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METABOLIC SYNDROME, ALZHEIMER DISEASE, SCHIZOPHRENIA, AND DEPRESSION: ROLE FOR LEPTIN, MELATONIN, KYNURENINE PATHWAYS, AND NEUROPEPTIDES

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Abstract: Metabolic dysregulation is intimately associated with a wide array of seemingly unrelated disorders, including schizophrenia, Alzheimer disease, and depression. Genetic susceptibility genes show significant overlap between Alzheimer disease and schizophrenia, suggesting overlap in underlying biological processes, including metabolic. The high levels of depression in both disorders is linked to these shared processes. This chapter reviews the data suggesting that changes in leptin levels and leptin resistance mediate many of these metabolic changes, including the regulation of tryptophan catabolites (TRYCATs) and neuropeptides, which in turn drives alterations in cognition, neurogenesis, and apoptotic pathways. On the basis of this, treatment implications are proposed including the use of melatonin, together with leptin, in the prevention and treatment of these poorly managed disorders.

13.1 INTRODUCTION

Schizophrenia and Alzheimer disease have some significant overlaps, including susceptibility genes and neuronal atrophy. This could be viewed as consistent with Kraepelin's original conceptualization of schizophrenia as *dementia praecox* (literally "early dementia"). As evidenced by neuroimaging studies, schizophrenic patients have ongoing volume loss in areas of the medial temporal lobe and frontal cortex [1], suggesting an ongoing, if relatively limited, neurodegenerative process, usually termed neuroprogression. Neuroprogression is associated with neuronal apoptosis, lowered neurogenesis, and neuroplasticity. Neuroprogression is at least partly driven, as in Alzheimer disease brain atrophy, by immunoinflammation as well as oxidative and nitrosative stress (O&NS) pathways [2].

Interestingly, many of the genes associated with the dementia process in Alzheimer disease, including B-site APP-cleaving protein-1 (BACE1), amyloid precursor protein (APP), fibroblast growth factor-1

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(FGF1), Notch, Neuregulin-1 (NRG-1), apolipoprotein E (ApoE), interleukin-18 (IL-18), presenilin-2 (PSEN2), and transforming growth factor-beta1 (TGF-β1), are susceptibility genes in schizophrenia [3–8]. This suggests overlaps in the processes associated with these two disorders. There are a number of ways in which this could occur.

The etiology of schizophrenia is strongly associated with maternal prenatal infection, both viral and bacterial [9], highlighting a powerful causal role for immuno-inflammatory changes in early development. Many schizophrenia susceptibility genes are most highly expressed in early development, suggesting an interaction of processes of prenatal infection with schizophrenia susceptibility genes. Recent data in animal models also shows a role for prenatal infection in the etiology of Alzheimer disease. Prenatal PolyI:C infection, a viral mimetic infection, at prenatal day 17 increases levels of Alzheimer disease associated peptide amyloid B in the adult offspring [10]. PolyI:C infection at earlier time points is associated with changes more linked to schizophrenia.

Another point of overlap of schizophrenia and Alzheimer disease is the increased levels of comorbid depression. Up to 61% of schizophrenic patients have comorbid depression; often going undiagnosed [11], and depression levels are high in Alzheimer disease, often seeming to mimic some of the cognitive changes of the early stages of the disease. Depression in Alzheimer disease is often conceptualized as prodromal, contributing to an episode of cognitive losses and neurodegeneration. Each depressive episode decreases measured cognitive abilities by 2–3% [12]. Recently it has been suggested that the early developmental etiology of schizophrenia actively primes for later increases in depression [13]. As to whether similar processes operate in Alzheimer disease requires further investigation.

A further point of overlap of schizophrenia, Alzheimer disease, and mood disorders is their association with metabolic dysregulation. Obesity and wider metabolic dysregulation increases the risk of Alzheimer disease and depression [14, 15], as well as being a susceptibility factor for antipsychotic induced metabolic dysregulation in schizophrenia. In the context of a prenatal etiology it is of note that maternal obesity is a significant modulator of obstetric complications, including preeclampsia, a known risk factor for a number of offspring disorders, including schizophrenia [16].

