regulating food intake and energy expenditure via its two key neuronal subpopulations: orexigenic neuropeptide Y (NPY)/agouti-related protein (AgRP)-expressing neurons and the anorexigenic proopiomelanocortin (POMC)/cocaine and amphetamine-regulated transcript (CART)-expressing neurons. The NPY/AgRP and POMC/CART-expressing neurons control energy balance by promoting and suppressing appetite, respectively [92]. Successful function of the hypothalamus is dependent on two major factors, locally efficient neurotransmission, and the integration of systemic signals.

Table 2. Hypothalamus nuclei associated with controlling energy homeostasis [93].

| Nuclei | Function |
|---------------------------------|---|
| Arcuate Nucleus (ARN) | Regulates energy balance by sensing alterations in hormonal and nutritional factors in the blood stream |
| Paraventricular Nucleus (PVN) | Maintains whole body energy homeostasis through the regulation of food intake by neuropeptides |
| Dorsal Medial Nucleus (DMN) | Controls physiological processes and circadian rhythms |
| Lateral Hypothalamus Area (LHA) | Mediate orexigenic, behavioral, and physiological responses |
| Ventromedial Nucleus (VMN) | Regulates energy balance and thermogenesis |

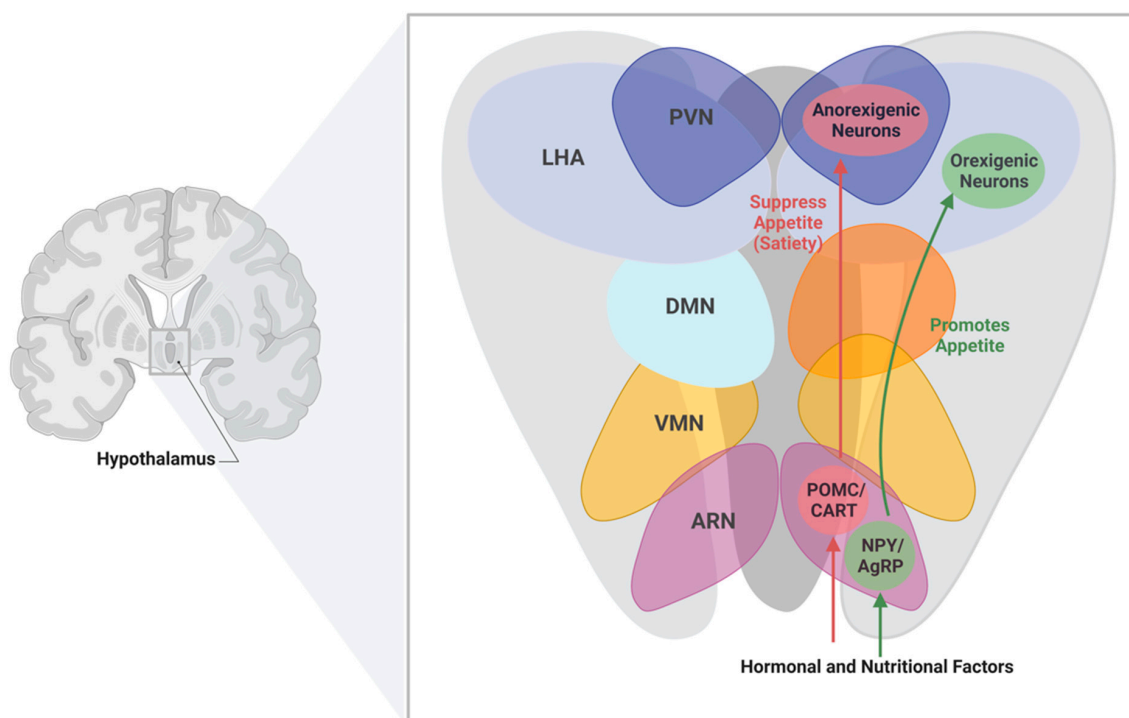


Figure 2. Hypothalamus nuclei associated with controlling energy homeostasis. Schematic representation of the frontal brain section indicating the location of the hypothalamus and the hypothalamic nuclei associated with energy homeostasis. Depending on the signals from the hormonal and nutritional factors, the neuronal connectivity can either suppress or promote appetite through POMC/CART or NPY/AgRP neurons in the ARN, respectively. Abbreviations: PVN: paraventricular nucleus; LHA: lateral hypothalamic area; DMN: dorsal medial nucleus; VMN: ventromedial nucleus; ARN: arcuate nucleus; POMC/CART: proopiomelanocortin/cocaine and amphetamine-regulated transcript; NPY/AgRP: neuropeptide Y/agouti-related protein. Created with BioRender.com.

5.1. Hypothalamic Neurotransmitters

As the hypothalamus undergoes rapid changes in circuit connectivity and function, it is important to sustain a balanced neurotransmission process between the hypothalamic neurons to maintain appropriate behavior and endocrine functions [94]. The hypothalamus is considered a primary site for appetite regulation in which orexigenic neurons (NPY/AgRP) and anorexigenic neurons (POMC/CART) regulate appetite. Amino acid neurotransmitters glutamate and GABA account for most of the synaptic activity in the hypothalamus [64]. As such, glutamatergic and GABAergic phenotypic markers, for example VGLUT2, have been reported in POMC+ neurons; glutamatergic innervation has also been reported in NPY+ and POMC+ neurons in the ARN [95,96]. These studies indicate the presence of a dense plexus of glutamatergic fibers in the hypothalamus. Interestingly, studies have also demonstrated that POMC+ neurons exhibit a level of plasticity in their expression of glutamatergic and GABAergic markers. Such plasticity promotes restoration of energy homeostasis in models of genetic interference [97]. Moreover, Trotta et al. reported that GABAergic-POMC neurons regulate food intake and energy balance through the DMN-NPY pathway *in vivo* [98], and several other studies have shown that GABA signaling is required in AgRP+ neurons to stimulate and maintain feeding behavior. However, the role of GABA release from POMC neurons remains unclear [99–101]. These studies indicate that the synaptic release of amino acid neurotransmitters by the hypothalamic ARN neurons has a significant role in modulating energy balance.

Monoamines, such as dopamine and serotonin, also play a role in appetite regulation. A study by Zhang et al. described the role of novel tyrosine hydroxylase (TH)-expressing neurons in the ARN and found that light-mediated optogenetic stimulation resulted in

dopamine release [102]. This increases food intake by inhibiting POMC+ neurons and stimulating NPY/AgRP+ neurons [102]. Dopamine secretion initiates feeding patterns (i.e., meal size, frequency, and duration) and regulates food intake in the VMN and LHA [103]. To balance this, serotonin is released in the LHA during enhanced feeding, promoting satiety [103]. Few studies have investigated the role of acetylcholine in the hypothalamus. Jeong et al. found that increased DMN cholinergic neuronal activity regulated food intake through ARC POMC neurons in vivo [104]. Others suggest acetylcholine modulates appetite suppression, and under fasting conditions, elevated cholinergic activity is observed in hypothalamic regions due to the anticipation of food intake [105,106].

5.2. Central Melanocortin System

The central melanocortin system is one of the most important systems in the regulation of appetite and energy homeostasis. It consists of neurons that produce endogenous melanocortins (melanocortin neurons) and the downstream neurons that express melanocortin receptors. Melanocortin neurons are POMC and AgRP neurons [107]. POMC is a preprohormone that undergoes post-translational processing (proteolytic cleavage) to produce the melanocyte stimulating hormone (MSH— α , β and γ). These peptides can bind to and activate the melanocortin receptors (MCRs). MCRs belong to the G protein-coupled receptor (GPCRs) family and five members have been characterized to date (MC1R to MC5R). These receptors were shown to be expressed in several tissues and therefore have distinct physiological functions [108]. MC1R is mainly expressed in the skin and hair follicles and are known to regulate melanogenesis; MC2R is expressed in the adrenal cortex and is considered the classical ACTH receptor; MC3R and MC4R are neural receptors as they are present at high levels in the CNS and they play a role in mediating energy homeostasis; and MC5R has a broad tissue distribution especially in exocrine glands [109]. A unique aspect about MCRs compared with other GPCRs is the existence of the endogenous antagonist AgRP which can bind to the receptors to prevent the binding of MSH [110]. Interestingly and despite being originally classified as a competitive antagonist, AgRP was later shown to have the capacity to activate different signaling pathways downstream MCRs and act as a biased agonist [111].

Similar to other members in the GPCRs family, the central melanocortin receptors can activate several signaling pathways. These receptors can couple to the three main heterotrimeric G proteins, Gs, Gi, and Gq [112]. Coupling to the stimulatory G protein subunit (Gs) can activate Adenylyl Cyclase (AC) resulting in the release of Cyclic Adenosine Monophosphate (cAMP) and activation of Protein kinase A (PKA). Coupling to Gi on the other hand leads to inhibiting AC. Studies have also showed that these receptors can couple to Gq which results in the activation Phospholipase C (PLC) leading to the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP2) into diacylglycerol (DAG) and inositol-1,4,5-trisphosphate (IP3). IP3 leads to the secretion of Ca^{2+} from intracellular stores while DAG activates PKC [113,114]. In addition to these G protein-dependent signaling pathways, many studies have presented evidence on the activation of a number of kinases by MC3R and MC4R including extracellular signal-regulated kinases 1/2 (ERK1/2), c-Jun N-terminal kinases (JNK), 5'AMP-activated protein kinase (AMPK), and protein kinase B (PKB or AKT) [111,114–119].

MC3R and MC4R were shown to play an important role in the regulation of glucose homeostasis and insulin sensitivity. This was first confirmed from knockout animal models that displayed elevated insulin levels and reduced insulin sensitivity in addition to the hyperphagia and obesity [120,121]. Studies also reported that treatment with the melanocortin agonists or antagonists can directly mediate insulin action [122,123]. Furthermore, patients with mutations in the MC4R gene were characterized by severe hyperinsulinemia [124]. A study also reported an increased risk of developing T2D in children and adults carrying a mutation in MC4R and this was independent of Body Mass Index (BMI) in children only [125]. However, a meta-analysis on more than 100,000 adults confirmed the significant association between MC4R rs17782313 polymorphism and increased T2D risk and this

association was independent of BMI [126]. Furthermore, the central melanocortin system was shown to directly control the peripheral lipid metabolism [127]. Specifically, using an antagonist against hypothalamic melanocortin receptors resulted in an increase in energy stores by affecting several peripheral tissues. For example, in the liver, increased triglycerides and lipoprotein synthesis and secretion was observed, in addition to decreased thermogenesis and glucose uptake in the brown adipose tissue as well as in muscles. Blocking neural MCRs also increased triglycerides synthesis as well as glucose uptake and insulin sensitivity in white adipose tissue [127]. It is also worth noting that pituitary MSH plays a role in promoting glucose uptake in the muscle; however, it was found that this effect is mediated by peripheral MC5R [128].

There is a significant association between the activity of the central melanocortin system and neurodegenerative changes [129]. Studies have shown that treatment with MC4R agonists has neuroprotective effects in cerebral ischemia [130] and in the progression of AD [131,132]. MC4R activation seems to have anti-inflammatory and anti-apoptotic effects that can help reduce DNA damage, decrease neuronal loss, and reduce hippocampal injuries. It has also been suggested that melanocortins can counteract the cognitive decline in AD and other neurodegenerative disorders by reducing the level of β -amyloid peptides in the cerebral cortex and hippocampus [132]. It was also suggested that melanocortins can target multiple pathophysiological pathways up- and downstream β -amyloid and tau causing an increase in synaptic transmission and plasticity [131]. Preclinical studies in animal models generated very promising data; as treatment with MC4R agonists such as α -MSH and melanotan-II reduced food consumption and improved insulin and glucose levels [122,123,127,133]. On the contrary, when antagonists such as AgRP or SHU9119 were used, an increase in appetite and body weight was observed leading to insulin resistance [133].

Establishing a role of the melanocortin system in regulating energy homeostasis and glucose metabolism created great interest in utilizing these functions in pharmacological applications. Several ligands were developed, and some compounds reached phase I and II clinical trials. The beneficial effects varied from reduction in appetite and weight loss to improvement in glucose metabolism [134]. However, the progress was halted due to some undesirable side effects including elevated heart rate and blood pressure. Recently, a highly selective MC4R agonist called Setmelanotide was approved by the Food and Drug Administration (FDA) for the treatment of monogenic obesity [135]. Setmelanotide did not cause any cardiovascular side effects; instead it was reported that it can reduce blood pressure and improve glucose homeostasis [136,137]. It would be important to investigate the possibility of re-purposing such approved drugs or use them to design melanocortin analogs for the treatment of T2D and metabolic disorders. Combination therapy is also becoming a viable option considering the complexity of the metabolic syndrome. In fact, a study reported that co-administration of Setmelanotide with the GLP-1 receptor agonist (liraglutide) in diet-induced obese mice was more effective than monotherapy in increasing insulin sensitivity, decreasing fat mass, and improving energy expenditure [138].

6. Regulating CNS Energetic Demands

6.1. Energy Metabolism in the Brain

The ability of the human brain to carry out complex behaviors, make decisions, and process social and emotional contexts comes with a high energy demand [139]. While it covers 2% of total body weight; the brain accounts for 20% of the body's resting metabolic rate and consumes 25% of the body's glucose [140]. The brain's own energy metabolism, or neuroenergetics, is maintained by the vascular supply of oxygen and glucose and adapts for localized neural activity [141,142]. It was reported that during synaptic transmission and ion influx regulation, a single resting neuron uses about 4.7×10^9 Adenosine 5'-triphosphate (ATP) molecules per second, indicating the staggering amount of neuronal energy usage for these processes [143].

