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Unraveling the complex interplay of immunometabolic systems that contribute to the neuroprogression of psychiatric disorders

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ABSTRACT

In this review article we present an integrative overview of parameters and mechanisms underlying psychiatric and neuropsychiatric disorders that involve the immune and autonomic nervous systems along with neurotransmission and specific endocrine mechanisms. At the center of these highly complex and interactive mechanisms is stress and stress perception by the afflicted individual. Stress reactivity is governed by genetic and epigenetic factors that have yet to be fully clarified. Stress is defined as a state of threatened homeostasis following exposure to extrinsic or intrinsic adverse forces. The major pathways activated by stressors are the HPA axis and the autonomic nervous system. Loss of dynamic variability in the autonomic nervous system, during which one branch dominates over the other for extended periods of time and across multiple environmental demands, is associated with illness and eventually chronic disease. This state of dysregulation can be achieved by excessive sympathetic activation, too little parasympathetic activation, or some combination of both. Autonomic dysregulation leads to immune system dysregulation which in turn interferes with the metabolism of tryptophan leading to the formation of toxic and diabetogenic metabolites. We introduce the concept of neuroprogression as a suitable conceptual framework that allows integration of the complex component mechanisms that contribute to recurrence and chronicity of mental disorders if left untreated or undertreated. The complex interactions among the autonomic, endocrine, immune and metabolic systems and associated cascades provide unique opportunities for development of novel therapeutic agents.

1. Introduction

Psychiatric and neuropsychiatric disorders are chronic, recurrent and relapsing conditions that affect the world's population with a significant lifetime prevalence. The etiopathologies of these conditions are complex and involve genetic and epigenetic burden, multisystem involvement and cross communications between and among such systems that only now we are beginning to unravel. Our treatment armamentaria are fairly limited with only a fraction of the afflicted individuals achieving remission. At this point in time we cannot cure any of these conditions and not infrequently we do not even achieve adequate symptomatic relief. For decades our investigative and pharmacologic approaches were guided by theories based on monoaminergic transmission. While these theories were heuristically extremely helpful, they failed to lead to widely effective treatment modalities. During the past two decades the role of the immune system has become clearer in regards to its contribution to psychopathology and mental illnesses in general both in regards to etiopathology but also in the development of promising new therapeutic interventions.

We introduce the concept of Neuroprogression in this review article because we believe this is a pertinent and appropriate concept to integrate many of the component mechanisms that are held responsible for the progressive, recurrent and relapsing course of a specific disorder (Berk, 2009; Post, Fleming, & Kapczinski, 2012). Neuroprogression can facilitate the 'staging' of the progressive course of the specific disorder based not only on phenomenological manifestations, but importantly on replicated morphological, biochemical, neurochemical, immunological, physiological and genetic aspects. These parameters can be standardized and used to stage neuropsychiatric disease entities not unlike the stages in oncology. Among the various pathophysiologic mechanisms that contribute to neuroprogression, neuroinflammation, oxidative stress, metabolic abnormalities and loss of synaptic plasticity feature prominently. Neuronal loss and structural changes in specific brain regions and structures, notably, the hippocampus, amygdala, orbitofrontal cortex, anterior cingulate cortex, basal ganglia and pituitary gland have been associated with progressive pathology in affective

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disorders (Haroon, Fleischer, & Felger, 2016; Price & Drevets, 2010). The significant clinical implications of neuroprogression in psychiatric disorders as well as the biological mechanisms underlying neuroprogression are obvious and should not be underestimated. Likely pathophysiological substrates include a sustained proinflammatory state, increased oxidative stress, metabolic aberrations and deficits in neuroprotection and neuroplasticity. There is also a complex interplay with the monoaminergic, cholinergic, glutamatergic and GABAergic neurotransmitter systems that require further elucidation. We will focus our discussion on the metabolism of tryptophan and the kynurenine pathway but it is underscored that other neurotransmitters are also dysregulated, notably catecholaminergic transmission. We are referring the interested reader to our recently published monograph (Halaris & Leonard, 2017).

2. Role of stress

Stress is defined as a state of threatened homeostasis following exposure to extrinsic or intrinsic adverse stimuli, events or triggers. Threats to the physical or mental integrity of the organism, can be real or perceived, single or repeated events generally of a negative nature (Chrousos & Gold, 1992). Stress can be physiological or psychological in nature and most often it is mixed. It can be acute or chronic in duration. Acute stress refers to stress that occurs for minutes or hours, whereas chronic stress persists for days, weeks, or months. Chronic stress, and especially the perception that the stressful event or predicament is inescapable, can ultimately lead to pervasive mental status changes and pathological alterations to the function and structure of organ systems possibly with irreversible damage (Olff, 1999). Stress activates key pathways, notably the hypothalamic-pituitary-adrenal (HPA) axis and the Autonomic Nervous System (ANS). Activation of the sympathetic branch (SNS) of the ANS leads to sympathoadrenal (SA) activation with resulting increases in plasma catecholamines, vasoconstriction, elevated heart rate, and platelet activation, these being contributory factors to cardiovascular morbidity and co-morbidity with neuropsychiatric disorders. Additionally, SNS activation leads to an imbalance in ANS function, that can be chronic in duration, with associated persistent reduction in vagal tone, as is the case in psychiatric and neurological disorders. These pathophysiological changes can affect profoundly vascular physiology and the immune system. Immune system activation following acute and chronic stress has been documented in the literature with associated increases in inflammatory biomarkers (Ader, Cohen, & Felten, 1995; Maes, Song, & Lin, 1998; Weik, Herforth, Kolb-Bachofen, & Danzer, 2008). Stress has been associated with depression in that it may trigger a depressive episode, exacerbate an existing episode and significantly affect the course of the disorder (Gold, Machado-Vieira, & Pavlatou, 2015). Thus, autonomic imbalance and decreased parasympathetic activity, in particular, may be the final common pathway to numerous diseases and conditions associated with increased morbidity and mortality. With respect to the association of stress with neuroinflammation, there is robust evidence that diverse psychosocial stressors, such as prenatal and postnatal stress and stressors in adult life, lead to microglial activation in the hippocampus abut other brain regions as well (Brydon, Edwards, Mohamed-Ali, & Steptoe, 2004; Galcia, Bonsall, & Bloomfield, 2016; Kim & Won, 2017; Won & Kim, 2016).