Increased O&NS and changes in immuno-inflammatory processes mediate many of their effects on cognition, neuroprogression, and neurodegeneration via the regulation of the tryptophan catabolite (TRYCAT) pathway [17]. Leptin, released by adipocytes, is a powerful regulator of food intake and metabolic processes. Leptin is also a significant immune regulator and would be expected to directly modulate TRYCAT activity, both centrally and peripherally, in turn contributing to processes of neuroprogression and neurodegeneration. The role of leptin in the regulation of overlapping aspects of neurodegenerative and related psychiatric disorders is the theme of this chapter.

13.2 TRYPTOPHAN CATABOLITE (TRYCAT) PATHWAYS

The TRYCAT pathways are an important mediator of the association of O&NS and immuno-inflammatory activation with alterations in glia-neuronal interactions and neuronal activity [17]. An emerging consensus proposes that O&NS interacts with changes in immuno-inflammatory activity, increasing levels of IFNγ and other proinflammatory cytokines, in turn activating indoleamine 2,3-dioxygenase (IDO). This drives tryptophan down the TRYCAT pathways, decreasing serotonin and melatonin production, in turn increasing depression and metabolic dysregulation. The TRYCATs, kynurenine (kyn) and kynureninc acid (KYNA), can also be produced via the activation of tryptophan 2,3-dioxygenase (TDO) by cortisol and the cAMP pathway [18]. TDO is highly expressed in the liver, but also in astrocytes and some neurons [19]. As well as the direct effects of various TRYCATs, including kyn, KYNA, 3-hydroxykynurenine (3-OHK) and quinolinic acid (QUIN) on neuronal activity both centrally and peripherally, it is proposed here that alterations in leptin drive changes in TRYCATs and neuropeptides, including substance P (SubP) and endogenous opioids, which are the effectors of these oxidative and inflammatory pathways in driving changes in local neuronal, glia, and immune activity, as well as survival.

13.3 LEPTIN AND TRYCATs

Following its release by adipocytes, leptin has to be transported across the blood–brain barrier (BBB), mediating its appetite suppressing effects predominantly in the hypothalamus. However, leptin receptors are expressed in many other CNS regions, including the hippocampus and frontal cortex, where leptin receptors are also evident in astrocytes, key neuronal regulators [20]. Leptin is known to activate many intracellular pathways, including signal transducer and activator of transcription (STAT)5, extracellular signal-regulated kinase (ERK)1/2 and phosphoinositol-3 kinase (PI3K)/Akt, increasing cell survival via the induction of the anti-apoptotic bcl-2 [21]. Leptin also decreases the release and effects of cortisol, possibly via increased bcl-2 associated anthanogene-1 (BAG-1). BAG-1 inhibits the nuclear transport of cortisol's glucocorticoid receptor (Gcr), decreasing cortisol's effects [22]. Leptin also inhibits the adenylyl cyclase (AC) pathway, decreasing levels of cyclic adenosine 3′,5′-mono-phosphate (cAMP) and protein kinase A (PKA). These inhibitory effects of leptin on cortisol and cAMP pathways suggest that leptin is a significant inhibitor of TDO and its products, the neuronal modulating kyn and KYNA.

KYNA inhibits the alpha 7 nicotinic acetylcholine receptor (a7nAChr), decreasing a7nAChr induction of frontal cortex glutamate, dopamine, and ACh release. This decreases levels of optimal cortex arousal, decreasing cognitive processing and contributing to the emergence of cognitive deficits. Increased central KYNA is evident in schizophrenia, mood disorders and mild cognitive impairment (MCI). MCI is generally seen as the forerunner to an Alzheimer disease diagnosis. This would suggest that leptin, via the inhibition of TDO and KYNA, would increase a7nAChr activity, optimizing arousal-associated cognition. And indeed this would seem to be the case, with CNS targeted leptin being proposed as a treatment for both Alzheimer disease and depression [23, 24]. An a7nAChr agonist reduces weight gain and wider metabolic dysregulation in the leptin resistance db/db mouse model of type 2 diabetes, suggesting a role for increased KYNA induced a7nAChr inhibition in metabolic syndrome [25]. A decrease in KYNA and increased QUIN and kyn is evident at more progressive stages of Alzheimer disease, contributing to excitotoxic neuronal loss [26].