6.2. Energy Substrates: Glucose, Ketone Bodies and Lactate

In the adult brain, glucose is considered as the main energy substrate entirely oxidized to CO₂ and H₂O via glycolysis. The tricarboxylic acid (TCA) cycle and oxidative phosphorylation also produce ATP for energy-dependent reactions similar to other tissues [144]. Glucose transporters (GLUTs) are expressed in different parts of the CNS and allow neuronal glucose uptake from the circulation (Table 3). Glucose is imported to the cytoplasm of the cell and converted to pyruvate via glycolysis [62,65]. Under anaerobic conditions, pyruvate is converted into lactate and released to the extracellular space [145]. Lactate is considered a by-product that can dysregulate brain function if present in excessive amounts [146,147]. However, in contexts demonstrated by in vitro modelling, lactate appears to be used as an alternative substrate to sustain synaptic plasticity and neuroprotection functions during tissue development [148]. In adults, lactate has been reported to cover up to 10% of the brain's energy requirement under steady state, leaving glucose as the main substrate [140].

Ketone bodies can also act as an energy substrate, especially in the case of diabetes or under conditions of starvation or fasting when glucose levels are low [144,149]. Physiologically, ketone bodies are generated in the liver when metabolism switches from carbohydrates to fats. Such conditions can be induced by a ketogenic diet (KD), which is a high fat and low carbohydrate diet [150]. Once ketone bodies cross the Blood–Brain Barrier (BBB), they enhance mitochondrial function, ATP generation, synaptic plasticity, and the myelination process at the early stages of brain development, making them a potential therapeutic target for neurodegenerative diseases [144,150]. Administering KD in patients with AD showed significant improvements in cognitive and executive functions [151]. Likewise, patients with Parkinson's also had enhanced non-motor functions and cognition [152]. Furthermore, studies demonstrated that ketone bodies can reduce glutamate excitatory neurotransmission effect and the firing rates of neurons by opening potassium ATP channels and activating GABA receptors providing a therapeutic mechanism for AD and epilepsy [153,154]. Hypometabolism is often accelerated in the context of insulin resistance which destabilizes the brain network, triggering diabetes-induced dementia [150,155]. Some studies have highlight the role of KD in improving insulin sensitivity and glycemic control [150,156]. Paradoxically, patients with diabetes are more prone to diabetic ketoacidosis, which can lead to comas or death. Diabetic ketoacidosis occurs when the body does not have enough insulin to trigger the use of glucose, lipids are then used to compensate, resulting in production of ketones and their build up in blood. Despite potential benefits of ketone bodies in neurodegenerative disease, prolonged exposure to them in the hypothalamus can further dysregulate insulin secretion and energy homeostasis, leading to hyperphagia and obesity [157,158].

Table 3. Glucose transporters (GLUTs) functions in the brain [159,160].

| Glucose Transporter | Function |
|---------------------|--|
| Glut1 | Maintaining glucose transportation into the CNS via BBB |
| Glut3 | Highly distributed in the brain and expressed in neurophil synapses activities |
| Glut4 | Regulating insulin signaling in the CNS |
| Glut8 | Supporting neuron cells glucose requirements |

6.3. Cell-Type Specific Mechanisms

At a cellular level of the CNS, glial cells (astrocytes, oligodendrocytes, and microglia) outnumber neurons by a factor of 10. Astrocytes alone account for almost 50% of total brain volume [145]. These cells play a role in regulating neurotransmitter release, developing synaptic junctions and controlling brain energy metabolism [161]. They express neurotransmitter receptors that enable them to detect synaptic activity and provide energy substrates to active neurons. This is achieved by astrocytes surrounding brain capillaries to

form a barrier for the uptake and distribution of substrates such as glucose [144]. Studies demonstrate that astrocytes exhibit high rates of glucose metabolism, as they are also the only brain cells capable of storing glycogen. A current leading hypothesis for maintaining activity in situations of low glucose and high neural firing is the formation of the astrocyte–neuron lactate shuttle (ANLS). The ANLS is formed when astrocytes sense increased neural activity from the release of glutamate at the synapse. This triggers glycolysis to produce lactate as a neuronal energy substrate (Figure 3) [147,162,163]. Furthermore, studies have reported the importance of the ANLS in long-term memory formation; and dysregulation of the lactate it supplies contributes to hypoxia-induced neurodegeneration and can also lead to stroke [164–166].

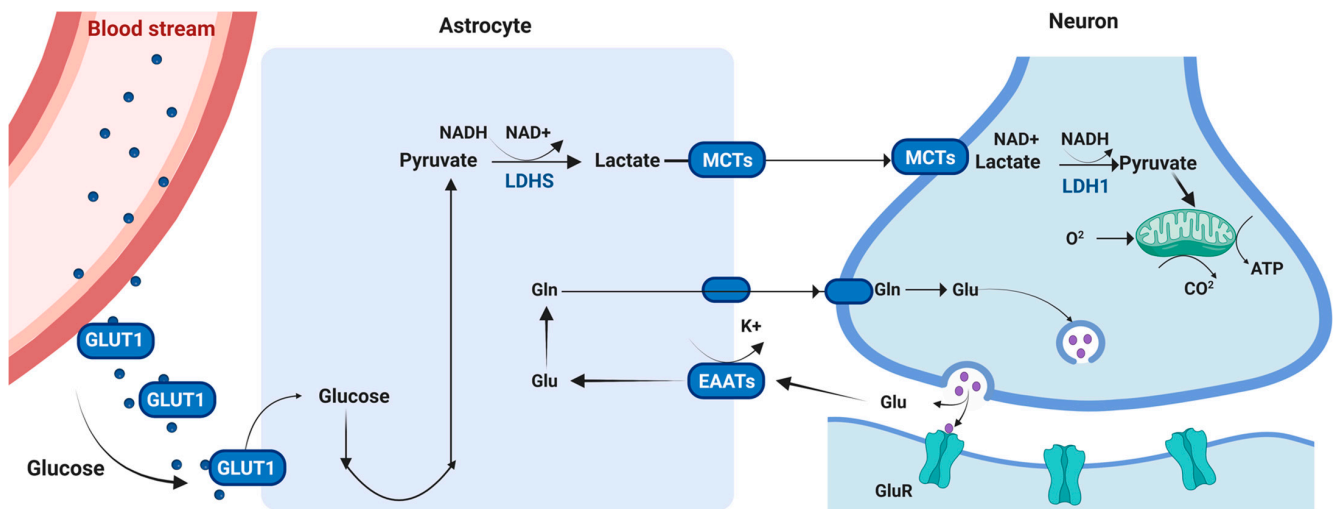


Figure 3. Astrocyte–Neuron Lactate Shuttle (ANLS) Formation. The ANLS is formed during an increase in neuronal energy demand. Astrocytes sense an increase in the glutamatergic excitatory pathway in the neuron and trigger glycolysis by up-taking glucose from the blood stream and converting it into lactate. Lactate is then transported to the neuron through MCTs in which is converted back into pyruvate and then shuttled into the mitochondria as a source of additional energy. Abbreviations: Glut1: glucose transporter protein 1; NADH: nicotinamide adenine dinucleotide with hydrogen; NAD: nicotinamide adenine dinucleotide; LDH: lactate dehydrogenase; MCTs: monocarboxylate transporters; ATP: adenosine 5'-triphosphate; Glu: glutamate; Gln: glutamine; EAATs: excitatory amino acid transporters; GluR: glutamatergic receptor. Created with BioRender.com.

6.4. Neuronal Bioenergetics and the Regulation of Neurotransmission

Dysregulation of neuronal bioenergetics significantly impacts synaptic transmission and brain function, facilitating the progression of neurodegenerative disorders [143,167]. Because neurons are highly polarized, continuous ATP generation is required to restore action potential events that maintain synaptic transmission which lead to neurotransmitter release [168]. In addition to ATP generation, mitochondria are essential for maintaining neuronal functions and survival by regulating processes such as amino acid synthesis, Ca^{2+} homeostasis, and apoptosis [143]. Thus, perturbed mitochondrial function leads to dysregulation of neuronal bioenergetics.

The actions of the main excitatory neurotransmitter, glutamate, depend on mitochondrial oxidative phosphorylation for a maintained transport process across plasma, vesicular, and mitochondrial membranes [169]. Mitochondrial failure results in a dramatic increase in glutamate release into the synaptic cleft with a 100-fold increase in its concentration leading to excitotoxicity [170]. Furthermore, in the case of diseases such as Parkinson's, alteration in dopaminergic neuron function has been linked to impaired mitochondrial bioenergetics since neurons increase energy demands and oxidative stress [171]. It has also been reported in AD that mitochondrial Ca^{2+} accumulation activates pyruvate dehydrogenase-(PDH)

kinase and inhibits the PDH complex (PDHC). This leads to insufficient acetyl-CoA production in the cerebral cortex and hippocampus, disrupting acetylcholine synthesis [172].

Oxidative damage and mitochondrial dysfunction are key pathological processes that mediate neurodegeneration in diabetes. Abnormalities in mitochondrial function, structure, and connectivity can impact behavior and contribute to obesity [173]. Moreira et al. showed that mice under HFD exhibited reduced ATP production, altered mitochondrial dynamics and fragmentation in the hippocampus [174]. HFD also led to deficits in electron transport chain function and in oxidative phosphorylation, with reduced expression of mitochondria associated proteins such as PGC-1 α and the mitochondrial transcription factor A (TFAM) *in vivo* [175]. Moreover, the link between insulin resistance and behavioral disorders such as anxiety and depression are associated with dysregulation of mitochondrial function and monoamine neurotransmitter homeostasis. This was demonstrated in neuron-specific insulin receptor knock-out mice that had elevated dopamine clearance and reduced mitochondrial oxidative activity [26]. Another study induced a diabetes-like phenotype in MitoPark a mouse model, which exhibits a Parkinsonian phenotype and mitochondrial dysfunction in dopamine neurons. This was observed *in vivo* and similar results were observed *ex vivo*, collectively indicating that mitochondrial dysfunction is associated with the progression of Parkinson's disease in the context of diabetes [176].

7. Metabolic Factors Affecting Neurotransmission

7.1. Glucose Metabolism

Since glucose is the main energy substrate for the brain, disturbance in its metabolic and signaling pathways can affect its utilization and energy supply to the brain. Glucose transporters play an essential role in maintaining neuronal homeostasis; and their presence in different parts of the brain can be influenced by the organism's diabetic status (Table 3) [159,160,177]. For example, Bussel et al. conducted an observational study and found that patients with T2D exhibited altered GABAergic neurotransmission and this was associated with lower cognitive function compared with patients without diabetes [178]. A study in a rodent model of T2D investigated the role of glycogen in supporting glutamate/GABA homeostasis *in vivo*; since glycogen can be used as a buffer to maintain glucose levels in the brain, use of a glycogen phosphorylase inhibitor reduced glutamate levels and increased GABA levels, disrupting neurotransmitter release [179]. Furthermore, results from another clinical study suggested that patients with diabetes had episodic memory decline which was significantly associated with abnormal amino acid neurotransmitter concentrations in the brain [180].

The dopaminergic system is also important in maintaining glucose metabolism as its activation leads to improved glucose tolerance and insulin sensitivity [181]. In the diabetic state, dysfunctional dopamine neurotransmission causes motor impairment and neurodegenerative damage [46]. Studies have also revealed that culturing dopaminergic PC12 (cells that exhibit mature features of dopaminergic neurons) under high glucose conditions lead to increased levels of reactive oxygen species (ROS) and apoptosis. This is attenuated when treating the dopaminergic neurons with the polyphenol compound resveratrol [182,183]. Diabetes also alters other monoamines in specific brain regions [184]. For example, under hyperglycemic conditions, serotonin neurotransmission is altered and decreased in the hippocampus of mice fed a high-fat diet, and this was associated with symptoms of behavioral and eating disorders [185]. Moreover, administering serotonin *in vivo* had a significant effect in improving glucose tolerance and utilization [186]. Another study also showed that imbalance in cholinergic neurotransmission led to cerebellar dysfunction in diabetic rats [187,188]. Further, low expression levels of nicotinic acetylcholine receptors (nAChRs) induced neuronal apoptosis in the hippocampus of diabetic mice and patients that resulted in impaired cognition [187,188].

7.2. Glycemic Variability

Glucose is critical for normal brain metabolism. Uncontrolled fluctuations in blood glucose levels stimulate ROS overproduction which makes patients with T2D more susceptible to microvascular complications [189]. Recent evidence suggests that fluctuation in glycemic peaks is associated with impairment in cognitive function [190,191]. A population-based study confirms this further, 5% of the study's cohort were diagnosed with AD and this was mainly dependent on age and the duration of diabetes [192]. Quincozes-Santos et al. showed that fluctuations in glucose levels affected astrocyte function in maintaining cell proliferation and glutamatergic metabolism, inducing cytotoxicity [193]. Another study evaluated the effect of fluctuating glycemic peaks on E/I balance in T2D patients and found significant changes in glutamate–GABA neurotransmission which contributes to the pathophysiology of T2D [84].

7.3. Insulin Signaling

Insulin plays a crucial role in controlling blood glucose levels by facilitating cellular glucose uptake in peripheral tissues. Disturbed insulin signaling in the brain may accelerate aging, affect synaptic plasticity, and promote neurodegeneration [194]. Previous studies have reported that insulin receptors are present in different brain regions and that it is synthesized in the central nervous system with a distinct role in glucose metabolism and neuromodulation [20,195]. Decreased PI3K levels were observed in the AD brain. The PI3K-AKT pathway facilitates glucose uptake upon activation by insulin and intranasal insulin administration was found to enhance memory and cognition in vivo [196]. Reduced acetylcholine in the brain also leads to cognitive impairment in AD, and abnormalities in insulin growth factor 1 (IGF-1), gene expression results in reductions in energy metabolism and acetylcholine transferase expression which in turn increases the severity of neurodegeneration [197]. Another study also supported this concept and found that impairment of acetylcholine synthesis is due to dysregulation of insulin secretion, whereas enhanced insulin levels reverse memory loss and cognitive impairment and are associated with elevated acetylcholine concentration in the brain [198]. Moreover, Duarte et al. stated that insulin acts as a modulator of the amino acid neurotransmitters GABA and glutamate which is another reflection of its neuroprotective functions [199]. In addition, emerging evidence has been reviewed to show that the modulatory effect of insulin on GABA/glutamate is important for long-term memory consolidation, whilst deterioration of insulin signaling leads to degenerative disorders, especially in aging patients with diabetes [200].