2.1. Stress and autonomic imbalance

The mammalian ANS has evolved through a dynamic balance between its sympathetic and its parasympathetic branches (Porges, 2011). All organs receive dual innervation by sympathetic and parasympathetic nerve fibers, while the endocrine system secretes sympathetic (epinephrine, norepinephrine) and parasympathetic (acetylcholine) hormones. These branches serve key functions aimed at protection and preservation of the organism: the sympathetic branch is associated with energy mobilization and the parasympathetic branch with vegetative and restorative functions. Homeostatic balance between the two branches is under genetic control and epigenetic modification brought about by environmental factors, most importantly stress and aging. Autonomic imbalance is a common feature of the biology of acute and chronic stress (Beauchaine & Thayer, 2015; Jarczok et al., 2013; Thayer & Lane, 2000; Thayer, Yamamoto, & Brosschot, 2009). The stress-related disruption in ANS homeostasis with a sustained shift in the balance of the ANS branches is a critical underlying mechanism in mood dysregulation as occurs in a variety of psychiatric disorders, notably depressive disorder, as the stress-related psychiatric disorder par excellence. The degree and chronicity of disruption in ANS homeostasis appears to be the tipping point determining the extent of diminution in parasympathetic tone. A consequence of diminution in vagal tone, especially if it persists, is disinhibition of the body's inflammatory response. Kevin Tracey described how the CNS regulates immune function through pathways he named "the inflammatory reflex" (Tracey, 2002). Cholinergic neurons inhibit acute inflammation, and suppression of parasympathetic activity inhibits the Cholinergic Antiinflammatory Pathway (CAIP) (Pavlov & Tracey, 2005; Tracey, 2007). The vagus nerve is the primary sensory and effector channel for this reflex. Through the inflammatory reflex, the persistent or recurrent low vagal tone induced by chronic stress may facilitate inflammation of the coronary arteries, articular joints, and contribute to fatigue and a sense of general malaise, each of which accentuates and prolongs the perception of stress. The elegant work by Tracey and Pavlov in identifying the CAIP has identified efferent vagal fibers originating in the dorsal motor nucleus (Pavlov & Tracey, 2005; Tracey, 2007). These efferent fibers modulate the release of inflammatory mediators from macrophages thereby preventing over-activation of the inflammatory process without inducing immunosuppression (Pavlov, Parrish, & Rosas-Ballina, 2009). The brain–immune interaction was elaborated in greater depth in a more recent publication by these authors highlighting the complexity of this issue (Pavlov & Tracey, 2015). The loss of dynamic variability in the autonomic nervous system, during which one branch dominates over the other for extended periods of time and across multiple environmental demands, is associated with illness and eventually chronic disease. Typical examples of such sequelae are cardiovascular diseases (Brook & Julius, 2000; Malliani & Montano, 2004; Thayer & Lane, 2007) and their high co-morbidity with depressive illness this being bidirectional relationship (Halaris, 2016).

2.2. Stress, autonomic imbalance and metabolic risk

Autonomic imbalance is at the root of the biology of acute and chronic stress. Several studies have established that autonomic imbalance may predict the development of metabolic risks and associated disorders (Licht, de Geus, & Penninx, 2013; Wulsin, 2015; Wulsin et al., 2016). In their studies Brunner et al and Chandola et al. (Brunner et al., 2002; Chandola, Brunner, & Marmot, 2006) presented strong evidence of a dose-response relationship between the severity of chronic stress and the severity of metabolic measures; the degree of psychological stress measures accounted for a substantial amount of the variance in metabolic syndrome measures. In a follow-up publication they described the contribution of work stress to coronary heart disease and the possible mechanisms underlying this association (Chandola et al., 2008). It is now accepted that adverse childhood events and trauma during critical developmental stages fosters a pattern of excessive sympathetic activity or low vagal tone. Persisting autonomic imbalance is now believed to be major risk factor for subsequent cardiovascular disease, obesity, type 2 diabetes (Dong et al., 2004; Thomas, Hypponen, & Power, 2008; Wegman & Stetler, 2009; Thorp & Schlaich, 2015). With respect to psychiatric disorders, chronic sympathetic activity and low vagal tone observed in chronic severe illnesses – schizophrenia, bipolar disorder, severe depression – have been causally associated with high rates of early onset of heart disease, diabetes, and obesity (Katon

et al., 2004; Mezuk et al., 2008; Rottenberg et al., 2014; Saha, Chant, & McGrath, 2007). Similarly, sufferers from post-traumatic stress disorder (PTSD) have an increased risk for metabolic syndrome and cardiovascular disease, as established in recent meta-analyses (Bartoli et al., 2013; Rosenbaum et al., 2015).

While the epidemiological and experimental evidence is compelling about the association between stress-related psychiatric disorders, autonomic imbalance and metabolic risk, what precise pathways induce or accelerate the onset and progression of the metabolic syndrome, obesity, diabetes, hypertension, cardiovascular disease? Behaviors can certainly shift autonomic balance in favor of sympathetic overactivity. Physical inactivity, consumption of intoxicating substances, use of tobacco or illicit drugs, lack of social interaction and insomnia each independently contribute to increased sympathetic and/or decreased parasympathetic activity (Bonnet & Arand, 2010; Kanady, Maguen, & Neylan, 2018; Kok et al., 2013). Thayer and Lane proposed a model that integrates autonomic, attentional, and affective systems into a functional and structural network that could help our understanding of emotional regulation and dysregulation (Thayer & Lane, 2000). Their model is based on earlier work by Benarroch (1993) who described the Central Autonomic Network (CAN) as an integrated component of an internal regulation system through which the brain controls visceromotor, neuroendocrine, and behavioral responses that are critical for goal-directed behavior and adaptability (Benarroch, 1993). In a recently published review article Wulsin et al. apply the neurovisceral integration concept to the clinical setting by proposing that autonomic imbalance plays a primary role in the development of metabolic risks. They discuss their testable model by providing a systematic review of the evidence in support of autonomic imbalance as a predictor for metabolic risks, and specific approaches to test this model as a guide to future research on the role of stress in metabolic disorders (Wulsin, Herman, & Thayer, 2018).

2.3. Stress, HPA axis, insulin resistance

The role the hypothalamic-pituitary-adrenal (HPA) axis plays in stress mediation/response has been well established and is widely accepted. Our understanding of the complex circuitries and interplays involved in the "translation" of stress and the associated perception by the individual to obesity, diabetes and the metabolic syndrome (MetS) in general, with or without co-morbid psychiatric disorders, has only recently become clearer (Joseph & Golden, 2017). The biological systems involved in mediating the link between stress and physiological functions include the HPA axis, the ANS and the immune system. The HPA axis is a tightly regulated system, including feedback loops, that represents one of the body's mechanisms for responding to acute and chronic stress. Activation of the HPA axis is accompanied by stimulation of the sympathetic nervous system, resulting in the release of catecholamines and activation of the immune system involving a cytokine cascade (Maes et al., 1998). Chronic stress may impair the feedback mechanisms that reestablish homeostasis thereby resulting in chronic elevations in levels of cortisol, catecholamines, and inflammatory markers. Using as an example diabetes and depression, the biological association between these two entities is hypothesized to be due to a dysregulated and overactive HPA axis, a shift in sympathetic nervous system tone toward enhanced sympathetic activity, and a proinflammatory state. A study by Siddiqui et al. is of direct relevance in demonstrating how chronic stress and endocrine stress responses are significantly associated with glucose intolerance, insulin resistance and diabetes mellitus (Siddiqui, Madhu, Sharma, & Desai, 2015).