Leptin is also associated with the activation of Amp-activated protein kinase (AMPK), which is classically seen as an energy sensor, being increased primarily by cAMP and Ca^{2+} in neurons. It is thought that increased AMPK activation can delay the appearance of Alzheimer disease, but its activation during the course of the disorder triggers detrimental effects [27], not dissimilar to the effects of estrogen and hormone replacement therapy [28]. Leptin also increases levels of the longevity associated protein sirtuin-1, another known mediator of mitochondrial energy production via peroxisome proliferator-activated receptor-γ (PPARγ) coactivator-1α (PGC-1α) [29]. The ability of leptin to decrease levels of hyperphosphorylated tau and amyloid B is partly dependent on the induction of AMPK and sirtuin-1. Sirtuin-1 is anti-apoptotic, decreasing levels of p53 [30]. Interestingly, the activation of the IDO pathway, as well as producing numerous neuroactive TRYCATs, ultimately increases levels of NAD +, in turn increasing sirtuin-1. This suggests that leptin has a role in the delicate balance between the production of specific TRYCAT products and the induction of metabolic regulators, with some of these effects being mediated via epigenetic regulation of patterned gene expressions [31].

13.3.1 Leptin Resistance

Under conditions of heightened leptin release, leptin loses its ability to activate its intracellular effector pathways, a phenomenon labelled *leptin resistance*. Leptin resistance occurs in obesity, wider metabolic syndrome, and in response to antipsychotic medication, resulting in heightened levels of circulating leptin and decreased transport of leptin over the BBB. This may be mediated by increased production and release of leptin by immune cells in the CNS. Leptin resistance is also suggested to occur in astrocytes, with chronic leptin increasing levels of astrocyte activation [32]. A number of factors are known to modulate leptin transport over the BBB. Raised levels of circulating triglycerides decrease BBB leptin transport [33]. At the blood-cerebral spinal fluid barrier, megalin mediates the transport of leptin, which is

inhibited by the effects of amyloid B [34]. In neurons and other cells, leptin resistance seems to be mediated by increased levels of cAMP, leading to the activation of exchange protein directly activated by cAMP (Epac) [35]. This suggests that increased TDO induction by cAMP would be associated with leptin resistance. The role of the cAMP path in mediating and modulating the effects of neuropeptides, including SubP and endogenous opioids, suggests that variations in leptin and leptin resistance will be coordinated with the effects of these neuronal modulating neuropeptides. The role of the cAMP pathway in the regulation of leptin resistance in different cell types *in vivo* requires further investigation.

Single nucleotide polymorphisms (SNPs) in leptin are associated with increased weight gain, including antipsychotic-induced weight gain [36]. The rate of diagnosis of schizoaffective disorder at initial psychotic presentations is less than 1%. However, one year later the level of schizoaffective disorder is around 15%, increasing further in later years [37]. These data suggest that leptin resistance may play a role in driving mood dysregulation. In the case of schizophrenia, and perhaps Alzheimer disease, leptin resistance would be acting on a prenatally primed risk for depression in the etiology of these disorders [17].

Leptin resistance has consequences for the regulation of stress, including via changes in cortisol and probably BAG-1. BAG-1 prevents the effects of chronic unpredictable mild stress (CUMS) in the induction of depression [22]. Given that the induction of depression is associated with cognitive decrements of 2–3% following each episode [12], this would suggest that variations in leptin and leptin resistance would modulate the consequences of CUMS, including its association with depression-linked neuroprogressive and neurodegenerative disorders. It remains to be determined whether leptin resistance would then alter the regulation of TRYCAT products by CUMS [38, 39]. Laugeray and colleagues [38, 39] found that CUMS increased levels of QUIN in the amygdala and striatum, also showing a trend increase in KYNA in the cortex. As such, variations in leptin would then modulate the CNS patterned response to stress, at least in part via the differential regulation of TRYCAT pathway products. As to whether leptin resistance and an altered stress response contribute to the mechanisms by which stress induces symptom exacerbations and treatment resistance in depression and schizophrenia, as well as degenerative processes in Alzheimer disease requires investigation. Certainly an increase in excitotoxic QUIN is associated with neuronal degeneration in Alzheimer disease, as well as the emergence of seizures [40].