7.4. Lipid Metabolism

Around 50% of the brain's dry weight is composed of lipids making it the second organ with highest lipid content after adipose tissue under physiological conditions. Compared with adipose tissue that acts as a long-term energy store for converting FAs to triglycerides for subsequent utilization by other tissues; the brain utilizes acylated lipids primarily to generate phospholipids for cell membranes [201]. The composition of FAs varies in the brain and neural tissue and is mainly rich with polyunsaturated FAs (PUFAs) such as arachidonic acid (AA), eicosatetraenoic acid, and docosahexaenoic acid (DHA) that are critical for maintaining the nervous system's normal function [201]. FAs can cross the BBB and be up taken by neurons and astrocytes via FA transporters such as Fatty Acid Transport Protein 1 (FATP1), Fatty Acid Transport Protein 4 (FATP4), and Cluster of Differentiation (CD)-36 [202]. Once released from the membrane, FAs are converted to a variety of bioactive mediators that enable them to participate in signal transduction [203]. Studies have showed that reduced BBB expression of Fatty Acid Binding Protein 5 (FABP5) led to lower DHA trafficking in AD, while mice lacking Fatty Acid Binding Protein 7 (FABP7) exhibited schizophrenic phenotypic traits [204,205]. This supports the fact that lipids/PUFAs play a role in regulating several brain functions, including neurotransmission, cell survival, and neuroinflammation; and dysregulation of such processes leads to various neurological disorders [203]. Literature on the effect of dietary lipids on neurotransmission

processes is limited. Sandoval-Salazar et al. investigated the effect of high-fat diet on GABA levels in the frontal cortex (FC) of the rat's hippocampus and found that high-fat diet significantly decreased GABA levels, disrupting the GABAergic inhibitory effect and role in appetite regulation [206]. In addition, Lizarbe and colleagues observed a strong switch from glutamatergic to GABAergic neurotransmission in the hypothalamus of high-fat diet-fed mice that disrupted the balance between orexigenic and anorexigenic networks, thus leading to impairment of appetite and energy homeostasis [207].

8. Perspectives and Future Work in the Field

The current literature was reviewed in the fields of diabetes and neuroscience. The association between the central regulation of energy balance and the development of obesity is clear: there is an increased risk of developing T2D in those patients that are obese. Loss of metabolic homeostasis in diabetes, both T2D and T1D, affects multiple organ systems, including the CNS. Indeed, patients with diabetes are at higher risk of developing CNS disorders as well as peripheral neuropathy. The development of nervous disorders is underpinned by a functional impairment. An important aspect in the function of the nervous system is appropriate neurotransmission function. All the literature cited above indicates that the neurotransmission process is affected by and can affect the susceptibility to the development of metabolic diseases. The mechanisms underlying impairments of neurotransmission and CNS function in diabetes are under active investigation, the literature has explained much of the potential mechanisms that link metabolic to neurological dysfunction. Future work in the areas described below further elucidate molecular and cellular mechanisms underlying the association between diabetes and neurological decline and importantly shed much needed on the directions of causality between metabolic and neurologic disturbance.

8.1. Emerging Role of Inflammation in Neurotransmitter Function

The nervous and immune systems are tightly intertwined as they modulate each other through sophisticated bidirectional crosstalk. Specifically, the brain is a highly immunologically active organ that hosts its own immune cells and allows others to circulate through its fluid filled borders in the meninges, the protective membranes that cover the CNS [208]. This is evident from multiple studies, for example knocking out immune cells from mice led to accelerated neurodegeneration that was accompanied by gliosis; while restoring these cells modulated the trophic/cytotoxic balance of glial cells and slowed disease progression [209]. Another study showed that patients with AD had a significant rise in the number of T-cells in the cerebrospinal fluid suggesting that they might have a role in AD progression [210]. On the contrary, instead of its neuroprotective role, the immune system can also cause cumulative damage to neurons due to chronic inflammatory reactions [211].

8.2. Neuroinflammation

Neuroinflammation refers to the accumulation of glial cells in the central nervous system in response to inflammation [211]. This occurs when astrocytes and microglia are activated immediately after injury leading to the secretion of proinflammatory cytokines (e.g., IL-1 β , TNF α), cytotoxic compounds, and ROS, triggering neuronal death [211]. GABA and glutamate receptor expression is altered under neuroinflammatory conditions causing impaired spatial learning, motor function, and cognitive decline [212]. Experimentally induced inflammation through administration of poly(I:C) during gestation, dysregulated prefrontal GABAergic expression and led to the development of long-term neuropsychiatric disorders in animal models [213]. Moreover, GABA suppresses the reactive response between astrocytes and microglia to inflammatory stimuli and reduces the release of TNF α and IL-6; while an increase in TNF α levels downregulates the inhibitory synaptic strength of GABAergic neurotransmission [214,215]. Another study also looked at the effect of parthenolide, an NF- κ B inhibitor, on diabetic rat models and found that the rats exhibited

enhanced cognition, reduced anxiety-like behavior, and decreased TNF α and IL-6 levels in the cortex and hippocampus; which was associated with the loss of GABA and glutamate homeostasis [216].

8.3. Hypothalamic Inflammation

Since the hypothalamus is a major site for appetite regulation and energy balance, hypothalamic inflammation is often suggested as a cause for dysregulation of feeding behavior and body weight [217]. Obesity can, in fact, be considered as a hypothalamic inflammatory disorder resulting from the accumulation of high-fat and high glycemic index products that accumulate as ectopic fat. This eventually leads to increased BBB permeability, tancytes damage, and activation of microglia and astrocytes pro-inflammatory pathways; which induces the secretion of cytokines such as IL-1 β and TNF α alongside ROS production in the hypothalamus [218]. This is evident in patients with diabetes and obesity as a result of dysregulated energy homeostasis [218]. Moreover, obese insulin-resistant rat models of AD exhibited elevated levels of pro-inflammatory cytokines and chemokines in the hypothalamus and other brain regions suggesting a correlation between AD and hypothalamic inflammation [219].

8.4. Hypothalamic Regulation of Energy Homeostasis: The Roles of Sleep and Thermogenesis

Thermal and sleep regulation are also associated with the hypothalamus' role in maintaining energy homeostasis. Previous studies indicate that AgRP and POMC stimulation promotes wakefulness and reduces sleep fragmentation, respectively [220]. The hypothalamus contains a sleep and thermal regulation center known as the ventrolateral preoptic (VLPO) area. The VLPO consists of a large population of GABAergic neurons that send signals to other brain regions to regulate sleep [220]. Disruption of GABAergic neurons in the LHA dysregulates sleep and induces vigorous eating habits. A study looked at GABAergic neurons in the DMN region of the mouse hypothalamus and found that these neurons play a role in sleep-wake changes elicited by exposure to warmth in mice, indicative of their role in maintaining sleep and energy homeostasis [221].

8.5. Therapeutic Approaches for Neurological Disorders

The use of natural-based nanomedicine presents a promising therapeutic approach in the prevention and treatment of neurodegenerative diseases. Several studies have reported on the effects of resveratrol or trans-resveratrol, a polyphenolic molecule, in neurological disorders [222]. Resveratrol has a potentially neuroprotective role in AD, it activates reactive protein kinase C and reduces A β toxicity [223]. In a randomized, double-blind trial, patients with mild-to-moderate AD maintained plasma and cerebrospinal fluid A β when treated with trans-resveratrol and had reduced markers of inflammation [224]. Another study reported that resveratrol treatment reduces Tau protein levels and inhibits its hyperpolarization in vivo [222]. Curcumin also presents beneficial effects on brain health through Tau inhibition, antioxidation, and enhancing neurogenesis and synaptogenesis [225]. Furthermore, catechins from green tea was found to provide neuroprotection and to stabilize neurodegenerative diseases [226]. Despite the promising effects of natural compounds, the treatment of neurological diseases requires an efficient drug delivery system that overcomes the complexity of the BBB microenvironment. The use of nanomedicine as a therapeutic strategy enhances the safety and efficacy when targeting CNS disorders [227]. Encapsulating curcumin in biodegradable poly lactic-co-glycolic acid nanoparticles enhanced its neuroprotective efficacy through the upregulation of genes linked to cell proliferation and differentiation in vitro, this reversed learning and memory defects in vivo [228]. Similar effects were also observed when resveratrol was encapsulated and coated using polylactic acid and polysorbate-80, respectively [229]. These studies indicate the importance of natural-based nanomedicine for treatment of neurological disorders, the use of nanocarriers enhances the stability and delivery of natural-based molecules to the brain.

9. Conclusions

Diabetes is a disorder of dysregulated insulin action or insulin production; the maintenance of energy balance strongly influences the development and progression of disease. Whether this be at the systemic or central level, the mechanisms that maintain energy balance have the potential to strongly influence disease course. In this review, we highlighted those alterations in the neurotransmitter function at synapses and their altered activities can disturb the normal function of the nervous system. These molecules are important in maintaining proper communication between neuronal cells and their microenvironment, centrally and peripherally. Effective neurotransmission in specific brain areas controls appetite and satiety, thus regulating energy homeostasis; several studies justified the association between dysfunctional neurotransmission and diabetes progression. Furthermore, other studies highlighted that risk factors such as insulin resistance and glycemic alterations are the actual contributors to altered neurotransmission in diabetes. Despite that, very limited studies have investigated this concept, and more studies will be required to identify the exact relationship between risk factors for the development of diabetes and dysregulated neurotransmitter function.

At the local tissue level, in the CNS effective neurotransmitter function is maintained by mechanisms that control energy supply to the brain. Several perspectives arose from reviewing the literature in this field. Firstly, considerable technological advances are required to advance this field, for example the development of inducible models that target specific neurotransmitters or their targets. Secondly, once testable candidates have been defined from the relevant models, their application to holistic in vitro or ex vivo screening models will promote selection of translational candidates. Lastly, innovative translational strategies require development, for example the use of intercalating peptides where appropriate, or the development of antisense oligonucleotide therapies that target specific neurotransmitters or neurotransmission machinery. As these areas progress, the repertoire of actionable therapeutic targets will be widened in the areas of metabolic disease, such as diabetes and obesity, as well as in aging or any other condition that is influenced by the neurotransmission process.

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References

1. World Health Organization (WHO). Diabetes. Available online: <https://www.who.int/news-room/fact-sheets/detail/diabetes> (accessed on 16 September 2022).
2. International Diabetes Federation. *IDF Diabetes Atlas 2021*, 10th ed.; International Diabetes Federation: Brussels, Belgium, 2021. Available online: https://diabetesatlas.org/idfawp/resource-files/2021/07/IDF_Atlas_10th_Edition_2021.pdf (accessed on 10 February 2023).
3. Malone, J.I.; Hansen, B.C. Does obesity cause type 2 diabetes mellitus (T2DM)? Or is it the opposite? *Pediatr. Diabetes* **2019**, *20*, 5–9. [[CrossRef](#)] [[PubMed](#)]
4. Denis, G.V.; Obin, M.S. “Metabolically healthy obesity”: Origins and implications. *Mol. Aspects Med.* **2013**, *34*, 59–70. [[CrossRef](#)] [[PubMed](#)]
5. Hall, K.D.; Farooqi, I.S.; Friedman, J.M.; Klein, S.; Loos, R.J.F.; Mangelsdorf, D.J.; O’Rahilly, S.; Ravussin, E.; Redman, L.M.; Ryan, D.H.; et al. The energy balance model of obesity: Beyond calories in, calories out. *Am. J. Clin. Nutr.* **2022**, *115*, 1243–1254. [[CrossRef](#)] [[PubMed](#)]
6. Pfeiffer, E.F.; Laube, H. Obesity and diabetes mellitus. *Adv. Metab. Disord.* **1974**, *7*, 243–255. [[PubMed](#)]
7. Kim, K.-S.; Choi, Y.K.; Kim, M.J.; Hwang, J.W.; Min, K.; Jung, S.Y.; Kim, S.-K.; Choi, Y.-S.; Cho, Y.-W. Umbilical Cord-Mesenchymal Stem Cell-Conditioned Medium Improves Insulin Resistance in C2C12 Cell. *Diabetes Metab. J.* **2021**, *45*, 260–269. [[CrossRef](#)]