In cases of clinical hypercortisolism, e.g., Cushing's syndrome, type 2 diabetes mellitus occurs in about one-third of affected individuals with associated visceral adiposity, lipolysis with free fatty acid release, skeletal muscle insulin resistance, decreased insulin secretion, and increased hepatic glucose production. There is a bidirectional relationship between hypercortisolism and neuropsychiatric conditions, including depression as the stress-related disorder par excellence, as evidenced by the high prevalence of MDD (50–81%), anxiety (66%), and bipolar disorders (30%) in Cushing's syndrome. The question is how subclinical hypercortisolism that occurs more commonly in states of stress and depression, can also lead to type 2 diabetes mellitus. The fact is that in states of subclinical hypercortisolism, similar changes occur which include glucometabolic disturbances and insulin resistance. These effects are believed to be mediated through glucocorticoid receptors that are more abundant on visceral than subcutaneous adipose tissue.[89] Thus, because cortisol leads to visceral adiposity and insulin resistance (metabolic precursors to diabetes), subclinical hypercortisolism may provide an additional biological explanatory link between depression and type 2 diabetes mellitus. Lastly, chronic exposure to high cortisol levels leads to structural and functional changes in various glucocorticoid receptor–rich brain regions fundamental for emotional and cognitive function, including the hippocampus, amygdala, and prefrontal cortex (Anagnostis, Athyros, & Tziomalos, 2009; Carvalho et al., 2015; Golden, 2007; Roozendaal, McEwen, & Chattarji, 2009; Steptoe et al., 2014;).

3. Neuroinflammation

Involvement of the immune system in major mental illnesses was first postulated in the early twentieth century, but it was not until the latter twentieth century that detailed studies began to be published. It is now accepted that the immune system and inflammatory processes contribute to brain-related pathologies in most, if not all, neurological and psychiatric disorders. Stress is a key factor in inducing immune system dysregulation in conjunction with genetic, epigenetic and environmental factors. Activation of the immune response can alter neurotransmission leading, among others, to serotonin deficiency, and increased production of neurotoxic substances contributing to disease progression. Aberrant levels of proinflammatory cytokines can be detected in serum, plasma, and cerebrospinal fluid of many patients with psychiatric and neuropsychiatric disorders. It is hypothesized that a proinflammatory state induces psychopathologic symptoms and is involved in the pathogenesis and pathophysiology of major mental illnesses. Proinflammatory cytokines are produced by activated cells of the immune system, such as activated endothelial cells, monocytes, monocyte-derived dendritic cells, macrophages, T cells and microglia. The realization that immune cells can be involved in mental illnesses has led to the macrophage-T-cell theory of depression and schizophrenia which was proposed in 1992 and adapted in 1995 (Smith, 1992; Smith & Maes, 1995). Indeed, receptors for inflammatory cytokines are present in various brain nuclei (Chesnokova & Melmed, 2002), which upon triggering deregulate important neurotransmitters and neurodevelopmental systems, facilitating the development of psychiatric signs and symptoms.

When the immune system is activated, an inflammatory response ensues with the release of proinflammatory and neurocytotoxic mediators. This occurs both centrally and peripherally. Peripheral inflammatory cells, such as mast cells and T cells, and peripherally released inflammatory mediators have been shown to enter the brain at least in loci where the blood–brain barrier (BBB) is permeable. These cells and inflammatory mediators induce and sustain chronic neuroinflammation directly or indirectly through astrocyte, microglia, neuronal and mast cell activation. This sequence of events can ultimately lead to neuronal death.

The term 'neuroinflammation' connotes inflammation of the nervous tissue and is an inflammatory response within the brain or spinal cord. It describes the changes in the CNS caused by a wide range of stimuli, such as infections, traumatic brain injury, physiological and psychological stress or infection. The ensuing CNS responses lead to adaptive or maladaptive changes in brain function, such as neurotransmitter dysregulation, impairment of synaptic plasticity, neuronal cell death and exacerbation of brain pathology (DiSbato, Quan, & Godbout, 2016). Neuroinflammatory processes underlie at least some

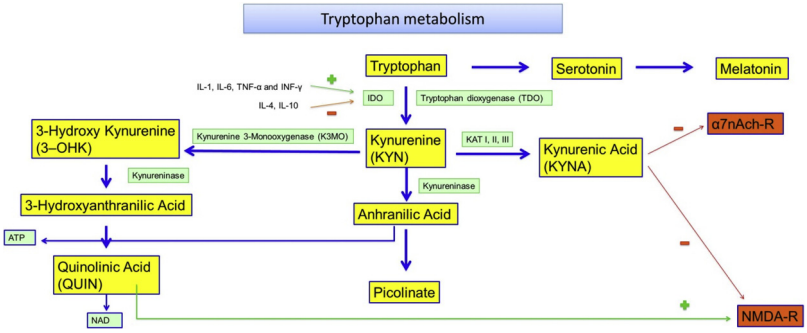

Fig. 1. Overview of the Tryptophan/Kynurenine Pathway.

psychiatric and neurological disorders and many excellent reviews are available (Khansari & Sperlagh, 2012; Lyman, Lloyd, & Ji, 2014). Inflammation is the response of the innate immune system aimed at protecting and defending the organism against any threat to its integrity, such as invasion by microorganisms, environmental stressors, chronic illnesses and emotional stresses, with the ultimate goal of restoring homeostasis. The inflammatory response can be localized and/or systemic and involves complexly orchestrated mobilization and interactions of various cell types and signaling molecules. Control and elimination of the noxious stimulus is achieved by phagocytosis and activation of the inflammasome. The inflammasome is an intracellular multiprotein oligomer and is a component of the innate immune system. By activating inflammatory processes, tissue repair and regeneration are enabled. Expressed in neurons inflammasomes promote the maturation of proinflammatory cytokines, notably IL-1β and IL-18. While the inflammatory response initially is intended to be beneficial and protective, if it is excessive and/or prolonged, it can induce pathological changes and cause tissue damage. For example, activated leucocytes, monocytes, endothelial cells target not only the initial site of inflammation but also remote sites following penetration into the brain parenchyma. These peripheral proinflammatory mediators can cross the BBB at the site of the circumventricular organs but also at other sites that become permeable under pathological conditions. The resulting neuroinflammatory response involves neurons, astrocytes and microglia and contributes causally, at least partially to psychiatric and neuropsychiatric disorders (Halaris, 2015).

4. The kynurenine pathway

4.1. Overview of the pathway

Tryptophan functions as a biochemical precursor for serotonin, which in turn has been strongly implicated in the pathogenesis of depression and possibly in other psychiatric disorders. Tryptophan metabolism is a point of conceptual confluence of the monoamine theory, the innate immune system, and the kynurenine pathway (KP). Additionally, the KP contributes to decreased insulin receptor function. Tryptophan is converted either to serotonin (5-HT) by tryptophan hydroxylase or its metabolism may be diverted away from 5-HT synthesis and towards the KP via the rate-limiting enzymes, indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO). IDO is located in the brain and many peripheral tissues, and TDO is located in the liver and activated by glucocorticoids.