13.3.2 Leptin Resistance, Decreased Leptin, and Neurodegeneration

A consequence of leptin resistance or decreased CNS leptin would be raised levels of astrocyte TDO and KYNA production, leading to the inhibition of the a7nAChr, and decreasing levels of arousal associated cognition, concurrent to decreasing levels of bcl-2 induced survival pathways. Such changes are relevant to data showing an interaction of metabolic syndrome with neuroprogressive and neurodegenerative disorders. Alterations in TDO, a7nAChr, and bcl-2 will modulate the cognitive deficits present in obesity [41], contributing to the susceptibility to Alzheimer disease in obese individuals [42, 43]. Many of these effects are likely to be induced as a consequence of leptin resistance.

However, it should be noted that in the absence of leptin resistance a decrease in leptin levels increases the risk of Alzheimer disease developing in elderly populations [44]. Over the natural progression of Alzheimer disease there is a progressive decrease in body mass index (BMI), in part mediated by amyloid B inhibition of leptin production. Through its activation of the PI3K/Akt pathway leptin phosphorylates and inhibits glycogen synthase kinase 3-beta (GSK-3b), which is proposed to mediate its protective effects centrally, including in the regulation of food intake and glucose metabolism [45]. In animals with leptin deficiency, hypothalmic GSK-3b inhibition prevents glucose dysregulation, whereas the overexpression of active GSK-3b increases hyperphagia, obesity, and glucose dysregulation [45]. The leptin inhibition of GSK-3b will decrease levels of tau hyper-phosphorylation and amyloid B production, subsequently decreasing levels of Alzheimer disease associated tangles and plaques [46]. The phosphorylation of GSK-3b will also prevent the phosphorylation and inhibition of Nrf-2 by GSK-3b, increasing levels of Nrf-2 driven endogenous anti-oxidants [47]. As well as being directly neuroprotective leptin

driven changes in oxidant status will also modulate TRYCAT pathway activity, and therefore neuronal activity [48]. Such protective effects will be lost in conditions of leptin resistance and decreased leptin production.

13.3.3 Leptin, Leptin Resistance, and Melatonin

In lower animals, leptin increases the levels of norepineoherine (NE) induced pineal melatonin and N-acetylserotonin (NAS) production via an increase in arylalkylamine-N-acetyltransferase (AANAT) [49]. Melatonin is decreased in many neurodegenerative, metabolic, and psychiatric disorders that are thought to be primarily mediated by increased levels of IDO and TDO driving tryptophan down the TRYCAT pathways and away from serotonin and melatonin production, or from raised levels of TNF-α, which inhibits pineal effluxes [50]. As to whether more direct effects of leptin via the regulation of AANAT are relevant to human pineal and immune cell melatonin and NAS production requires further investigation. Melatonin has many similar effects to leptin, inhibiting AC and increasing natural killer (NK) cell cytotoxicity, as well as wider immune modulation [51]. Melatonin also decreases levels of diet-induced obesity, lowering levels of triglycerides and leptin in cases of leptin resistance [52]. Overall, this could suggest mutual regulatory interactions between leptin and melatonin.

Melatonin also increases levels of mitochondrial oxidative phosphorylation [53], enhancing metabolic activity and favoring the differentiation of mesenchymal stem cells into osteoblasts, strengthening bone and decreasing adipocyte differentiation [54]. An increase in osteoporosis is evident in both schizophrenia and Alzheimer disease [55]. Increased levels of BAG-1, which acts as a chaperone for vitamin D3 to the nuclear vitamin D receptor, might mediate some of this efficacy, thereby enhancing the bone-promoting effects of vitamin D3 [56]. As such melatonin, including via its interaction with leptin, significantly modulates metabolic activity and wider metabolic-associated deficits. It requires investigation as to whether the co-administration of leptin and melatonin would have any additive effects in the treatment of the metabolic dysregulation association with neurodegenerative and neuroprogressive disorders, or whether the sequential use of melatonin and leptin would be efficacious in cases of leptin resistance.