8. Eo, H.; Valentine, R.J. Saturated Fatty Acid-Induced Endoplasmic Reticulum Stress and Insulin Resistance Are Prevented by Imoxin in C2C12 Myotubes. *Front. Physiol.* **2022**, *13*, 842819. [[CrossRef](#)]
9. Batista, T.M.; Haider, N.; Kahn, C.R. Defining the underlying defect in insulin action in type 2 diabetes. *Diabetologia* **2021**, *64*, 994–1006. [[CrossRef](#)]
10. Bäckdahl, J.; Franzén, L.; Massier, L.; Li, Q.; Jalkanen, J.; Gao, H.; Andersson, A.; Bhalla, N.; Thorell, A.; Rydén, M.; et al. Spatial mapping reveals human adipocyte subpopulations with distinct sensitivities to insulin. *Cell Metab.* **2021**, *33*, 1869–1882.e6. [[CrossRef](#)]
11. Perry, R.J.; Zhang, D.; Guerra, M.T.; Brill, A.L.; Goedeke, L.; Nasiri, A.R.; Rabin-Court, A.; Wang, Y.; Peng, L.; Dufour, S.; et al. Glucagon stimulates gluconeogenesis by INSP3R1-mediated hepatic lipolysis. *Nature* **2020**, *579*, 279–283. [[CrossRef](#)]
12. Dimitriadis, G.D.; Maratou, E.; Kountouri, A.; Board, M.; Lambadiari, V. Regulation of Postabsorptive and Postprandial Glucose Metabolism by Insulin-Dependent and Insulin-Independent Mechanisms: An Integrative Approach. *Nutrients* **2021**, *13*, 159. [[CrossRef](#)]
13. Cerf, M.E. Beta cell dysfunction and insulin resistance. *Front. Endocrinol.* **2013**, *4*, 37. [[CrossRef](#)]
14. Esser, N.; Legrand-Poels, S.; Piette, J.; Scheen, A.J.; Paquot, N. Inflammation as a link between obesity, metabolic syndrome and type 2 diabetes. *Diabetes Res. Clin. Pract.* **2014**, *105*, 141–150. [[CrossRef](#)]
15. Pradhan, A.D.; Manson, J.E.; Rifai, N.; Buring, J.E.; Ridker, P.M. C-reactive protein, interleukin 6, and risk of developing type 2 diabetes mellitus. *JAMA* **2001**, *286*, 327–334. [[CrossRef](#)]
16. Karamanou, M.; Protogerou, A.; Tsoucalas, G.; Androutsos, G.; Poulakou-Rebelakou, E. Milestones in the history of diabetes mellitus: The main contributors. *World J. Diabetes* **2016**, *7*, 1–7. [[CrossRef](#)]
17. Margolis, R.U.; Altszuler, N. Insulin in the Cerebrospinal Fluid. *Nature* **1967**, *215*, 1375–1376. [[CrossRef](#)]
18. Devaskar, S.U.; Giddings, S.J.; Rajakumar, P.A.; Carnaghi, L.R.; Menon, R.K.; Zahm, D.S. Insulin gene expression and insulin synthesis in mammalian neuronal cells. *J. Biol. Chem.* **1994**, *269*, 8445–8454. [[CrossRef](#)]
19. Havrankova, J.; Schmechel, D.; Roth, J.; Brownstein, M. Identification of insulin in rat brain. *Proc. Natl. Acad. Sci. USA* **1978**, *75*, 5737–5741. [[CrossRef](#)]
20. Havrankova, J.; Roth, J.; Brownstein, M. Insulin receptors are widely distributed in the central nervous system of the rat. *Nature* **1978**, *272*, 827–829. [[CrossRef](#)]
21. Dyer, A.H.; Vahdatpour, C.; Sanfeliu, A.; Tropea, D. The role of Insulin-Like Growth Factor 1 (IGF-1) in brain development, maturation and neuroplasticity. *Neuroscience* **2016**, *325*, 89–99. [[CrossRef](#)]
22. Cai, W.; Xue, C.; Sakaguchi, M.; Konishi, M.; Shirazian, A.; Ferris, H.A.; Li, M.E.; Yu, R.; Kleinridders, A.; Pothos, E.N.; et al. Insulin regulates astrocyte gliotransmission and modulates behavior. *J. Clin. Investig.* **2018**, *128*, 2914–2926. [[CrossRef](#)]
23. Arnold, S.E.; Arvanitakis, Z.; Macauley-Rambach, S.L.; Koenig, A.M.; Wang, H.-Y.; Ahima, R.S.; Craft, S.; Gandy, S.; Buettner, C.; Stoeckel, L.E.; et al. Brain insulin resistance in type 2 diabetes and Alzheimer disease: Concepts and conundrums. *Nat. Rev. Neurol.* **2018**, *14*, 168–181. [[CrossRef](#)] [[PubMed](#)]
24. Ghasemi, R.; Dargahi, L.; Haeri, A.; Moosavi, M.; Mohamed, Z.; Ahmadiani, A. Brain Insulin Dysregulation: Implication for Neurological and Neuropsychiatric Disorders. *Mol. Neurobiol.* **2013**, *47*, 1045–1065. [[CrossRef](#)] [[PubMed](#)]
25. Kullmann, S.; Heni, M.; Hallschmid, M.; Fritsche, A.; Preissl, H.; Häring, H.-U. Brain Insulin Resistance at the Crossroads of Metabolic and Cognitive Disorders in Humans. *Physiol. Rev.* **2016**, *96*, 1169–1209. [[CrossRef](#)] [[PubMed](#)]
26. Kleinridders, A.; Cai, W.; Cappellucci, L.; Ghazarian, A.; Collins, W.R.; Vienberg, S.G.; Pothos, E.N.; Kahn, C.R. Insulin resistance in brain alters dopamine turnover and causes behavioral disorders. *Proc. Natl. Acad. Sci. USA* **2015**, *112*, 3463–3468. [[CrossRef](#)] [[PubMed](#)]
27. Morton, G.J.; Cummings, D.E.; Baskin, D.G.; Barsh, G.S.; Schwartz, M.W. Central nervous system control of food intake and body weight. *Nature* **2006**, *443*, 289–295. [[CrossRef](#)]
28. Brüning, J.C.; Gautam, D.; Burks, D.J.; Gillette, J.; Schubert, M.; Orban, P.C.; Klein, R.; Krone, W.; Müller-Wieland, D.; Kahn, C.R. Role of Brain Insulin Receptor in Control of Body Weight and Reproduction. *Science* **2000**, *289*, 2122–2125. [[CrossRef](#)]
29. Vogt, M.C.; Brüning, J.C. CNS insulin signaling in the control of energy homeostasis and glucose metabolism—From embryo to old age. *Trends Endocrinol. Metab.* **2013**, *24*, 76–84. [[CrossRef](#)]
30. Okamoto, H.; Nakae, J.; Kitamura, T.; Park, B.-C.; Dragatsis, I.; Accili, D. Transgenic rescue of insulin receptor-deficient mice. *J. Clin. Investig.* **2004**, *114*, 214–223. [[CrossRef](#)]
31. Erichsen, J.M.; Fadel, J.R.; Reagan, L.P. Peripheral versus central insulin and leptin resistance: Role in metabolic disorders, cognition, and neuropsychiatric diseases. *Neuropharmacology* **2022**, *203*, 108877. [[CrossRef](#)]
32. Ruud, J.; Steculorum, S.M.; Brüning, J.C. Neuronal control of peripheral insulin sensitivity and glucose metabolism. *Nat. Commun.* **2017**, *8*, 15259. [[CrossRef](#)]
33. Grote, C.W.; Groover, A.L.; Ryals, J.M.; Geiger, P.C.; Feldman, E.L.; Wright, D.E. Peripheral nervous system insulin resistance in ob/ob mice. *Acta Neuropathol. Commun.* **2013**, *1*, 15. [[CrossRef](#)]
34. Palta, P.; Carlson, M.C.; Crum, R.M.; Colantuoni, E.; Sharrett, A.R.; Yasar, S.; Nahin, R.L.; DeKosky, S.T.; Snitz, B.; Lopez, O.; et al. Diabetes and Cognitive Decline in Older Adults: The Ginkgo Evaluation of Memory Study. *J. Gerontol. Ser. A* **2018**, *73*, 123–130. [[CrossRef](#)]
35. Spauwen, P.J.J.; Köhler, S.; Verhey, F.R.J.; Stehouwer, C.D.A.; van Boxtel, M.P.J. Effects of Type 2 Diabetes on 12-Year Cognitive Change. *Diabetes Care* **2013**, *36*, 1554–1561. [[CrossRef](#)]

36. Tuligenga, R.H.; Dugravot, A.; Tabák, A.G.; Elbaz, A.; Brunner, E.J.; Kivimäki, M.; Singh-Manoux, A. Midlife type 2 diabetes and poor glycaemic control as risk factors for cognitive decline in early old age: A post-hoc analysis of the Whitehall II cohort study. *Lancet Diabetes Endocrinol.* **2014**, *2*, 228–235. [CrossRef]
37. Garcia-Serrano, A.M.; Duarte, J.M.N. Brain Metabolism Alterations in Type 2 Diabetes: What Did We Learn from Diet-Induced Diabetes Models? *Front. Neurosci.* **2020**, *14*, 229. [CrossRef]
38. Karvani, M.; Simos, P.; Stavrakaki, S.; Kapoukranidou, D. Neurocognitive impairment in type 2 diabetes mellitus. *Hormones* **2019**, *18*, 523–534. [CrossRef]
39. Wang, K.-C.; Woung, L.-C.; Tsai, M.-T.; Liu, C.-C.; Su, Y.-H.; Li, C.-Y. Risk of Alzheimer's Disease in Relation to Diabetes: A Population-Based Cohort Study. *Neuroepidemiology* **2012**, *38*, 237–244. [CrossRef]
40. González, A.; Calfío, C.; Churrua, M.; Maccioni, R.B. Glucose metabolism and AD: Evidence for a potential diabetes type 3. *Alzheimer's Res. Ther.* **2022**, *14*, 56. [CrossRef]
41. Thomas, K.R.; Bangen, K.J.; Weigand, A.J.; Edmonds, E.C.; Sundermann, E.; Wong, C.G.; Eppig, J.; Werhane, M.L.; Delano-Wood, L.; Bondi, M.W. Type 2 Diabetes Interacts with Alzheimer Disease Risk Factors to Predict Functional Decline. *Alzheimer Dis. Assoc. Disord.* **2020**, *34*, 10–17. [CrossRef]
42. Singh, A.; Kukreti, R.; Saso, L.; Kukreti, S. Mechanistic Insight into Oxidative Stress-Triggered Signaling Pathways and Type 2 Diabetes. *Molecules* **2022**, *27*, 950. [CrossRef]
43. Li, J.; Liu, D.; Sun, L.; Lu, Y.; Zhang, Z. Advanced glycation end products and neurodegenerative diseases: Mechanisms and perspective. *J. Neurol. Sci.* **2012**, *317*, 1–5. [CrossRef] [PubMed]
44. Kong, Y.; Wang, F.; Wang, J.; Liu, C.; Zhou, Y.; Xu, Z.; Zhang, C.; Sun, B.; Guan, Y. Pathological Mechanisms Linking Diabetes Mellitus and Alzheimer's Disease: The Receptor for Advanced Glycation End Products (RAGE). *Front. Aging Neurosci.* **2020**, *12*, 217. [CrossRef] [PubMed]
45. Momeni, Z.; Neapetung, J.; Pacholko, A.; Kiir, T.A.B.; Yamamoto, Y.; Bekar, L.K.; Campanucci, V.A. Hyperglycemia induces RAGE-dependent hippocampal spatial memory impairments. *Physiol. Behav.* **2021**, *229*, 113287. [CrossRef] [PubMed]
46. Pérez-Taboada, I.; Alberquilla, S.; Martín, E.D.; Anand, R.; Vietti-Michelina, S.; Tebeka, N.N.; Cantley, J.; Cragg, S.J.; Moratalla, R.; Vallejo, M. Diabetes Causes Dysfunctional Dopamine Neurotransmission Favoring Nigrostriatal Degeneration in Mice. *Mov. Disord.* **2020**, *35*, 1636–1648. [CrossRef]
47. Gaspar, J.M.; Baptista, F.I.; Macedo, M.P.; Ambrósio, A.F. Inside the Diabetic Brain: Role of Different Players Involved in Cognitive Decline. *ACS Chem. Neurosci.* **2016**, *7*, 131–142. [CrossRef]
48. Moon, J.-M.; Thapliyal, N.; Hussain, K.K.; Goyal, R.N.; Shim, Y.-B. Conducting polymer-based electrochemical biosensors for neurotransmitters: A review. *Biosens. Bioelectron.* **2018**, *102*, 540–552. [CrossRef]
49. Tavakolian-Ardakani; Hosu; Cristea; Mazloum-Ardakani; Marrazza Latest Trends in Electrochemical Sensors for Neurotransmitters: A Review. *Sensors* **2019**, *19*, 2037. [CrossRef]
50. Da, Y.; Luo, S.; Tian, Y. Real-Time Monitoring of Neurotransmitters in the Brain of Living Animals. *ACS Appl. Mater. Interfaces* **2022**, *15*, 138–157. [CrossRef]
51. Intachai, K.; Chattipakorn, S.C.; Chattipakorn, N.; Shinlapawittayatorn, K. Revisiting the Cardioprotective Effects of Acetylcholine Receptor Activation against Myocardial Ischemia/Reperfusion Injury. *Int. J. Mol. Sci.* **2018**, *19*, 2466. [CrossRef]
52. Goldstein, D.S. "Sick-but-not-dead": Multiple paths to catecholamine deficiency in Lewy body diseases. *Stress* **2020**, *23*, 633–637. [CrossRef]
53. Brennenstuhl, H.; Jung-Klawitter, S.; Assmann, B.; Opladen, T. Inherited Disorders of Neurotransmitters: Classification and Practical Approaches for Diagnosis and Treatment. *Neuropediatrics* **2019**, *50*, 2–14. [CrossRef]
54. Potier, B.; Lallemand, L.; Parrot, S.; Huguët-Lachon, A.; Gourdon, G.; Dutar, P.; Gomes-Pereira, M. DM1 Transgenic Mice Exhibit Abnormal Neurotransmitter Homeostasis and Synaptic Plasticity in Association with RNA Foci and Mis-Splicing in the Hippocampus. *Int. J. Mol. Sci.* **2022**, *23*, 592. [CrossRef]
55. Teleanu, R.I.; Niculescu, A.-G.; Roza, E.; Vladâncenco, O.; Grumezescu, A.M.; Teleanu, D.M. Neurotransmitters—Key Factors in Neurological and Neurodegenerative Disorders of the Central Nervous System. *Int. J. Mol. Sci.* **2022**, *23*, 5954. [CrossRef]
56. Xu, Y.; Tong, Q. Expanding neurotransmitters in the hypothalamic neurocircuitry for energy balance regulation. *Protein Cell* **2011**, *2*, 800–813. [CrossRef]
57. Satarker, S.; Bojja, S.L.; Gurram, P.C.; Mudgal, J.; Arora, D.; Nampoothiri, M. Astrocytic Glutamatergic Transmission and Its Implications in Neurodegenerative Disorders. *Cells* **2022**, *11*, 1139. [CrossRef]
58. Bonansco, C.; Fuenzalida, M. Plasticity of Hippocampal Excitatory-Inhibitory Balance: Missing the Synaptic Control in the Epileptic Brain. *Neural Plast.* **2016**, *2016*, 8607038. [CrossRef]
59. Hampe, C.S.; Mitoma, H.; Manto, M. GABA and Glutamate: Their Transmitter Role in the CNS and Pancreatic Islets. In *GABA and Glutamate—New Developments in Neurotransmission Research*; Samardzic, J., Ed.; InTechOpen: London, UK, 2018; ISBN 978-953-51-3821-1. Available online: <http://www.intechopen.com/books/gaba-and-glutamate-new-developments-in-neurotransmission-research/gaba-and-glutamate-their-transmitter-role-in-the-cns-and-pancreatic-islets> (accessed on 10 February 2023).
60. Bi, D.; Wen, L.; Wu, Z.; Shen, Y. GABAergic dysfunction in excitatory and inhibitory (E/I) imbalance drives the pathogenesis of Alzheimer's disease. *Alzheimer's Dement.* **2020**, *16*, 1312–1329. [CrossRef]
61. Aosaki, T.; Miura, M.; Suzuki, T.; Nishimura, K.; Masuda, M. Acetylcholine-dopamine balance hypothesis in the striatum: An update: Acetylcholine-dopamine balance hypothesis. *Geriatr. Gerontol. Int.* **2010**, *10*, S148–S157. [CrossRef]