IDO catalyzes the conversion of tryptophan to kynurenine. Within the KP, kynurenine metabolism is bifurcated into a neuroprotective and a neurotoxic pathway. Kynurenine acetyl transferase (KAT) converts kynurenine to kynurenic acid (KynA) which is neuroprotective insofar as it competitively antagonizes quinolinic acid (QA) at the N-methyl-D-aspartate (NMDA) receptor.

Following the inflammation induced activation of the tryptophan-KP, quinolinic acid accumulates leading to the activation of the NMDA-glutamate receptors (Bender & Mcreanor, 1985) and thereby inducing excitotoxic neurodegenerative changes (Schwarcz, Whetsell, & Mangeno, 1983) and apoptosis of astrocytes (Guillemin, Wang, & Brew, 2005). As the astrocytes lack kynurenine monooxygenase which leads to the synthesis of quinolinic acid, KynA is the main end product of KP in astrocytes. Under physiological conditions, KynA acts as a NMDA receptor antagonist by binding to the glycine site on the NMDA receptor. In addition, KynA is an antagonist of the alpha-7 nicotinic acetylcholine receptor and an agonist of the non-alpha-7 acetylcholine receptor (Hilmas, Pereira, & Alkondon, 2001). The effect of KynA on the alpha-7 nicotinic acetylcholine receptors results in a reduction in the release of monoamine neurotransmitters in the brain (Myint, 2012). Thus, the reduction in the synthesis of KynA, combined with the increase in quinolinic acid, results in an increase in neurodegenerative changes which contribute to neuroprogression.

Alternatively, kynurenine is metabolized by kynurenine 3-monooxygenase (KMO) into 3-OH-kynurenine (3 H K), the parent compound of QA, which is well recognized for its excitotoxicity at the NMDA receptor but also functions as an intermediate in the de novo synthesis of NAD. Specific pro-inflammatory cytokines have been shown to be potent IDO upregulators. In this context then, a pro-inflammatory state, even in cases of "low-grade inflammation," albeit of prolonged duration or recurrence, can exert sustained diversion of tryptophan metabolism toward KP metabolites with associated neurotoxic, apoptotic and diabetogenic sequelae, as will be described below (Hattori & Kotake, 1989; Kotaki, Ueda, & Mori, 1975; Myint, 2013; Myint & Kim, 2003). An overview of the Tryptophan/Kynurenine Pathway is presented in Fig. 1 below.

Activation of the stress axis in depression results in an increase in both proinflammatory cytokines and other inflammatory components together with an increase in glucocorticoids. Proinflammatory cytokines increase the activity of the tryptophan-kynurenine pathway by activating indoleamine 2,3-dioxygenase while the glucocorticoids have a similar effect by activating liver tryptophan dioxygenase. In depression, this results in the synthesis of the neurotoxin quinolinic acid and a number of intermediate kynurenines which have a diabetogenic effect. As a consequence of glucocorticoid receptor and insulin receptor desensitization by inflammatory mediators and glucocorticoids, brain glucose metabolism is compromised. This, in combination with the neurotoxic effects of quinolinic acid and proinflammatory cytokines, contributes to the neurodegenerative changes which occur in major depression, particularly in the elderly. The complex pathways involved are illustrated in Fig. 2 below.

4.2. Relationship to stress and inflammation

The conversion of tryptophan (Tryp) to kynurenine is under bimodal regulation by IDO and TDO, the latter enzyme being under the control of the HPA axis. Animal studies suggest that IDO governs the activation of the KP in the acute setting, such as challenge with administration of a lipopolysaccharide (LPS), whereas TDO exerts its

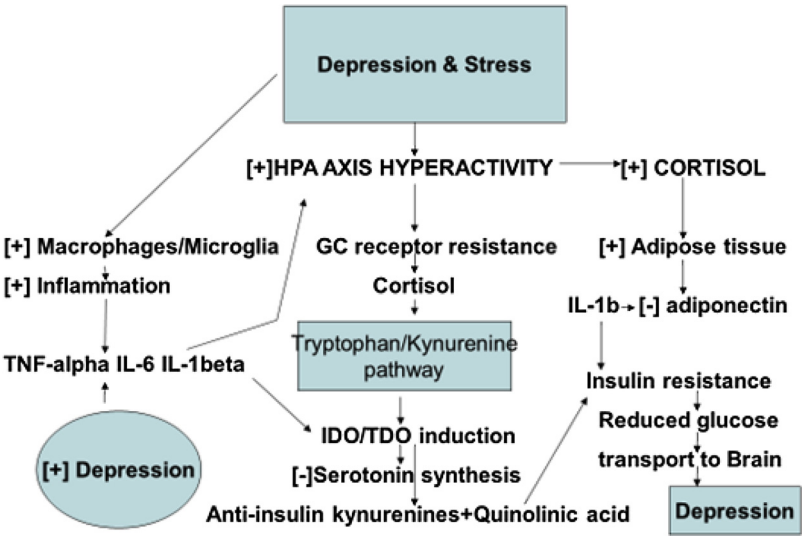

Fig. 2. Links between endocrine and immune changes in major depression.

regulatory effect on KP in the setting of chronic low-grade inflammatory stress. This bimodal regulation of KP activation allows for the distribution of inflammatory load according to the chronicity of the stressor. Based on our review of the literature, we propose the following. If we accept the premise that baseline Kyn/Tryp values represent chronic rather than acute stress in a patient sample, then the reported Kyn/Tryp ratios may be more representative of TDO-predominant rather than IDO-predominant regulatory control. Computation of this ratio may aid in the differentiation of the type of enzymatic activation and thereby an indirect marker of stress perception by the patient and associated HPA activation. To differentiate the relative contributions of IDO and TDO, and to account for other forms of compensatory responses to chronic progressive inflammatory burden, future studies could pair Kyn/Tryp ratios with IDO and KMO gene transcription and expression levels.

4.3. Intervention points

Within this framework, IDO is increasingly recognized as the key regulatory pivotal point between tryptophan metabolism towards 5-HT synthesis, versus the KP. This line of reasoning is supported by preclinical data outlining the neuroprotective effects of direct IDO inhibition (Comim, Freiberger, & Ventura, 2017; O'Farrell, Fagan, Connor, & Harkin, 2017; Souza, Jesse, & de Gomes, 2017), as well as strong clinical data demonstrating the reversal of refractoriness to antidepressant treatment in response to inflammatory modulation in unipolar depression, bipolar depression, and bipolar mania (Andrade, 2014; Brundin, Sellgren, & Lim, 2016; Halaris, Myint, & Savant, 2015). While the molecular basis for this clinical benefit is still unclear, the prevailing theory rests on the premise that IDO enzymatic activity is inducible by pro-inflammatory cytokines, (Myint & Kim, 2003) and is therefore indirectly attenuated by inflammatory modulation to suppress stress/depression-associated KP abnormalities in an IDO dependent manner.