13.3.4 Wider Leptin and Melatonin Interactions

IGF-1 Insulin-like growth factor-1 (IGF-1), like leptin, decreases levels of amyloid B production and tau hyperphosphorylation. Amyloid B inhibits the production of leptin by the mammalian target of rapamycin complex-1 (mTORC1) pathway and inhibits IGF-1 production by the Janus kinase (JAK)/STAT pathway [57]. Given that IGF-1 can activate the mTORC1 pathway and leptin activates the JAK/STAT path, IGF-1 and leptin will mutually induce one another as evidenced in the rabbit hippocampus [57]. This may have some relevance to the ligand independent effects of the estrogen receptor-alpha (ER-α), which forms a complex with the IGF-1r and VDAC1 within caveolae in the plasma membrane leading to estrogen-like trophic effects [58].

Neurogenesis Of relevance to the changes associated with neurodegenerative and neuroprogressive disorders, leptin increases proliferation of neuronal progenitors, contributing to the neuroprotection afforded in depression and Alzheimer disease models [59]. Any increase in BAG-1 by leptin and melatonin, via decreased cortisol Gcr activation, will inhibit cortisol suppression of neurogenesis as well as inhibiting stress enhancement of adipocyte differentiation and wider neuronal atrophy [60, 61]. The maintenance or enhancement of neurogenesis will inhibit the course of schizophrenia.

Substance P An increase in SubP is associated with depression [62]. Stress also increases the release of SubP [63]. Activation of the SubP neurokinin-1 receptor (NK1r) is essential for the dopamine response to stress [64]. In NK1r knockout rodents there are significant changes in serotonergic, as well as dopaminergic and noradrenergic activity in the prefrontal cortex [65–67]. Inhibition of SubP and the NK1r are clinical targets for anti-depressant treatment [68, 69], as well as pain management [68]. An increase in SubP in conjunction with increased kyn/KYNA ratio is likely to

contribute to the high levels of comorbid somatization in depression and schizophrenia [70], suggesting efficacy of melatonin and leptin, as well as the inhibition of SubP in the treatment of this common comorbidity. There is currently a paucity of data on SubP changes in schizophrenia, out with its role in respiration pneumonia [71], although antipsychotics may differentially regulate SubP levels [72].

SubP activation of the NK-1r increases cAMP and therefore will increase levels of TDO-induced kyn and KYNA, contributing to alterations in cognition and mood, as well as nociception and possibly leptin resistance. As well as modulating levels of stress associated cortisol production; leptin and melatonin will inhibit SubP effects via the inhibition of the AC/cAMP pathway. This may have relevance to the SubP induction of VEGF from mast cells and astrocytes, with VEGF increasing BBB permeability [73].

Activation of the NK1r prevents the internalization and desensitization of the μ-opioid receptor by decreasing beta-arrestin2 in CNS regions, including the striatum, amygdala, and locus coeruleus [74]. SubP in the amygdala is associated with the induction of fear and anxiety [75]. The NK1r is variably expressed in different amygdala nuclei [76]. This could suggest significant interactions between the levels and activity of the μ-opioid receptor and NK1r in different amygdala nuclei, with relevance to both the etiology of schizophrenia [77] as well as to the induction and course of depression and Alzheimer disease. SubP in the central amygdala has anxiolytic effects leading to decreased alcohol consumption in rodents [78, 79], which suggests differential effects of SubP in different amygdala nuclei. Whether the differential rate of maturation of amygdala subnuclei over the course of normal development interact with the effects of maternal infection in the etiology of schizophrenia and perhaps Alzheimer disease, to drive the differential expression of the opioids, μ-opioid receptor, SubP and NK1r in amygdala subnuclei, requires further investigation. This would suggest an early developmental etiology to the association of depression with both schizophrenia and Alzheimer disease. Variations in placental leptin and melatonin production, which are dramatically altered in obstetric complication such as preeclampsia [80], could then have a significant impact on the etiological biochemical underpinnings of later neuroprogressive and neurodegenerative disorders.