62. André, V.M.; Cepeda, C.; Levine, M.S. Dopamine and Glutamate in Huntington's Disease: A Balancing Act: Dopamine-Glutamate Balance in Huntington's Disease. *CNS Neurosci. Ther.* **2010**, *16*, 163–178. [CrossRef]
63. Lee, S.-E.; Lee, Y.; Lee, G.H. The regulation of glutamic acid decarboxylases in GABA neurotransmission in the brain. *Arch. Pharm. Res.* **2019**, *42*, 1031–1039. [CrossRef]
64. Delgado, T.C. Glutamate and GABA in Appetite Regulation. *Front. Endocrinol.* **2013**, *4*, 103. Available online: <http://journal.frontiersin.org/article/10.3389/fendo.2013.00103/abstract> (accessed on 2 September 2022). [CrossRef] [PubMed]
65. Niyonambaza, S.D.; Kumar, P.; Xing, P.; Mathault, J.; De Koninck, P.; Boisselier, E.; Boukadoum, M.; Miled, A. A Review of Neurotransmitters Sensing Methods for Neuro-Engineering Research. *Appl. Sci.* **2019**, *9*, 4719. [CrossRef]
66. Gowrishankar, R.; Hahn, M.K.; Blakely, R.D. Good riddance to dopamine: Roles for the dopamine transporter in synaptic function and dopamine-associated brain disorders. *Neurochem. Int.* **2014**, *73*, 42–48. [CrossRef] [PubMed]
67. Yoshikawa, T.; Nakamura, T.; Yanai, K. Histamine N-Methyltransferase in the Brain. *Int. J. Mol. Sci.* **2019**, *20*, 737. [CrossRef]
68. Chen, Z.-R.; Huang, J.-B.; Yang, S.-L.; Hong, F.-F. Role of Cholinergic Signaling in Alzheimer's Disease. *Molecules* **2022**, *27*, 1816. [CrossRef]
69. Picón-Pagès, P.; Garcia-Buendia, J.; Muñoz, F.J. Functions and dysfunctions of nitric oxide in brain. *Biochim. Biophys. Acta BBA-Mol. Basis Dis.* **2019**, *1865*, 1949–1967. [CrossRef]
70. Huang, Z.; Xie, N.; Illes, P.; Di Virgilio, F.; Ulrich, H.; Semyanov, A.; Verkhatsky, A.; Sperlagh, B.; Yu, S.-G.; Huang, C.; et al. From purines to purinergic signalling: Molecular functions and human diseases. *Signal Transduct. Target. Ther.* **2021**, *6*, 162. [CrossRef]
71. Arumugasamy, S.K.; Chellasamy, G.; Gopi, S.; Govindaraju, S.; Yun, K. Current advances in the detection of neurotransmitters by nanomaterials: An update. *TrAC Trends Anal. Chem.* **2020**, *123*, 115766. [CrossRef]
72. Lasseigne, A.M.; Echeverry, F.A.; Ijaz, S.; Michel, J.C.; Martin, E.A.; Marsh, A.J.; Trujillo, E.; Marsden, K.C.; Pereda, A.E.; Miller, A.C. Electrical synaptic transmission requires a postsynaptic scaffolding protein. *eLife* **2021**, *10*, e66898. [CrossRef]
73. Belousov, A.B.; Fontes, J.D. Neuronal gap junctions: Making and breaking connections during development and injury. *Trends Neurosci.* **2013**, *36*, 227–236. [CrossRef]
74. Totland, M.Z.; Rasmussen, N.L.; Knudsen, L.M.; Leithe, E. Regulation of gap junction intercellular communication by connexin ubiquitination: Physiological and pathophysiological implications. *Cell. Mol. Life Sci.* **2020**, *77*, 573–591. [CrossRef]
75. Nagy, J.I.; Li, W.; Hertzberg, E.L.; Marotta, C.A. Elevated connexin43 immunoreactivity at sites of amyloid plaques in alzheimer's disease. *Brain Res.* **1996**, *717*, 173–178. [CrossRef]
76. Choudhury, S.P.; Bano, S.; Sen, S.; Suchal, K.; Kumar, S.; Nikolajeff, F.; Dey, S.K.; Sharma, V. Altered neural cell junctions and ion-channels leading to disrupted neuron communication in Parkinson's disease. *npj Park. Dis.* **2022**, *8*, 66. [CrossRef]
77. Charvériat, M.; Mouthon, F.; Rein, W.; Verkhatsky, A. Connexins as therapeutic targets in neurological and neuropsychiatric disorders. *Biochim. Biophys. Acta BBA-Mol. Basis Dis.* **2021**, *1867*, 166098. [CrossRef]
78. Ahmadian, E.; Eftekhari, A.; Samiei, M.; Maleki Dizaj, S.; Vinken, M. The role and therapeutic potential of connexins, pannexins and their channels in Parkinson's disease. *Cell. Signal.* **2019**, *58*, 111–118. [CrossRef]
79. Güemes, A.; Georgiou, P. Review of the role of the nervous system in glucose homeostasis and future perspectives towards the management of diabetes. *Bioelectron. Med.* **2018**, *4*, 9. [CrossRef]
80. Pignalosa, F.C.; Desiderio, A.; Mirra, P.; Nigro, C.; Perruolo, G.; Ulianich, L.; Formisano, P.; Beguinot, F.; Miele, C.; Napoli, R.; et al. Diabetes and Cognitive Impairment: A Role for Glucotoxicity and Dopaminergic Dysfunction. *Int. J. Mol. Sci.* **2021**, *22*, 12366. [CrossRef]
81. Sickmann, H.M.; Waagepetersen, H.S.; Schousboe, A.; Benie, A.J.; Bouman, S.D. Obesity and Type 2 Diabetes in Rats are Associated with Altered Brain Glycogen and Amino-Acid Homeostasis. *J. Cereb. Blood Flow Metab.* **2010**, *30*, 1527–1537. [CrossRef]
82. Kamal, A.; Biessels, G.-J.; Gispen, W.H.; Ramakers, G.M.J. Synaptic transmission changes in the pyramidal cells of the hippocampus in streptozotocin-induced diabetes mellitus in rats. *Brain Res.* **2006**, *1073–1074*, 276–280. [CrossRef]
83. Huang, X.-T.; Li, C.; Peng, X.-P.; Guo, J.; Yue, S.-J.; Liu, W.; Zhao, F.-Y.; Han, J.-Z.; Huang, Y.-H.; Cheng, Q.-M.; et al. An excessive increase in glutamate contributes to glucose-toxicity in β -cells via activation of pancreatic NMDA receptors in rodent diabetes. *Sci. Rep.* **2017**, *7*, 44120. [CrossRef]
84. d'Almeida, O.C.; Violante, I.R.; Quendera, B.; Moreno, C.; Gomes, L.; Castelo-Branco, M. The neurometabolic profiles of GABA and Glutamate as revealed by proton magnetic resonance spectroscopy in type 1 and type 2 diabetes. *PLoS ONE* **2020**, *15*, e0240907. [CrossRef] [PubMed]
85. Gandhi, G.K.; Ball, K.K.; Cruz, N.F.; Diemel, G.A. Hyperglycaemia and Diabetes Impair Gap Junctional Communication among Astrocytes. *ASN Neuro* **2010**, *2*, AN20090048. [CrossRef] [PubMed]
86. Head, W.S.; Orseth, M.L.; Nunemaker, C.S.; Satin, L.S.; Piston, D.W.; Benninger, R.K.P. Connexin-36 Gap Junctions Regulate In Vivo First- and Second-Phase Insulin Secretion Dynamics and Glucose Tolerance in the Conscious Mouse. *Diabetes* **2012**, *61*, 1700–1707. [CrossRef] [PubMed]
87. St. Clair, J.R.; Westacott, M.J.; Farnsworth, N.L.; Kravets, V.; Schleicher, W.E.; Miranda, J.; Heintz, A.; Ludin, N.W.; Benninger, R.K. Restoring Connexin-36 Function in Diabetogenic Environments Precludes Mouse and Human Islet Dysfunction. *bioRxiv* **2020**. Available online: <http://biorxiv.org/lookup/doi/10.1101/2020.11.03.366179> (accessed on 21 January 2023).
88. Das, U.N. Obesity: Genes, brain, gut, and environment. *Nutrition* **2010**, *26*, 459–473. [CrossRef]

89. Wallace, C.W.; Fordahl, S.C. Obesity and dietary fat influence dopamine neurotransmission: Exploring the convergence of metabolic state, physiological stress, and inflammation on dopaminergic control of food intake. *Nutr. Res. Rev.* **2021**, *35*, 236–251. [[CrossRef](#)]
90. Wang, G.-J.; Volkow, N.D.; Logan, J.; Pappas, N.R.; Wong, C.T.; Zhu, W.; Netusll, N.; Fowler, J.S. Brain dopamine and obesity. *Lancet* **2001**, *357*, 354–357. [[CrossRef](#)]
91. Mehay, D.; Silberman, Y.; Arnold, A.C. The Arcuate Nucleus of the Hypothalamus and Metabolic Regulation: An Emerging Role for Renin–Angiotensin Pathways. *Int. J. Mol. Sci.* **2021**, *22*, 7050. [[CrossRef](#)]
92. Sa, M.; Park, M.G.; Lee, C.J. Role of Hypothalamic Reactive Astrocytes in Diet-Induced Obesity. *Mol. Cells* **2022**, *45*, 65–75. [[CrossRef](#)]
93. Schneeberger, M.; Gomis, R.; Claret, M. Hypothalamic and brainstem neuronal circuits controlling homeostatic energy balance. *J. Endocrinol.* **2014**, *220*, T25–T46. [[CrossRef](#)]
94. Dietrich, M.O.; Horvath, T.L. Hypothalamic control of energy balance: Insights into the role of synaptic plasticity. *Trends Neurosci.* **2013**, *36*, 65–73. [[CrossRef](#)]
95. Jarvie, B.C.; Hentges, S.T. Expression of GABAergic and glutamatergic phenotypic markers in hypothalamic proopiomelanocortin neurons. *J. Comp. Neurol.* **2012**, *520*, 3863–3876. [[CrossRef](#)]
96. Kiss, J.; Csaba, Z.; Csáki, Á.; Halász, B. Glutamatergic innervation of neuropeptide Y and pro-opiomelanocortin-containing neurons in the hypothalamic arcuate nucleus of the rat. *Eur. J. Neurosci.* **2005**, *21*, 2111–2119. [[CrossRef](#)]
97. Jones, G.L.; Wittmann, G.; Yokosawa, E.B.; Yu, H.; Mercer, A.J.; Lechan, R.M.; Low, M.J. Selective Restoration of *Pomc* Expression in Glutamatergic POMC Neurons: Evidence for a Dynamic Hypothalamic Neurotransmitter Network. *Eneuro* **2019**, *6*, 1–21. [[CrossRef](#)]
98. Trotta, M.; Bello, E.P.; Alsina, R.; Tavella, M.B.; Ferrán, J.L.; Rubinstein, M.; Bumashny, V.F. Hypothalamic *Pomc* expression restricted to GABAergic neurons suppresses *Npy* overexpression and restores food intake in obese mice. *Mol. Metab.* **2020**, *37*, 100985. [[CrossRef](#)]
99. Wu, Q.; Boyle, M.P.; Palmiter, R.D. Loss of GABAergic Signaling by AgRP Neurons to the Parabrachial Nucleus Leads to Starvation. *Cell* **2009**, *137*, 1225–1234. [[CrossRef](#)]
100. Krashes, M.J.; Shah, B.P.; Koda, S.; Lowell, B.B. Rapid versus Delayed Stimulation of Feeding by the Endogenously Released AgRP Neuron Mediators GABA, NPY, and AgRP. *Cell Metab.* **2013**, *18*, 588–595. [[CrossRef](#)]
101. Suyama, S.; Yada, T. New insight into GABAergic neurons in the hypothalamic feeding regulation. *J. Physiol. Sci.* **2018**, *68*, 717–722. [[CrossRef](#)]
102. Zhang, X.; van den Pol, A.N. Hypothalamic arcuate nucleus tyrosine hydroxylase neurons play orexigenic role in energy homeostasis. *Nat. Neurosci.* **2016**, *19*, 1341–1347. [[CrossRef](#)]
103. Meguid, M.M.; Fetissov, S.O.; Varma, M.; Sato, T.; Zhang, L.; Laviano, A.; Rossi-Fanelli, F. Hypothalamic dopamine and serotonin in the regulation of food intake. *Nutrition* **2000**, *16*, 843–857. [[CrossRef](#)]
104. Jeong, J.H.; Lee, D.K.; Jo, Y.-H. Cholinergic neurons in the dorsomedial hypothalamus regulate food intake. *Mol. Metab.* **2017**, *6*, 306–312. [[CrossRef](#)]
105. Herman, A.M.; Ortiz-Guzman, J.; Kochukov, M.; Herman, I.; Quast, K.B.; Patel, J.M.; Tepe, B.; Carlson, J.C.; Ung, K.; Selever, J.; et al. A cholinergic basal forebrain feeding circuit modulates appetite suppression. *Nature* **2016**, *538*, 253–256. [[CrossRef](#)] [[PubMed](#)]
106. Thinnis, A.; Klein, J. Food-Induced Increase of Acetylcholine in Mouse Hypothalamus. *ACS Chem. Neurosci.* **2019**, *10*, 1892–1899. [[CrossRef](#)]
107. Girardet, C.; Butler, A.A. Neural melanocortin receptors in obesity and related metabolic disorders. *Biochim. Biophys. Acta* **2014**, *1842*, 482–494. [[CrossRef](#)] [[PubMed](#)]
108. Dib, L.; San-Jose, L.M.; Ducrest, A.-L.; Salamin, N.; Roulin, A. Selection on the Major Color Gene Melanocortin-1-Receptor Shaped the Evolution of the Melanocortin System Genes. *Int. J. Mol. Sci.* **2017**, *18*, 2618. [[CrossRef](#)] [[PubMed](#)]
109. Tao, Y.-X. The melanocortin-4 receptor: Physiology, pharmacology, and pathophysiology. *Endocr. Rev.* **2010**, *31*, 506–543. [[CrossRef](#)]
110. Ollmann, M.M.; Wilson, B.D.; Yang, Y.K.; Kerns, J.A.; Chen, Y.; Gantz, I.; Barsh, G.S. Antagonism of central melanocortin receptors in vitro and in vivo by agouti-related protein. *Science* **1997**, *278*, 135–138. [[CrossRef](#)]
111. Yang, Z.; Tao, Y.-X. Biased signaling initiated by agouti-related peptide through human melanocortin-3 and -4 receptors. *Biochim. Biophys. Acta* **2016**, *1862*, 1485–1494. [[CrossRef](#)]
112. Yang, L.-K.; Tao, Y.-X. Biased signaling at neural melanocortin receptors in regulation of energy homeostasis. *Biochim. Biophys. Acta Mol. Basis Dis.* **2017**, *1863*, 2486–2495. [[CrossRef](#)]
113. Newman, E.A.; Chai, B.-X.; Zhang, W.; Li, J.-Y.; Ammori, J.B.; Mulholland, M.W. Activation of the melanocortin-4 receptor mobilizes intracellular free calcium in immortalized hypothalamic neurons. *J. Surg. Res.* **2006**, *132*, 201–207. [[CrossRef](#)]
114. Chai, B.; Li, J.-Y.; Zhang, W.; Ammori, J.B.; Mulholland, M.W. Melanocortin-3 receptor activates MAP kinase via PI3 kinase. *Regul. Pept.* **2007**, *139*, 115–121. [[CrossRef](#)]
115. Minokoshi, Y.; Alquier, T.; Furukawa, N.; Kim, Y.-B.; Lee, A.; Xue, B.; Mu, J.; Fofelle, F.; Ferré, P.; Birnbaum, M.J.; et al. AMP-kinase regulates food intake by responding to hormonal and nutrient signals in the hypothalamus. *Nature* **2004**, *428*, 569–574. [[CrossRef](#)]