4.4. The KP and insulin receptor function

As noted above, under stressful situations and in conjunction with stress associated with psychiatric and neuropsychiatric disorders, IDO and TDO are activated and result in the metabolism of tryptophan being diverted to KP metabolites (Myint & Kim, 2003). Kynurenine is a substrate for both kynurenase and kynurenine aminotransferase. In depression related disorders the former enzyme is activated leading to the formation of quinolinic acid, an agonist at NMDA receptors, and the diabetogenic kynurenine metabolites anthranilic acid and 3-hydroxyanthranilic acid. By reducing the activity of insulin, these substrates further contribute to the reduction in the availability of glucose for sustaining brain metabolism (Hattori & Kotake, 1989; Kotaki et al., 1975). This neurodegenerative, diabetogenic pathway is normally balanced under non-stress conditions by the synthesis of the NMDA glutamate agonist, kynurenic acid, which is formed by the action of kynurenine aminotransferase. This neuroprotective pathway is decreased in depression while the neurodegenerative arm of the tryptophan-KP is increased (Myint, 2013).

However, a chronic decrease in high energy substrates resulting from a deficit in glucose and essential cofactors may also be of importance in causing an increase in neuronal apoptosis (Moudrian, Heyes, & Pan, 1989). The situation is further complicated by the increase in oxygen free radicals caused by xanthurenic acid and 3HK which damage the mitochondrial membranes thereby resulting in a reduction in the synthesis of ATP and other high energy intermediates (Sofic, Halket, & Pryzborowska, 1989).

In summary, this pathway is an important link between neuroinflammation, the hyperactive HPA axis, brain monoamines and the pathological changes underlying major psychiatric disorders. I cannot think of another pathway which integrates these events so completely.

5. The concept of neuroprogression

Neuroprogression is a term used to signify the progressive, recurrent and relapsing course of a specific disorder (Berk, 2009; Post et al., 2012). In some instances, it is already possible to 'stage' the course of the disorder based on clinical manifestations, and, to the extent that morphological, biochemical, neurochemical, immunological, physiological and genetic aspects have been established, such parameters as well. An excellent example to illustrate the utility of this concept is cancer diagnosis and treatment. In a similar vein, parameters can be standardized and used to stage neuropsychiatric disease entities although more research to validate promising parameters must still be undertaken. Likely pathophysiological substrates that contribute to neuroprogression include neuroinflammation, oxidative stress, metabolic abnormalities, deficits in neuroprotection and neuroplasticity and loss of synaptic plasticity. Neuronal loss and structural changes in the hippocampus, amygdala, orbitofrontal cortex, anterior cingulate cortex, basal ganglia and pituitary gland have already been associated with progressive pathology in certain psychiatric disorders (Haroon et al., 2016; Price & Drevets, 2010). There is also a complex interplay with the monoaminergic, cholinergic, glutamatergic and GABAergic

neurotransmitter systems that require further elucidation. Such changes are associated with dysfunctional monoaminergic, glutamatergic, cholinergic and peptidergic pathways. The recent findings of Haroon and Miller (2017) and Haroon, Miller, and Sanacora (2017) on the changes in the brain glutamatergic system in neuroprogression are particularly relevant. Glutamatergic transmission has recently received attention with the elegant MR spectroscopy studies published by Haroon et al (Haroon & Miller, 2017; Haroon et al., 2017b). The significant clinical implications of neuroprogression in psychiatric disorders as well as the biological mechanisms underlying neuroprogression are obvious and should not be underestimated.

Therefore, there is an urgent need to direct investigative attention toward arresting and ideally reversing neuroprogression. Exploration of pharmacological, nonpharmacological or combined interventions should be prioritized. Indeed, in the beginning of the new millennium, the accrued knowledge of inflammatory processes in psychiatric and neurological conditions and the complex mechanisms mediating them have led some researchers to test nonsteroidal anti-inflammatory drugs as adjunctive therapeutic interventions. Basic findings have revealed that elevated proinflammatory mediators are directly or indirectly associated with the arachidonic acid cascade. For example, prostaglandin E_2 levels have been found to be elevated both in serum and cerebrospinal fluid as well as in the saliva of at least some patients (Ohishi, Ueno, & Nishino, 1988) and *in vitro* studies have shown an increased prostaglandin (PG) production from patients' lymphocytes (Song & Leonard, 2006), while antidepressant medications inhibit it (Yaron, Shirazi, & Jundovich, 1999). PGs play a central role in the inflammatory response partly because of their vasodilating properties and partly because they enhance proinflammatory cytokine production (e.g., IL-6 and TNF-α). These cytokines have been repeatedly found to be elevated in depressed patients (Hestad, Tonseth, & Stoen, 2003; Lanquillon, Krieg, Bening-AbuShach, & Vedder, 2000; Mueller & Schwarz, 2004) as has been the expression of a key enzyme, cyclooxygenase-2 (COX-2). Galecki et al (Galecki, Galecka, & Maes, 2012) have shown that mRNA expression of COX-2 and phospholipase A_2-IIA, a rate-limiting enzyme that generates arachidonic acid, is increased in patients with recurrent depression. Similar findings have been reported in schizophrenia (Mueller & Schwarz, 2010). This pathophysiologically important polarization of the immune system may be ameliorated by a selective COX-2 inhibitor (Mueller, Ulmschneider, & Scheppach, 2004). A detailed description of the few but compelling published studies of coxibs in psychiatric disorders can be found in Boufidou and Halaris (Boufidou & Halaris, 2017).

6. Novel targets and promising individualized interventions

We have introduced the concept of neuroprogression in the preceding section. We will now address specific interventions aimed at ameliorating, arresting or even reversing neuroprogressive mechanisms through pharmacological, nonpharmacological, or combined interventions. We view this as an emerging new priority in reversing and even preventing the chronicity of psychiatric and neuropsychiatric disorders. A two-pronged approach will be required: a) expansion of our current diagnostic armamentarium to include validated biomarkers aimed at assessing on a strictly individualized basis abnormalities that have been associated with the disease entity being diagnosed; b) design of individualized treatment plans that include novel combinatorial intervention as we will outline below. Fig. 3 depicts some of the proposed novel targets for intervention to maximize treatment outcomes and thereby arrest or even avert a neuroprogressive course of the disease entity.