Interestingly SubP, although not affecting basal levels of either AANAT activity or melatonin secretion in rat pineal organ cultures, does inhibit the NE-induced increase in AANAT activity, as well as NAS and melatonin secretion [81]. This suggests that SubP has opposing effects to leptin regarding the regulation of AANAT. This is not only relevant to pineal melatonin production and its decrease in depression, Alzheimer disease, and schizophrenia, but also to the production of melatonin by glia and immune cells [82], which seems important in the termination of immune cell inflammatory responses. This suggests that SubP will alter melatonin and leptin interactions.

Opioids The μ-opioid receptor is negatively coupled to the AC/cAMP/PKA pathway and would be expected to inhibit TDO induction by cAMP, as well as many other cAMP regulated genes [83]. However, under more prolonged activation and in CNS cells, the μ-opioid receptor can activate cAMP pathways [84, 85], dependent on μ-opioid receptor presence within plasma membrane lipid rafts [86, 87]. As such, the central μ-opioid receptor, via cAMP pathways, will have a role in the regulation of TDO and circadian genes such as Period-1, which are altered in depression, Alzheimer disease, and schizophrenia [88, 89], as well as a role in the regulation of SubP and its neurokinin (NK) receptors [90]. The adjunctive use of low dose morphine with antipsychotics improves treatment efficacy, suggesting further the importance of the opioidergic system in the pathophysiology of schizophrenia at different CNS sites [91]. Increased μ-opioid receptor levels in the hypothalamus and nucleus accumbens are associated with increased food intake, whereas an increase in the amygdala enhances the palatability of fat [92]. The opioidergic system also modulates BACE-1 and amyloid B production [93].

Increased IFNγ is the main inducer of IDO, and unlike IL-1β, IL-6, IL-13 or TNFα, IFNγ decreases levels of the μ-opioid receptor [94, 95]. The μ-opioid receptor is expressed in TH2 but not TH1 T-cells; highlighting that cytokine-mediated changes in levels of the μ-opioid receptor will modulate immune as well as neuronal activity and nociceptive regulation. Increased central levels and activity of the μ-opioid receptor are evident in depression under conditions of emotional exposure during an fMRI

[96]. Such enhanced μ-opioid receptor activations positively correlate with IL-18 levels. IL-18 is a major inducer of IFNγ and is a susceptibility factor for schizophrenia and Alzheimer disease [97, 98]. This could suggest that μ-opioid receptors are altered in association with increased IDO and TRYCAT pathway activation, with IFNγ negatively feeding back on μ-opioid receptor levels. The μ-opioid receptor is stimulatory in microglia but immunosuppressive in peripheral macrophages including via decreasing levels of TLR-4 [99], suggesting differential peripheral versus central effects of IFNγ on μ-opioid receptor effects. As such, the changes in the μ-opioid receptor are intimately associated with inflammatory and TRYCAT changes, giving the μ-opioid receptor an effector role in driving changes in immune as well as neuronal activity.

Both leptin and melatonin increase levels of TH1 T-cell activity and can contribute to increased IFNγ, in turn decreasing levels of the μ-opioid receptor. However, both leptin and melatonin, via the inhibition of the AC/cAMP pathway, will modulate the effects of μ-opioid receptor activation, perhaps differentially in the periphery versus centrally. As such, leptin resistance will also have indirect effects on food intake, fat palatability, and mood and immune regulation via its modulation of the induction and activity of the μ-opioid receptor. This is also likely to be relevant in the early developmental etiology of neuroprogressive and neurodegenerative disorders.

Maternal high-fat diet (mHFD) during pregnancy increases the levels of the mu-opioid receptor and its endogenous ligand enkephalin twofold at specific time points in the offspring, concurrently increasing levels of the dopamine transporter tenfold [100]. In the context of a role for maternal infection and immuno-inflammatory activity in the etiology of Alzheimer disease, and especially schizophrenia, it would seem likely that mHFD would interact with such immuno-inflammatory activation, modulating not only metabolic dysregulation in the offspring but also the susceptibility to these adult onset disorders. Alterations in the levels of the μ-opioid receptor in amygdala subregions are proposed not only to increase fat palatability but also to modulate the developmental influence of the relatively early maturing amygdala on the development of other brain regions [77]. Such changes in amygdala activity, classically associated with mood disorders, allow an early developmental link to priming for depression in neurodegenerative and neuroprogressive disorders, and the association of depression with progressive cognitive decrements. As such, the regulation of the cAMP pathways by leptin and melatonin would have wider impacts on neuropeptides regulation of neuronal development and patterned activity, as well as on TRYCAT pathway expressions.