116. Vongs, A.; Lynn, N.M.; Rosenblum, C.I. Activation of MAP kinase by MC4-R through PI3 kinase. *Regul. Pept.* **2004**, *120*, 113–118. [[CrossRef](#)]
117. Sutton, G.M.; Duos, B.; Patterson, L.M.; Berthoud, H.-R. Melanocortinergic modulation of cholecystokinin-induced suppression of feeding through extracellular signal-regulated kinase signaling in rat solitary nucleus. *Endocrinology* **2005**, *146*, 3739–3747. [[CrossRef](#)]
118. Chai, B.; Li, J.-Y.; Zhang, W.; Wang, H.; Mulholland, M.W. Melanocortin-4 receptor activation inhibits c-Jun N-terminal kinase activity and promotes insulin signaling. *Peptides* **2009**, *30*, 1098–1104. [[CrossRef](#)]
119. Damm, E.; Buech, T.R.H.; Gudermann, T.; Breit, A. Melanocortin-induced PKA activation inhibits AMPK activity via ERK-1/2 and LKB-1 in hypothalamic GT1-7 cells. *Mol. Endocrinol.* **2012**, *26*, 643–654. [[CrossRef](#)]
120. Huszar, D.; Lynch, C.A.; Fairchild-Huntress, V.; Dunmore, J.H.; Fang, Q.; Berkemeier, L.R.; Gu, W.; Kesterson, R.A.; Boston, B.A.; Cone, R.D.; et al. Targeted disruption of the melanocortin-4 receptor results in obesity in mice. *Cell* **1997**, *88*, 131–141. [[CrossRef](#)]
121. Chen, A.S.; Marsh, D.J.; Trumbauer, M.E.; Frazier, E.G.; Guan, X.M.; Yu, H.; Rosenblum, C.I.; Vongs, A.; Feng, Y.; Cao, L.; et al. Inactivation of the mouse melanocortin-3 receptor results in increased fat mass and reduced lean body mass. *Nat. Genet.* **2000**, *26*, 97–102. [[CrossRef](#)]
122. Fan, W.; Dinulescu, D.M.; Butler, A.A.; Zhou, J.; Marks, D.L.; Cone, R.D. The central melanocortin system can directly regulate serum insulin levels. *Endocrinology* **2000**, *141*, 3072–3079. [[CrossRef](#)]
123. Obici, S.; Feng, Z.; Tan, J.; Liu, L.; Karknias, G.; Rossetti, L. Central melanocortin receptors regulate insulin action. *J. Clin. Investig.* **2001**, *108*, 1079–1085. [[CrossRef](#)]
124. Farooqi, I.S.; Keogh, J.M.; Yeo, G.S.H.; Lank, E.J.; Cheetham, T.; O'Rahilly, S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. *N. Engl. J. Med.* **2003**, *348*, 1085–1095. [[CrossRef](#)]
125. Thearle, M.S.; Muller, Y.L.; Hanson, R.L.; Mullins, M.; Abdusamad, M.; Tran, J.; Knowler, W.C.; Bogardus, C.; Krakoff, J.; Baier, L.J. Greater Impact of Melanocortin-4 Receptor Deficiency on Rates of Growth and Risk of Type 2 Diabetes During Childhood Compared With Adulthood in Pima Indians. *Diabetes* **2012**, *61*, 250–257. [[CrossRef](#)] [[PubMed](#)]
126. Xi, B.; Takeuchi, F.; Chandak, G.R.; Kato, N.; Pan, H.W.; Zhou, D.H.; Pan, H.Y.; Mi, J.; AGEN-T2D Consortium. Common polymorphism near the MC4R gene is associated with type 2 diabetes: Data from a meta-analysis of 123,373 individuals. *Diabetologia* **2012**, *55*, 2660–2666. [[CrossRef](#)] [[PubMed](#)]
127. Nogueiras, R.; Wiedmer, P.; Perez-Tilve, D.; Veyrat-Durebex, C.; Keogh, J.M.; Sutton, G.M.; Pfluger, P.T.; Castaneda, T.R.; Neschen, S.; Hofmann, S.M.; et al. The central melanocortin system directly controls peripheral lipid metabolism. *J. Clin. Investig.* **2007**, *117*, 3475–3488. [[CrossRef](#)] [[PubMed](#)]
128. Enriori, P.J.; Chen, W.; Garcia-Rudaz, M.C.; Grayson, B.E.; Evans, A.E.; Comstock, S.M.; Gebhardt, U.; Müller, H.L.; Reinehr, T.; Henry, B.A.; et al. α -Melanocyte stimulating hormone promotes muscle glucose uptake via melanocortin 5 receptors. *Mol. Metab.* **2016**, *5*, 807–822. [[CrossRef](#)] [[PubMed](#)]
129. Shpakov, A.O.; Derkach, K.V.; Berstein, L.M. Brain signaling systems in the Type 2 diabetes and metabolic syndrome: Promising target to treat and prevent these diseases. *Future Sci. OA* **2015**, *1*, FSO25. [[CrossRef](#)]
130. Giuliani, D.; Mioni, C.; Altavilla, D.; Leone, S.; Bazzani, C.; Minutoli, L.; Bitto, A.; Cainazzo, M.-M.; Marini, H.; Zaffe, D.; et al. Both early and delayed treatment with melanocortin 4 receptor-stimulating melanocortins produces neuroprotection in cerebral ischemia. *Endocrinology* **2006**, *147*, 1126–1135. [[CrossRef](#)]
131. Giuliani, D.; Bitto, A.; Galantucci, M.; Zaffe, D.; Ottani, A.; Irrera, N.; Neri, L.; Cavallini, G.M.; Altavilla, D.; Botticelli, A.R.; et al. Melanocortins protect against progression of Alzheimer's disease in triple-transgenic mice by targeting multiple pathophysiological pathways. *Neurobiol. Aging* **2014**, *35*, 537–547. [[CrossRef](#)]
132. Giuliani, D.; Galantucci, M.; Neri, L.; Canalini, F.; Calevoro, A.; Bitto, A.; Ottani, A.; Vandini, E.; Sena, P.; Sandrini, M.; et al. Melanocortins protect against brain damage and counteract cognitive decline in a transgenic mouse model of moderate Alzheimer's disease. *Eur. J. Pharmacol.* **2014**, *740*, 144–150. [[CrossRef](#)]
133. Balthasar, N.; Dalgaard, L.T.; Lee, C.E.; Yu, J.; Funahashi, H.; Williams, T.; Ferreira, M.; Tang, V.; McGovern, R.A.; Kenny, C.D.; et al. Divergence of melanocortin pathways in the control of food intake and energy expenditure. *Cell* **2005**, *123*, 493–505. [[CrossRef](#)]
134. Fani, L.; Bak, S.; Delhanty, P.; van Rossum, E.F.C.; van den Akker, E.L.T. The melanocortin-4 receptor as target for obesity treatment: A systematic review of emerging pharmacological therapeutic options. *Int. J. Obes.* **2014**, *38*, 163–169. [[CrossRef](#)]
135. Markham, A. Setmelanotide: First Approval. *Drugs* **2021**, *81*, 397–403. [[CrossRef](#)]
136. Kievit, P.; Halem, H.; Marks, D.L.; Dong, J.Z.; Glavas, M.M.; Sinnayah, P.; Pranger, L.; Cowley, M.A.; Grove, K.L.; Culler, M.D. Chronic treatment with a melanocortin-4 receptor agonist causes weight loss, reduces insulin resistance, and improves cardiovascular function in diet-induced obese rhesus macaques. *Diabetes* **2013**, *62*, 490–497. [[CrossRef](#)]
137. Kühnen, P.; Clément, K.; Wiegand, S.; Blankenstein, O.; Gottesdiener, K.; Martini, L.L.; Mai, K.; Blume-Peytavi, U.; Grüters, A.; Krude, H. Proopiomelanocortin Deficiency Treated with a Melanocortin-4 Receptor Agonist. *N. Engl. J. Med.* **2016**, *375*, 240–246. [[CrossRef](#)]
138. Clemmensen, C.; Finan, B.; Fischer, K.; Tom, R.Z.; Legutko, B.; Seherer, L.; Heine, D.; Grassl, N.; Meyer, C.W.; Henderson, B.; et al. Dual melanocortin-4 receptor and GLP-1 receptor agonism amplifies metabolic benefits in diet-induced obese mice. *EMBO Mol. Med.* **2015**, *7*, 288–298. [[CrossRef](#)]
139. Camandola, S.; Mattson, M.P. Brain metabolism in health, aging, and neurodegeneration. *EMBO J.* **2017**, *36*, 1474–1492. [[CrossRef](#)]