6.1. C-reactive protein

A promising diagnostic marker for stress-related psychiatric disorders is serum C-Reactive Protein (CRP), a historically recognized non-specific diagnostic marker of inflammation. CRP is a non-glycosylated serum protein of 115 kDa, comprised of 5 identical globular subunits of 23 kDa arranged in a cyclic pentameric disc configuration. CRP is produced in the liver and its synthesis and release from hepatocytes is upregulated by cytokines, such as IL-6, that are activated during early inflammation. Commonly studied within the context of vascular medicine, elevated CRP is a risk factor for atherosclerosis and cardiovascular disease. Because of its fundamental link to host defense processes involving inflammation, its role as a contributing factor to any protective or pathological process involving human tissues is expanding. Recently, CRP has become the focus of psychiatric research, specifically as it relates to Major Depressive Disorder (MDD). Many, but not all, patients diagnosed with MDD have been shown to exhibit significantly higher levels of CRP when compared to non-depressed healthy control subjects (Topić, Miličić, & Štimac, 2013). This finding extends to the general population beyond those diagnosed with MDD as demonstrated by Wium-Andersen et al (Wium-Andersen, Ørsted, Nielsen, & Nordestgaard, 2013). In their study, CRP levels and psychological distress were quantified in 73,131 men and women representative of the Copenhagen population. After adjusting for confounding variables such as age, sex, smoking, physical activity, and chronic disease, elevated levels of CRP correlated to an increased risk for psychological distress and depression (Wium-Andersen et al., 2013). The link between MDD, CRP, and, by association, inflammation thus raises important questions about MDD etiopathology and treatment. The genetics governing the expression of CRP have been elucidated, and the possible relationship of CRP structural isoforms to the pathological processes occurring in inflammatory conditions including psychiatric disorders are also been studied. Once suitable laboratory methods have been developed to accurately distinguish between the pentameric and monomeric isomers, this marker has great promise to become a routine biomarker for psychiatric diagnostic testing.

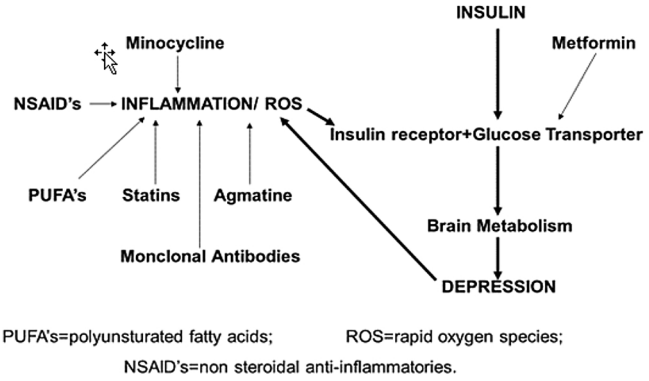

Fig. 3. Sites of action of putative antidepressants: targets linked to disrupted brain metabolism.

6.2. Cyclooxygenase-2

The key role of cyclooxygenase-2 (COX-2) is the conversion of arachidonic acid to prostaglandins, which are precursors for synthesis of pro-inflammatory cytokines. However, the growing recognition of expanded roles of COX-2 may generate rationale for 'off-target' benefits of COX-2 inhibitors, notably celecoxib, as augmentation strategies that transcend their anti-inflammatory benefit through the reduction of inflammatory burden (Galecki, Talarowska, Bobinska, & Szemraj, 2014; Schlichtiger, Pekcec, & Bartmann, 2010). Preclinical studies indicate celecoxib potentiated the effects of reboxetine and fluoxetine on norepinephrine and 5-HT output, and that CBX alone enhanced 5-HT output (Johansson, Falk, Marcus, & Svensson, 2012). The disruption of COX-2 promotes the accumulation of arachidonic acid, which is associated with preferential shunting towards neuroprotective eicosanoids (Strauss, 2008). Interestingly, recent models distinguish acute and

chronic effects of prostaglandin E2 (PGE2), a downstream COX2 metabolite (PGE2). In the acute setting, the neuronal PGE receptor 2 (EP2) mediates neuroprotection in a cAMP/PKA dependent manner, whereas chronic COX2 activation mediates neuroinflammation in a microglial EP2 dependent manner. Chronic COX2 production in neuroglial and neurons is known to promote vascular damage, metabolic dysregulation, and oxidative stress following Traumatic brain injury (Strauss, Barbe, & Marshall, 2000).

In addition to proinflammatory cytokines, prostaglandin E2 (PGE2) is also increased in the blood and cerebrospinal fluid of patients with major depression (Calabrese, Skwerer, & Barna, 1986). Since inflammation associated with arthritis and other inflammatory disorders, is attenuated by treatment with non-steroidal anti-inflammatory drugs (NSAID's), it has been hypothesized that such drugs should be beneficial in reducing the impact of chronic low-grade inflammation associated with stress related psychiatric disorders, such as depression. Aspirin would be a suitable candidate for PGE2 inhibition, however, it has adverse effects of long-term use due to its inhibition of the synthesis of PGE2 by COX-1 in the wall of the gastric mucosa. The new generation of NSAID's selectively inhibit COX-2, an enzyme that is induced by inflammatory cytokines acting on neurons particularly in the hippocampus and cortex (Kohler, Krogh, Mors, & Benros, 2016). Celecoxib has emerged as the prime candidate from among marketed NSAIDS's in North America to test the hypothesis that inhibition of COX-2 should result in reduction of PGE2 synthesis, particularly in the brain. Based on experimental evidence that celecoxib reduces the stress response and cognitive deficits in the rat (Casolini, Catalami, & Zuena, 2002) and also the behavioral and immune changes in the olfactory bulbectomized rat model of depression (Myint, Steinbusch, & Geoghegan, 2007), a series of studies were undertaken that we will briefly refer to here.

A number of open, and randomized, double-blind trials have been reported. One open study showed superiority of adjunctive aspirin to fluoxetine (Mendlewicz, Kriwin, & Oswald, 2006). Overall the results of using celecoxib adjunctively have been positive in that celecoxib enhanced the response of antidepressants with overall good tolerability and safety. Agents used concurrently included fluoxetine, reboxetine, sertraline and mood stabilizers (Akhondzadeh, Tabatabace, & Amini, 2007; Abbasi, Hosseini, & Modabbernia, 2012; Mueller, 2015; Mueller, Schwarz, & Dehning, 2006). Adjunctive treatment of celecoxib with an antidepressant has also been shown to be beneficial in patients with bipolar disorder. Thus, Nery and coworkers (Nery, Monkul, & Hatch, 2008) showed that celecoxib treatment produced a rapid onset antidepressant response and similar findings have been reported by Halaris and colleagues in a group of treatment resistant bipolar depressed patients given escitalopram and celecoxib (Castillo, Murata, & Schwarz, 2019; Edberg, Hoppensteadt, & Walborn, 2018; Halaris, Alvi, Meresh, & Sharma, 2014). A cautious point of view was expressed by Maes (Maes, 2012) about targeting COX-2 in depression raising issues that must be addressed with rigorous and extended studies before this treatment approach can be endorsed for general use. The concerns about possible cardiovascular risk associated with prolonged use COX-2 inhibitors (Solomon, McMurray, & Pfeffer, 2005) have been largely satisfied following the extensive efficacy and safety study conducted Pfizer and reported at a fairly recent meeting of the American Heart Association. In summary, modulation of inflammation via co-administration of the COX-2 inhibitor, celecoxib is a viable approach to reverse treatment resistance but it is long term safety awaits further investigation. Lastly, as Eyre et al. (Eyre, Stuart, & Baune, 2014) suggest in their review, additional immune factors beyond pro- and anti-inflammatory cytokines may effectively contribute to the understanding of the neurobiology of clinical depression. We also agree with Maes that inflammation is not the one and only factor that should be considered in designing a balanced and individualized approach to arrest neuroprogression.