In a community population sample of older adults, a predisposition to depression was associated with obesity, but only in those showing evidence of metabolic dysregulation, including increased triglycerides, cholesterol, and C-reactive protein [101]. This highlights the necessity of metabolic dysregulation in mediating increases in depression and in the depression-associated cognitive decrements that contribute to neurodegenerative and neuroprogressive disorders. It requires investigation as to whether the metabolically healthy and unhealthy obese have been differentially primed in early development, as well as to the role of melatonin and leptin interactions and their impacts via TRYCATs and neuropeptide regulation.

13.4 TREATMENT IMPLICATIONS

A number of treatments, with very limited efficacy, are used in the management of Alzheimer disease, some of which also have clinical relevance in the treatment of neuroprogressive disorders such as schizophrenia and depression. The discussion in this chapter provides a frame of reference for these treatment effects, including the role of O&NS and immuno-inflammation, as well as TRYCAT and neuropeptide pathways in driving metabolic changes that are relevant to the etiology, course, and management of neurodegenerative and neuroprogressive adult onset disorders. Variations in leptin and melatonin are significant regulators and coordinators of these effects.

13.4.1 Acetylcholinesterase Inhibitors

The rationale for the use of acetylcholinesterase inhibitors (AChEi) is their increase in arousal-associated cognition via increased availability of ACh. As such AChEi, such as donepezil, will compensate the increased KYNA inhibition of the

a7nAChr, improving cognition. AChEi are widely used in the treatment of schizophrenia. Donepezil is also known to increase the phosphorylation and inhibition of GSK-3b, contributing to metabolic regulation and neuronal survival [102]. However, over a six-month treatment period in mild to moderate Alzheimer disease patients, donepezil decreased levels of leptin, as well as increasing levels of adiponectin. Concurrently, there was a significant decrease in BMI and waist circumference [103]. Given the association of decreased leptin and weight loss with the progression of Alzheimer disease, this study questions the utility of AChEi on their own and perhaps suggests that the adjunctive use of leptin may be of clinical benefit.

13.4.2 Metformin

A consequence of metabolic dysregulation is an increased risk of type 2 diabetes, which in turn increases the risk of Alzheimer disease. In leptin deficient db/db mice, metabolic dysregulation is associated with increased levels of amyloid B and hyperphosphorylated tau. Metformin decreased the levels of these changes associated with Alzheimer disease [104], improving prefrontal cortex connectivity [105]. Recent data in rodents suggests that there could be a positive feedback loop between Alzheimer disease associated amyloid B and the changes occurring in type 2 diabetes [106]. The effect of metformin in HepG2 cells is via increased AMPK and sirtuin-1 and a decrease in the apoptotic protein p53, suggesting combined anti-apoptotic and metabolic efficacy [107]. A recent meta-analysis showed some limited efficacy for the adjunctive use of metformin in preventing the metabolic dysregulation induced by antipsychotics [108].

13.4.3 Leptin

Leptin has been widely used in human trials in the treatment of many conditions, although research has focused mostly on the treatment of metabolic dysregulation. Leptin has proven to be safe at different concentrations in diverse patient groups [109]. As such, the efficacy of leptin in models of Alzheimer disease and depression, and its potential in the treatment of schizophrenia, suggests significant clinical promise in these poorly managed disorders. Leptin's inhibition of the cAMP and cortisol induction of TDO and KYNA is likely to directly modulate cognitive functioning. The leptin enhancement of the anti-apoptotic bcl-2 and its phosphorylation and inhibition of GSK-3b will increase neuronal survival under challenge, decreasing neuroprogression and neurodegeneration. Leptin induction of sirtuin-1, decreased in Alzheimer disease [110] and schizophrenia [111] will also contribute to its neuroprotective and metabolic benefits. Its inhibition of the cAMP pathway is likely to decrease the depression and pain-enhancing effects of SubP via the NK-1r, as well as modulating the diverse effects of the μ-opioid receptor. As previously highlighted, leptin is intimately linked to many aspects of the etiology, course, and management of both neuroprogressive and neurodegenerative disorders. Leptin may also have a role in the regulation of melatonin and NAS via its modulation of NE induced pineal AANAT.