140. Pellerin, L. Food for thought: The importance of glucose and other energy substrates for sustaining brain function under varying levels of activity. *Diabetes Metab.* **2010**, *36*, S59–S63. [CrossRef]
141. Killeen, P.R.; Russell, V.A.; Tannock, R. Neuroenergetics. *Curr. Dir. Psychol. Sci.* **2016**, *25*, 124–129. [CrossRef]
142. Magistretti, P.J.; Allaman, I. A Cellular Perspective on Brain Energy Metabolism and Functional Imaging. *Neuron* **2015**, *86*, 883–901. [CrossRef]
143. Mahadevan, H.M.; Hashemiaghdam, A.; Ashrafi, G.; Harbauer, A.B. Mitochondria in Neuronal Health: From Energy Metabolism to Parkinson's Disease. *Adv. Biol.* **2021**, *5*, 2100663. [CrossRef]
144. Magistretti, P.J.; Allaman, I. Brain Energy and Metabolism. In *Neuroscience in the 21st Century*; Pfaff, D.W., Volkow, N.D., Eds.; Springer: New York, NY, USA, 2016; pp. 1879–1909, ISBN 978-1-4939-3473-7. Available online: http://link.springer.com/10.1007/978-1-4939-3474-4_56 (accessed on 11 September 2022).
145. Sifat, A.E.; Nozohouri, S.; Archie, S.R.; Chowdhury, E.A.; Abbruscato, T.J. Brain Energy Metabolism in Ischemic Stroke: Effects of Smoking and Diabetes. *Int. J. Mol. Sci.* **2022**, *23*, 8512. [CrossRef]
146. Martin, W.R.W.; Wieler, M.; Hanstock, C.C. Is brain lactate increased in Huntington's disease? *J. Neurol. Sci.* **2007**, *263*, 70–74. [CrossRef] [PubMed]
147. Schurr, A. Lactate, glucose and energy metabolism in the ischemic brain (Review). *Int. J. Mol. Med.* **2002**, *10*, 131–136. Available online: <http://www.spandidos-publications.com/10.3892/ijmm.10.2.131> (accessed on 11 September 2022). [CrossRef] [PubMed]
148. Margineanu, M.B.; Mahmood, H.; Fiumelli, H.; Magistretti, P.J. L-Lactate Regulates the Expression of Synaptic Plasticity and Neuroprotection Genes in Cortical Neurons: A Transcriptome Analysis. *Front. Mol. Neurosci.* **2018**, *11*, 375. [CrossRef] [PubMed]
149. Silva, B.; Mantha, O.L.; Schor, J.; Pascual, A.; Plaçais, P.-Y.; Pavlowsky, A.; Preat, T. Glia fuel neurons with locally synthesized ketone bodies to sustain memory under starvation. *Nat. Metab.* **2022**, *4*, 213–224. [CrossRef]
150. Chung, J.Y.; Kim, O.Y.; Song, J. Role of ketone bodies in diabetes-induced dementia: Sirtuins, insulin resistance, synaptic plasticity, mitochondrial dysfunction, and neurotransmitter. *Nutr. Rev.* **2022**, *80*, 774–785. [CrossRef]
151. Jensen, N.J.; Wodschow, H.Z.; Nilsson, M.; Rungby, J. Effects of Ketone Bodies on Brain Metabolism and Function in Neurodegenerative Diseases. *Int. J. Mol. Sci.* **2020**, *21*, 8767. [CrossRef]
152. Phillips, M.C.L.; Murtagh, D.K.J.; Gilbertson, L.J.; Asztely, F.J.S.; Lynch, C.D.P. Low-fat versus ketogenic diet in Parkinson's disease: A pilot randomized controlled trial: Low-Fat Versus Ketogenic Diet in PD. *Mov. Disord.* **2018**, *33*, 1306–1314. [CrossRef]
153. Hertz, L.; Chen, Y.; Waagepetersen, H.S. Effects of ketone bodies in Alzheimer's disease in relation to neural hypometabolism, β -amyloid toxicity, and astrocyte function. *J. Neurochem.* **2015**, *134*, 7–20. [CrossRef]
154. Ma, W.; Berg, J.; Yellen, G. Ketogenic Diet Metabolites Reduce Firing in Central Neurons by Opening KATP Channels. *J. Neurosci.* **2007**, *27*, 3618–3625. [CrossRef]
155. Mujica-Parodi, L.R.; Amgalan, A.; Sultan, S.F.; Antal, B.; Sun, X.; Skiena, S.; Lithen, A.; Adra, N.; Ratai, E.-M.; Weistuch, C.; et al. Diet modulates brain network stability, a biomarker for brain aging, in young adults. *Proc. Natl. Acad. Sci. USA* **2020**, *117*, 6170–6177. [CrossRef]
156. Hussain, T.A.; Mathew, T.C.; Dashti, A.A.; Asfar, S.; Al-Zaid, N.; Dashti, H.M. Effect of low-calorie versus low-carbohydrate ketogenic diet in type 2 diabetes. *Nutrition* **2012**, *28*, 1016–1021. [CrossRef]
157. Carneiro, L.; Geller, S.; Hébert, A.; Repond, C.; Fioramonti, X.; Leloup, C.; Pellerin, L. Hypothalamic sensing of ketone bodies after prolonged cerebral exposure leads to metabolic control dysregulation. *Sci. Rep.* **2016**, *6*, 34909. [CrossRef]
158. Carneiro, L.; Geller, S.; Fioramonti, X.; Hébert, A.; Repond, C.; Leloup, C.; Pellerin, L. Evidence for hypothalamic ketone body sensing: Impact on food intake and peripheral metabolic responses in mice. *Am. J. Physiol.-Endocrinol. Metab.* **2016**, *310*, E103–E115. [CrossRef]
159. Reagan, L.P.; Rosell, D.R.; Alves, S.E.; Hoskin, E.K.; McCall, A.L.; Charron, M.J.; McEwen, B.S. GLUT8 glucose transporter is localized to excitatory and inhibitory neurons in the rat hippocampus. *Brain Res.* **2002**, *932*, 129–134. [CrossRef]
160. Ren, H.; Yan, S.; Zhang, B.; Lu, T.Y.; Arancio, O.; Accili, D. Glut4 expression defines an insulin-sensitive hypothalamic neuronal population. *Mol. Metab.* **2014**, *3*, 452–459. [CrossRef]
161. Beard, E.; Lengacher, S.; Dias, S.; Magistretti, P.J.; Finsterwald, C. Astrocytes as Key Regulators of Brain Energy Metabolism: New Therapeutic Perspectives. *Front. Physiol.* **2022**, *12*, 825816. [CrossRef]
162. Mason, S. Lactate Shuttles in Neuroenergetics—Homeostasis, Allostatics and Beyond. *Front. Neurosci.* **2017**, *11*, 43. Available online: <http://journal.frontiersin.org/article/10.3389/fnins.2017.00043/full> (accessed on 9 September 2022). [CrossRef]
163. Staricha, K.; Meyers, N.; Garvin, J.; Liu, Q.; Rarick, K.; Harder, D.; Cohen, S. Effect of high glucose condition on glucose metabolism in primary astrocytes. *Brain Res.* **2020**, *1732*, 146702. [CrossRef]
164. Suzuki, A.; Stern, S.A.; Bozdagi, O.; Huntley, G.W.; Walker, R.H.; Magistretti, P.J.; Alberini, C.M. Astrocyte-Neuron Lactate Transport Is Required for Long-Term Memory Formation. *Cell* **2011**, *144*, 810–823. [CrossRef]
165. Descalzi, G.; Gao, V.; Steinman, M.Q.; Suzuki, A.; Alberini, C.M. Lactate from astrocytes fuels learning-induced mRNA translation in excitatory and inhibitory neurons. *Commun. Biol.* **2019**, *2*, 247. [CrossRef]
166. Yamagata, K. Lactate Supply from Astrocytes to Neurons and its Role in Ischemic Stroke-induced Neurodegeneration. *Neuroscience* **2022**, *481*, 219–231. [CrossRef] [PubMed]
167. Knott, A.B.; Perkins, G.; Schwarzenbacher, R.; Bossy-Wetzel, E. Mitochondrial fragmentation in neurodegeneration. *Nat. Rev. Neurosci.* **2008**, *9*, 505–518. [CrossRef] [PubMed]

168. Li, S.; Sheng, Z.-H. Energy matters: Presynaptic metabolism and the maintenance of synaptic transmission. *Nat. Rev. Neurosci.* **2022**, *23*, 4–22. [[CrossRef](#)] [[PubMed](#)]
169. Nicholls, D.G.; Brand, M.D.; Gerencser, A.A. Mitochondrial bioenergetics and neuronal survival modelled in primary neuronal culture and isolated nerve terminals. *J. Bioenerg. Biomembr.* **2015**, *47*, 63–74. [[CrossRef](#)]
170. Rossi, D.J.; Oshima, T.; Attwell, D. Glutamate release in severe brain ischaemia is mainly by reversed uptake. *Nature* **2000**, *403*, 316–321. [[CrossRef](#)]
171. Pacelli, C.; Giguère, N.; Bourque, M.-J.; Lévesque, M.; Slack, R.S.; Trudeau, L.-É. Elevated Mitochondrial Bioenergetics and Axonal Arborization Size Are Key Contributors to the Vulnerability of Dopamine Neurons. *Curr. Biol.* **2015**, *25*, 2349–2360. [[CrossRef](#)]
172. Wong, K.Y.; Roy, J.; Fung, M.L.; Heng, B.C.; Zhang, C.; Lim, L.W. Relationships between Mitochondrial Dysfunction and Neurotransmission Failure in Alzheimer’s Disease. *Aging Dis.* **2020**, *11*, 1291. [[CrossRef](#)]
173. Kleinridders, A.; Ferris, H.A.; Tovar, S. Editorial: Crosstalk of Mitochondria with Brain Insulin and Leptin Signaling. *Front. Endocrinol.* **2018**, *9*, 761. [[CrossRef](#)]
174. Moreira, P.I.; Santos, M.S.; Moreno, A.M.; Seiça, R.; Oliveira, C.R. Increased Vulnerability of Brain Mitochondria in Diabetic (Goto-Kakizaki) Rats With Aging and Amyloid- β Exposure. *Diabetes* **2003**, *52*, 1449–1456. [[CrossRef](#)]
175. Petrov, D.; Pedrós, I.; Artiach, G.; Sureda, F.X.; Barroso, E.; Pallàs, M.; Casadesús, G.; Beas-Zarate, C.; Carro, E.; Ferrer, I.; et al. High-fat diet-induced deregulation of hippocampal insulin signaling and mitochondrial homeostasis deficiencies contribute to Alzheimer disease pathology in rodents. *Biochim. Biophys. Acta BBA-Mol. Basis Dis.* **2015**, *1852*, 1687–1699. [[CrossRef](#)]
176. Hong, C.-T.; Chen, K.-Y.; Wang, W.; Chiu, J.-Y.; Wu, D.; Chao, T.-Y.; Hu, C.-J.; Chau, K.-Y.; Bamodu, O. Insulin Resistance Promotes Parkinson’s Disease through Aberrant Expression of α -Synuclein, Mitochondrial Dysfunction, and Deregulation of the Polo-Like Kinase 2 Signaling. *Cells* **2020**, *9*, 740. [[CrossRef](#)]
177. Gluchowska, K.; Pliszka, M.; Szablewski, L. Expression of glucose transporters in human neurodegenerative diseases. *Biochem. Biophys. Res. Commun.* **2021**, *540*, 8–15. [[CrossRef](#)]
178. Van Bussel, F.C.G.; Backes, W.H.; Hofman, P.A.M.; Puts, N.A.J.; Edden, R.A.E.; van Boxtel, M.P.J.; Schram, M.T.; Stehouwer, C.D.A.; Wildberger, J.E.; Jansen, J.F.A. Increased GABA concentrations in type 2 diabetes mellitus are related to lower cognitive functioning. *Medicine* **2016**, *95*, e4803. [[CrossRef](#)]
179. Sickmann, H.M.; Waagepetersen, H.S.; Schousboe, A.; Benie, A.J.; Bouman, S.D. Brain glycogen and its role in supporting glutamate and GABA homeostasis in a type 2 diabetes rat model. *Neurochem. Int.* **2012**, *60*, 267–275. [[CrossRef](#)]
180. Thielen, J.; Gancheva, S.; Hong, D.; Rohani Rankouhi, S.; Chen, B.; Apostolopoulou, M.; Anadol-Schmitz, E.; Roden, M.; Norris, D.G.; Tendolkar, I. Higher GABA concentration in the medial prefrontal cortex of Type 2 diabetes patients is associated with episodic memory dysfunction. *Hum. Brain Mapp.* **2019**, *40*, 4287–4295. [[CrossRef](#)]
181. Ter Horst, K.W.; Lammers, N.M.; Trinko, R.; Opland, D.M.; Figeo, M.; Ackermans, M.T.; Booij, J.; van den Munckhof, P.; Schuurman, P.R.; Fliers, E.; et al. Striatal dopamine regulates systemic glucose metabolism in humans and mice. *Sci. Transl. Med.* **2018**, *10*, eaar3752. [[CrossRef](#)]
182. Su, C.-J.; Shen, Z.; Cui, R.-X.; Huang, Y.; Xu, D.-L.; Zhao, F.-L.; Pan, J.; Shi, A.-M.; Liu, T.; Yu, Y.-L. Thioredoxin-Interacting Protein (TXNIP) Regulates Parkin/PINK1-mediated Mitophagy in Dopaminergic Neurons under High-glucose Conditions: Implications for Molecular Links Between Parkinson’s Disease and Diabetes. *Neurosci. Bull.* **2020**, *36*, 346–358. [[CrossRef](#)]
183. Renaud, J.; Bournival, J.; Zottig, X.; Martinoli, M.-G. Resveratrol Protects DAergic PC12 Cells from High Glucose-Induced Oxidative Stress and Apoptosis: Effect on p53 and GRP75 Localization. *Neurotox. Res.* **2014**, *25*, 110–123. [[CrossRef](#)]
184. Lacković, Z.; Škovič, M.; Kuci, Z.; Relja, M. Effect of Long-Lasting Diabetes Mellitus on Rat and Human Brain Monoamines. *J. Neurochem.* **1990**, *54*, 143–147. [[CrossRef](#)]
185. Zemdegs, J.; Quesseveur, G.; Jarriault, D.; Pénicaud, L.; Fioramonti, X.; Guiard, B.P. High-fat diet-induced metabolic disorders impairs 5-HT function and anxiety-like behavior in mice: Correlation between metabolic disorders and anxiety. *Br. J. Pharmacol.* **2016**, *173*, 2095–2110. [[CrossRef](#)]
186. Derkach, K.V.; Bondareva, V.M.; Chistyakova, O.V.; Berstein, L.M.; Shpakov, A.O. The Effect of Long-Term Intranasal Serotonin Treatment on Metabolic Parameters and Hormonal Signaling in Rats with High-Fat Diet/Low-Dose Streptozotocin-Induced Type 2 Diabetes. *Int. J. Endocrinol.* **2015**, *2015*, 245459. [[CrossRef](#)] [[PubMed](#)]
187. Antony, S.; Kumar, T.P.; Mathew, J.; Anju, T.; Paulose, C. Hypoglycemia induced changes in cholinergic receptor expression in the cerebellum of diabetic rats. *J. Biomed. Sci.* **2010**, *17*, 7. [[CrossRef](#)] [[PubMed](#)]
188. Xu, Y.; Cao, K.; Guo, B.; Xiang, J.; Dong, Y.-T.; Qi, X.-L.; Yu, W.-F.; Xiao, Y.; Guan, Z.-Z. Lowered levels of nicotinic acetylcholine receptors and elevated apoptosis in the hippocampus of brains from patients with type 2 diabetes mellitus and db/db mice. *Aging* **2020**, *12*, 14205–14218. [[CrossRef](#)] [[PubMed](#)]
189. Quagliaro, L.; Picconi, L.; Assaloni, R.; Martinelli, L.; Motz, E.; Ceriello, A. Intermittent High Glucose Enhances Apoptosis Related to Oxidative Stress in Human Umbilical Vein Endothelial Cells. *Diabetes* **2003**, *52*, 2795–2804. [[CrossRef](#)] [[PubMed](#)]
190. Kim, C.; Sohn, J.-H.; Jang, M.U.; Kim, S.-H.; Choi, M.-G.; Ryu, O.-H.; Lee, S.; Choi, H.-C. Association between Visit-to-Visit Glucose Variability and Cognitive Function in Aged Type 2 Diabetic Patients: A Cross-Sectional Study. *PLoS ONE* **2015**, *10*, e0132118. [[CrossRef](#)]
191. Minami, T.; Ito, Y.; Yamada, M.; Furuta, R.; Minagawa, F.; Kamata, K.; Kameda, A.; Terauchi, Y. The effect of long-term past glycemic control on executive function among patients with type 2 diabetes mellitus. *Diabetol. Int.* **2020**, *11*, 114–120. [[CrossRef](#)]