6.3. Drugs which target insulin and glucose transporters

As stated previously, inflammation and hypercortisolemia are contributory factors to insulin receptor dysfunction. Insulin resistance plays a crucial role in the metabolic changes associated with major depression and related psychiatric disorders and administration of insulin should reverse insulin resistance. The insulin receptor could therefore be a target for the development of novel antidepressants. It has been shown that patients with MDD and Alzheimer's disease (AD) have a reduced insulin receptor sensitivity (Talbot, Wang, & Kazi, 2012). Especially patients with AD have a hypophosphorylated insulin receptor and the insulin receptor substrate (Steen, Terry, & Rivera, 2005).

In cognitively intact healthy subjects, increasing insulin signaling improves memory. In their study, Benedict et al. demonstrated that prolonged intranasal administration of insulin improved memory and mood in the absence of systemic side effects. They concluded that these findings could be of relevance for the treatment of patients with memory disorders like in AD (Benedict, Hallschmid, & Schultes, 2007). Furthermore, verbal memory, which depends on the activation of the frontal cortex, improved following the intranasal administration of insulin. Freiherr and coworkers (Freiherr, Hallschmid, & Frey, 2013) reviewed studies on the use of intranasal insulin in the treatment and prevention of AD. They concluded that intranasal insulin studies have demonstrated that enhancing brain insulin signaling improves memory and learning processes in both cognitively healthy and impaired humans. They provided a strong rationale for the hypothesis that pharmacological strategies bolstering brain insulin signaling, such as intranasal administration of insulin, could have significant potential in the treatment and prevention of AD.

An alternative to the direct application of insulin, is the use of antidiabetic drugs exploiting their effects on brain function. Metformin is one of the most extensively used oral antidiabetics for the treatment of type 2 diabetes (DM2). The mode of action of metformin includes reduction in the peripheral glucose level due to inhibition of liver gluconeogenesis and a reduction in available glycogen. There is also evidence that metformin increases the sensitivity of insulin receptors and stimulates AMP-activated protein kinase (Pernicova & Korbonits, 2014). Metformin is lipophilic and therefore penetrates into the brain. In vitro studies have demonstrated that metformin can prevent the formation of beta amyloid plaques and the hyperphosphorylation of tau protein (Gupta, Bisht, & Dey, 2011), both of which are increased in the brain of elderly depressed patients but of greater density in those with dementia. Experimentally it has also been shown that metformin increases neurogenesis and reduces the effects of oxidative stress (Hwang, Kim, & Joo, 2010).

6.4. Minocycline

Minocycline is a tetracycline antibiotic that crosses the blood-brain barrier and exerts anti-inflammatory and anti-oxidant effects in basic and clinical studies (Soczynska, Mansur, & Brietzke, 2012). Minocycline increases neurogenesis, reduces the release of proinflammatory cytokines from activated microglia and displays anti-oxidant activity. It inhibits the activation, migration and/or proliferation of T-cells, neutrophils and microglia and inhibits the release of proinflammatory cytokines. The anti-inflammatory effects of minocycline, which have been reported experimentally and clinically, are independent of its antibiotic properties (Levine, Cholestoy, & Zimmerman, 1996).

Its potential antidepressant drug efficacy was suggested over 20 years ago (Levine et al., 1996). Subsequent studies confirmed this efficacy. In an open label study, minocycline proved effective in unipolar psychotic depression (Miyaoke, Wake, & Furuya, 2012) and in a double-blind, placebo controlled, randomized trial it demonstrated antidepressant effects for mild to moderate depression in HIV patients (Emadi-Kouchok, Mohammadinegad, & Asadotlah-Amin, 2016). By contrast, in a major clinical trial in bipolar disorder, there was no

significant effect of the drug, but the drug might be useful as adjunctive treatment for bipolar depression (Savitz, Misaki, & Wurfel, 2018). Clearly, minocycline deserves further investigation either as monotherapy or as adjunctive treatment.

6.5. Statins

The statins are a group of HMG-CoA reductase inhibitors which are widely used to reduce high cholesterol levels and thereby prevent serious cardiovascular events. In addition to their effects on cholesterol metabolism, statins have anti-inflammatory effects and have been used successfully as adjunctive treatments for major depression (Salagre, Fernandez, & Dodd, 2016). A meta-analysis has indicated that statins are effective in enhancing the antidepressant efficacy of different types of antidepressants (You, Lu, & Zhao, 2013). While there may be a use for statins as adjunctive treatments for depression in the future, based on the current clinical evidence it would appear that other approaches to the development of novel antidepressants, already discussed above, deserve priority consideration.

6.6. Monoclonal antibodies as putative antidepressants

Recently Berk et al. (2019) critically assessed the role of immune biomarkers which could be of value in identifying immune modulating treatments for their potential antidepressant efficacy. There is evidence that antibodies to the proinflammatory cytokines, such as TNF-alpha, which can be elevated in depression and other psychiatric disorders and in chronic inflammatory conditions, such as psoriasis and rheumatoid arthritis, can attenuate not only the symptoms associated with joint pain and skin lesions but also reduce symptoms of fatigue and depression which are frequently associated with inflammatory disorders. A few published clinical trials provide evidence that monoclonal antibodies have potential antidepressant activity associated with the reduction in inflammation. Etanercept (Tyring, Gottlieb, & Papp, 2006), infliximab (Raison, Rutherford, & Woolwine, 2013) and adalimumab (Menter, Augustin, & Signorovitch, 2010) have been noted for their activity in reducing depressive symptoms concurrently with the reduction in the inflammatory cytokines. The study by Raison and colleagues (Raison et al., 2013) is particularly pertinent as it indicated that the anti-TNF alpha monoclonal antibody, infliximab, produced a positive antidepressant response in a group of patients with therapy resistant depression. However, more recently McIntyre, Subramaniapillai, and Lee (2019) have undertaken a well-designed, prospective trial of infliximab which failed to find any difference between infliximab and placebo. Berk, Walker, and Nierenberg (2019) therefore concluded that the promise of a biomarker –guided therapy that would aid in selecting immune modulating treatments remains elusive.

These results indicate that direct immunomodulation of proinflammatory cytokines is worthy of consideration when developing a new generation of antidepressants. Of course, the question remains, how do these antibodies exert their antidepressant effect, if they cannot cross the blood-brain-barrier.