13.4.4 Melatonin

Many preclinical studies over recent years have shown a powerful benefit of melatonin in the treatment of diet-induced obesity [52]. Melatonin is a powerful anti-oxidant, anti-inflammatory, and immune regulator as well as an agent that increases levels of mitochondrial oxidative phosphorylation [53]. Its use clinically has been relatively undertested perhaps due to lack of interest from pharmaceutical companies, given its prescription-free availability in many countries. Melatonin's role in the etiology, course and management of schizophrenia has been recently described, including in offsetting the metabolic dysregulation induced by antipsychotics [112]. Melatonin has very significant efficacy in many preclinical models of Alzheimer disease and, like leptin, seems to favorably modulate many factors thought to be significant in Alzheimer disease, including increasing sirtuin-1 [113]. Melatonin decreases leptin resistance preclinically, and as previously suggested, may allow subsequent use of leptin, providing additional metabolic and wider benefits. Whether melatonin and leptin have additive or synergistic interactions in the regulation of BAG-1 requires investigation.

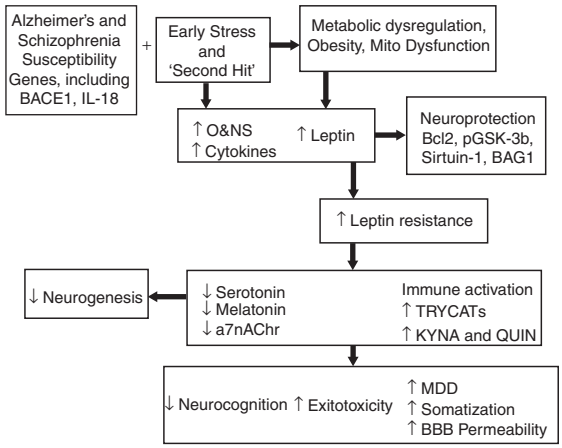

Fig. 13.1 Alzheimer and schizophrenia susceptibility genes interact with maternal infection, preeclampsia, and subsequent "second hits" to drive changes in metabolic regulation, increasing obesity and mitochondrial dysfunction. This leads to increased oxidative and nitrosative stress (O&NS), pro-inflammatory cytokines, and leptin. Leptin has a number of neuroprotective effects, increasing pro-survival proteins. However, an increase in cAMP drives increased leptin resistance, contributing to increased TDO and removal of tryptophan from serotonin and melatonin production while increasing tryptophan catabolites (TRYCATs), such as kynurenic acid (KYNA) and quinolinic acid (QUIN). This is concurrent to altered immune regulation. This combines to decrease neurogenesis and contribute to decrements in cognition while increasing excitotoxicity, depression (MDD), somatization, and blood–brain barrier (BBB) permeability.

The antipsychotic olanzapine increases prefrontal cortex ACh in rodents, which depends on leptin expression [114]. Olanzapine decreases rodent melatonin production by 55% [115], with preliminary data in schizophrenic patients showing beneficial effects of melatonin on parameters of metabolic dysregulation [116]. This highlights the interactive nature of melatonin and leptin with mediators of metabolic dysregulation.

13.5 CONCLUSION

The seemingly unrelated adult onset disorders of schizophrenia and Alzheimer disease have significant overlap, including genetic susceptibility genes. The high levels of depression in both disorders may reflect process changes involving metabolic dysregulation, as highlighted in Figure 13.1. Changes in levels of leptin and leptin resistance mediate many of these metabolic changes, including via the regulation of TRYCATs and neuropeptides, in turn driving alterations in cognition, neurogenesis, and apoptotic pathways. The utilization of melatonin, including in conjunction with leptin in the absence of leptin resistance, may prove of significant value in the prevention and treatment of these poorly managed disorders.

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