192. Li, T.-C.; Yang, C.-P.; Tseng, S.-T.; Li, C.-I.; Liu, C.-S.; Lin, W.-Y.; Hwang, K.-L.; Yang, S.-Y.; Chiang, J.-H.; Lin, C.-C. Visit-to-Visit Variations in Fasting Plasma Glucose and HbA1c Associated With an Increased Risk of Alzheimer Disease: Taiwan Diabetes Study. *Diabetes Care* **2017**, *40*, 1210–1217. [[CrossRef](#)]
193. Quincozes-Santos, A.; Bobermin, L.D.; de Assis, A.M.; Gonçalves, C.-A.; Souza, D.O. Fluctuations in glucose levels induce glial toxicity with glutamatergic, oxidative and inflammatory implications. *Biochim. Biophys. Acta BBA-Mol. Basis Dis.* **2017**, *1863*, 1–14. [[CrossRef](#)]
194. Spinelli, M.; Fusco, S.; Grassi, C. Brain Insulin Resistance and Hippocampal Plasticity: Mechanisms and Biomarkers of Cognitive Decline. *Front. Neurosci.* **2019**, *13*, 788. [[CrossRef](#)]
195. Havrankova, J.; Roth, J.; Brownstein, M.J. Concentrations of Insulin and of Insulin Receptors in the Brain are Independent of Peripheral Insulin Levels. *J. Clin. Investig.* **1979**, *64*, 636–642. [[CrossRef](#)]
196. Gabbouj, S.; Ryhänen, S.; Marttinen, M.; Wittrahm, R.; Takalo, M.; Kempainen, S.; Martiskainen, H.; Tanila, H.; Haapasalo, A.; Hiltunen, M.; et al. Altered Insulin Signaling in Alzheimer’s Disease Brain—Special Emphasis on PI3K-Akt Pathway. *Front. Neurosci.* **2019**, *13*, 629. [[CrossRef](#)]
197. Rivera, E.J.; Goldin, A.; Fulmer, N.; Tavares, R.; Wands, J.R.; de la Monte, S.M. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer’s disease: Link to brain reductions in acetylcholine. *J. Alzheimer’s Dis.* **2005**, *8*, 247–268. [[CrossRef](#)]
198. Dubey, S.K.; Lakshmi, K.K.; Krishna, K.V.; Agrawal, M.; Singhvi, G.; Saha, R.N.; Saraf, S.; Saraf, S.; Shukla, R.; Alexander, A. Insulin mediated novel therapies for the treatment of Alzheimer’s disease. *Life Sci.* **2020**, *249*, 117540. [[CrossRef](#)]
199. Duarte, A.I.; Santos, M.S.; Seça, R.; Oliveira, C.R. de Insulin affects synaptosomal GABA and glutamate transport under oxidative stress conditions. *Brain Res.* **2003**, *977*, 23–30. [[CrossRef](#)]
200. Zhao, W.-Q.; Chen, H.; Quon, M.J.; Alkon, D.L. Insulin and the insulin receptor in experimental models of learning and memory. *Eur. J. Pharmacol.* **2004**, *490*, 71–81. [[CrossRef](#)]
201. Bruce, K.D.; Zsombok, A.; Eckel, R.H. Lipid Processing in the Brain: A Key Regulator of Systemic Metabolism. *Front. Endocrinol.* **2017**, *8*, 60. Available online: <http://journal.frontiersin.org/article/10.3389/fendo.2017.00060/full> (accessed on 9 October 2022). [[CrossRef](#)]
202. Barber, C.N.; Raben, D.M. Lipid Metabolism Crosstalk in the Brain: Glia and Neurons. *Front. Cell. Neurosci.* **2019**, *13*, 212. [[CrossRef](#)]
203. Bazinet, R.P.; Layé, S. Polyunsaturated fatty acids and their metabolites in brain function and disease. *Nat. Rev. Neurosci.* **2014**, *15*, 771–785. [[CrossRef](#)]
204. Low, Y.L.; Jin, L.; Morris, E.R.; Pan, Y.; Nicolazzo, J.A. Pioglitazone Increases Blood–Brain Barrier Expression of Fatty Acid-Binding Protein 5 and Docosahexaenoic Acid Trafficking into the Brain. *Mol. Pharm.* **2020**, *17*, 873–884. [[CrossRef](#)]
205. Watanabe, A.; Toyota, T.; Owada, Y.; Hayashi, T.; Iwayama, Y.; Matsumata, M.; Ishitsuka, Y.; Nakaya, A.; Maekawa, M.; Ohnishi, T.; et al. Fbp7 Maps to a Quantitative Trait Locus for a Schizophrenia Endophenotype. *PLoS Biol.* **2007**, *5*, e297. [[CrossRef](#)]
206. Sandoval-Salazar, C.; Ramírez-Emiliano, J.; Trejo-Bahena, A.; Oviedo-Solís, C.I.; Solís-Ortiz, M.S. A high-fat diet decreases GABA concentration in the frontal cortex and hippocampus of rats. *Biol. Res.* **2016**, *49*, 15. [[CrossRef](#)] [[PubMed](#)]
207. Lizarbe, B.; Cherix, A.; Duarte, J.M.N.; Cardinaux, J.-R.; Gruetter, R. High-fat diet consumption alters energy metabolism in the mouse hypothalamus. *Int. J. Obes.* **2019**, *43*, 1295–1304. [[CrossRef](#)] [[PubMed](#)]
208. Kwon, D. Guardians of the brain: How a special immune system protects our grey matter. *Nature* **2022**, *606*, 22–24. [[CrossRef](#)] [[PubMed](#)]
209. Beers, D.R.; Henkel, J.S.; Zhao, W.; Wang, J.; Appel, S.H. CD4+ T cells support glial neuroprotection, slow disease progression, and modify glial morphology in an animal model of inherited ALS. *Proc. Natl. Acad. Sci. USA* **2008**, *105*, 15558–15563. [[CrossRef](#)]
210. Gate, D.; Saligrama, N.; Leventhal, O.; Yang, A.C.; Unger, M.S.; Middeldorp, J.; Chen, K.; Lehallier, B.; Channappa, D.; De Los Santos, M.B.; et al. Clonally expanded CD8 T cells patrol the cerebrospinal fluid in Alzheimer’s disease. *Nature* **2020**, *577*, 399–404. [[CrossRef](#)]
211. Morales, I.; Guzmán-Martínez, L.; Cerda-Troncoso, C.; Farías, G.A.; Maccioni, R.B. Neuroinflammation in the pathogenesis of Alzheimer’s disease. A rational framework for the search of novel therapeutic approaches. *Front. Cell. Neurosci.* **2014**, *8*, 112. Available online: <http://journal.frontiersin.org/article/10.3389/fncel.2014.00112/abstract> (accessed on 10 October 2022). [[CrossRef](#)]
212. Wang, D.-S.; Zurek, A.A.; Lecker, I.; Yu, J.; Abramian, A.M.; Avramescu, S.; Davies, P.A.; Moss, S.J.; Lu, W.-Y.; Orser, B.A. Memory Deficits Induced by Inflammation Are Regulated by α 5-Subunit-Containing GABAA Receptors. *Cell Rep.* **2012**, *2*, 488–496. [[CrossRef](#)]
213. Richetto, J.; Calabrese, F.; Riva, M.A.; Meyer, U. Prenatal Immune Activation Induces Maturation-Dependent Alterations in the Prefrontal GABAergic Transcriptome. *Schizophr. Bull.* **2014**, *40*, 351–361. [[CrossRef](#)]
214. Lee, M.; Schwab, C.; McGeer, P.L. Astrocytes are GABAergic cells that modulate microglial activity. *Glia* **2011**, *59*, 152–165. [[CrossRef](#)]
215. Pribiag, H.; Stellwagen, D. TNF- Downregulates Inhibitory Neurotransmission through Protein Phosphatase 1-Dependent Trafficking of GABAA Receptors. *J. Neurosci.* **2013**, *33*, 15879–15893. [[CrossRef](#)]

216. Khare, P.; Datusalia, A.K.; Sharma, S.S. Parthenolide, an NF- κ B Inhibitor Ameliorates Diabetes-Induced Behavioural Deficit, Neurotransmitter Imbalance and Neuroinflammation in Type 2 Diabetes Rat Model. *Neuromol. Med.* **2017**, *19*, 101–112. [[CrossRef](#)]
217. Le Thuc, O.; Stobbe, K.; Cansell, C.; Nahon, J.-L.; Blondeau, N.; Rovère, C. Hypothalamic Inflammation and Energy Balance Disruptions: Spotlight on Chemokines. *Front. Endocrinol.* **2017**, *8*, 197. [[CrossRef](#)]
218. Dionysopoulou, S.; Charmandari, E.; Bargiota, A.; Vlahos, N.F.; Mastorakos, G.; Valsamakis, G. The Role of Hypothalamic Inflammation in Diet-Induced Obesity and Its Association with Cognitive and Mood Disorders. *Nutrients* **2021**, *13*, 498. [[CrossRef](#)]
219. Maciejczyk, M.; Żebrowska, E.; Chabowski, A. Insulin Resistance and Oxidative Stress in the Brain: What's New? *Int. J. Mol. Sci.* **2019**, *20*, 874. [[CrossRef](#)]
220. Jiang, H. Hypothalamic GABAergic neurocircuitry in the regulation of energy homeostasis and sleep/wake control. *Med. Rev.* **2022**, *2*, 531–540. Available online: <https://www.degruyter.com/document/doi/10.1515/mr-2022-0022/html> (accessed on 30 September 2022). [[CrossRef](#)]
221. Li, L.; Zhang, M.-Q.; Sun, X.; Liu, W.-Y.; Huang, Z.-L.; Wang, Y.-Q. Role of Dorsomedial Hypothalamus GABAergic Neurons in Sleep–Wake States in Response to Changes in Ambient Temperature in Mice. *Int. J. Mol. Sci.* **2022**, *23*, 1270. [[CrossRef](#)]
222. Fonseca-Santos, B.; Chorilli, M. The uses of resveratrol for neurological diseases treatment and insights for nanotechnology based-drug delivery systems. *Int. J. Pharm.* **2020**, *589*, 119832. [[CrossRef](#)]
223. Han, Y.-S.; Zheng, W.-H.; Bastianetto, S.; Chabot, J.-G.; Quirion, R. Neuroprotective effects of resveratrol against β -amyloid-induced neurotoxicity in rat hippocampal neurons: Involvement of protein kinase C: Neuroprotective effect of resveratrol. *Br. J. Pharmacol.* **2004**, *141*, 997–1005. [[CrossRef](#)]
224. Gu, J.; Li, Z.; Chen, H.; Xu, X.; Li, Y.; Gui, Y. Neuroprotective Effect of Trans-Resveratrol in Mild to Moderate Alzheimer Disease: A Randomized, Double-Blind Trial. *Neurol. Ther.* **2021**, *10*, 905–917. [[CrossRef](#)]
225. Salehi, B.; Calina, D.; Docea, A.; Koirala, N.; Aryal, S.; Lombardo, D.; Pasqua, L.; Taheri, Y.; Marina Salgado Castillo, C.; Martorell, M.; et al. Curcumin's Nanomedicine Formulations for Therapeutic Application in Neurological Diseases. *J. Clin. Med.* **2020**, *9*, 430. [[CrossRef](#)]
226. Mandel, S.A.; Amit, T.; Kalfon, L.; Reznichenko, L.; Youdim, M.B.H. Targeting Multiple Neurodegenerative Diseases Etiologies with Multimodal-Acting Green Tea Catechins. *J. Nutr.* **2008**, *138*, 1578S–1583S. [[CrossRef](#)] [[PubMed](#)]
227. Hanif, S.; Muhammad, P.; Chesworth, R.; Rehman, F.U.; Qian, R.; Zheng, M.; Shi, B. Nanomedicine-based immunotherapy for central nervous system disorders. *Acta Pharmacol. Sin.* **2020**, *41*, 936–953. [[CrossRef](#)] [[PubMed](#)]
228. Yavarpour-Bali, H.; Ghasemi-Kasman, M.; Pirzadeh, M. Curcumin-loaded nanoparticles: A novel therapeutic strategy in treatment of central nervous system disorders. *Int. J. Nanomed.* **2019**, *14*, 4449–4460. [[CrossRef](#)] [[PubMed](#)]
229. Da Rocha Lindner, G.; Bonfanti Santos, D.; Colle, D.; Gasnhar Moreira, E.L.; Daniel Prediger, R.; Farina, M.; Khalil, N.M.; Mara Mainardes, R. Improved neuroprotective effects of resveratrol-loaded polysorbate 80-coated poly(lactide) nanoparticles in MPTP-induced Parkinsonism. *Nanomedicine* **2015**, *10*, 1127–1138. [[CrossRef](#)]

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