6.7. Polyamines as modulators of inflammation

Agmatine and spermidine are examples of endogenous polyamines found in mammals. We will focus on agmatine as we believe it is of significant relevance to the topic of this review article. Agmatine is synthesized from the amino acid arginine by arginine decarboxylase and is an intermediary in the biosynthesis of polyamines, a pathway also related to the synthesis of important neurotransmitters, such as glutamate and GABA. Agmatine is widely distributed in mammals and is specifically transported into neurons by a cationic amino acid transporter. Agmatine is expressed in a highly restricted network of neurons mainly in the rostral brainstem and forebrain and is widely distributed in the cytoplasm of neurons within the neocortex, critical region in the adaptive response to stress. In the brain, agmatine is further metabolized by nitric oxide synthase to nitric oxide and by a separate pathway to spermidine and spermine (Moretti, Matheus, & de Olivereira, 2014). Thus, agmatine is important in the brain as a source of nitric oxide and the polyamines spermidine and spermine, in addition to its possible neurotransmitter function and ability to interact with other neurotransmitter pathways (Reis & Regunathan, 1998). At the cellular level, agmatine has a high affinity for alpha$_2$ adrenoceptors and imidazoline binding sites (Li, Regunathan, & Barrow, 1994) and, in addition, for nicotinic cholinergic receptors, serotonin 5HT$_3$ receptors and by acting as an antagonist at ligand gated cationic channels particularly on NMDA glutamate receptors. Agmatine reduces hypoxia induced neuronal damage in vitro and protects the integrity of mitochondria from oxidative stress. In hippocampal neuronal cultures, agmatine reduces the neurotoxic effects of activated NMDA glutamate receptors which contribute to its neuroprotective profile (Wang, Iyo, & Miguel-Hidalgo, 2006).

Agmatine is present in the serum in high concentrations. Its relationship to stress has been documented in basic and clinical studies. Specifically, increased agmatine concentrations have been associated with stressful stimuli in rat brain (Aricioglu & Altunbas, 2003; Zhu, Wang, & Cai, 2008) and in the serum of MDD patients (Halaris & Piletz, 2007; Halaris, Zhu, Feng, & Piletz, 1999). Increased agmatine levels have also been found in astrocytes and macrophages submitted to stressful conditions (Hong, Son, & Yun, 2014; Regunathan & Piletz, 2003). We have shown that plasma concentrations of agmatine are reduced in depression and normalized following effective antidepressant treatment (Halaris et al., 1999). From the therapeutic perspective, agmatine is of potential importance because it has been demonstrated that it has antidepressant, anti-anxiety, and cognitive enhancing properties which reflect its broad neuroregulatory effects by modulating neurotrophic pathways (Zhu et al., 2008). Agmatine dose dependently reduces deficits in memory and learning induced in rodents by scopolamine (Moosavi, Khale, & Abbasi, 2002). Despite the paucity of clinical data, experimental data does suggest that agmatine, or agmatine-like compounds, could provide a series of novel psychotropic drugs not only for the treatment of depression but also for neurological disorders, such as Parkinson's disease, epilepsy and stroke, in which neuroinflammatory and neurodegenerative components play a role (Moretti et al., 2014). With such a broad effect on so many neurotransmitter systems and neuroregulatory pathways, it is surprising that relatively little interest has been shown in its therapeutic potential. Given the therapeutic potential of agmatine for the management of CNS disorders of a variety of etiopathologies we strongly encourage expansion of endeavors to develop novel pharmacologic compounds involving agmatinergic transmission.

6.8. Pharmacogenomics

Pharmacogenomics, or the science of specific genes controlling the expression of proteins that are responsible for metabolizing pharmacotherapeutic agents, and also a host of biochemical processes such as neurotransmission, is of major relevance to psychiatric practice. Pharmacogenomics has been gaining acceptance, albeit slowly, in medical practice in general and particularly in psychiatric practice. The gold standard in psychiatric practice is to achieve remission and restore the patient as close to optimal state of functionality as possible. And yet only one third of affectively ill patients achieve remission often requiring several "trials and errors" before achieving an acceptable response. Pharmacogenomics aims to identify pharmacokinetic and pharmacodynamic factors, unique to the individual, that may impede treatment response and resistance and contribute significantly to neuroprogression and chronicity of neuropsychiatric disorders.

The overarching goal of striving to practice personalized medicine is significantly aided by pharmacogenomic testing and marketed products offer pharmacogenomics panels citing evidence that the results improve

outcomes for patients with a psychiatric diagnosis. A major contributing factor to treatment non-response is incompatibility between the chosen pharmacologic agent and the genetic makeup of the patient, which controls the expression of specific enzymes known as the cytochrome P450 system expressed in the liver. This system is largely responsible for metabolizing externally delivered compounds and rendering them inert and able to be excreted from the organism thereby detoxifying the body. Depending on the marketed panel, additional and relevant genes are tested, referred to as pharmacodynamic genes, such as the serotonin transporter, the serotonin receptor 2A and the HLA alleles. The latter are responsible for mediating dermatologic reactions that could lead to serious outcomes. Over decades the choice of, for example, an antidepressant agent, was based on the patient's presenting symptoms and history of illness including prior trials of failed or successful treatment regimens, the STARD guidelines, and the practitioner's best, educated guess. This "hit or miss" approach has been the modus operandi for a long time until the concept of pharmacogenomic guidance in the decision-making tree by the practitioner became reality. So, given the obvious advantage to pharmacogenomic testing, why hasn't it yet found wide acceptance? One reasonable answer is that it takes time for any innovation to receive wide acceptance. However, in this specific area of endeavor, prior study shortcomings, notably small numbers of genes and variants available for validated testing, small sample sizes and short durations of trials have contributed to skepticism on the part of practitioners. To advance research, combinatorial pharmacogenomic (PGx) algorithms integrate *multiple* pharmacokinetic (PK) and pharmacodynamic (PD) genes enabling more accurate predictions of response to a specific agent.

7. Conclusions

In this review article we presented an integrative overview of parameters and mechanisms underlying psychiatric and neuropsychiatric disorders that involve the immune and autonomic nervous systems along with neurotransmission and specific endocrine mechanisms. At the center of these highly complex and interactive mechanisms is stress and stress perception by the afflicted individual. The major pathways activated by stressors are the HPA axis and the autonomic nervous system. Autonomic dysregulation leads to immune system dysregulation which in turn interferes with the metabolism of tryptophan leading to the formation of toxic and diabetogenic metabolites. We introduce the concept of neuroprogression as a suitable conceptual framework that allows integration of the complex component mechanisms that contribute to recurrence and chronicity of mental disorders if left untreated or undertreated. The complex interactions among the autonomic, endocrine, immune and metabolic systems and associated cascades provide unique opportunities for development of novel therapeutic agents. We have presented promising novel targets aimed at ameliorating, arresting or even reversing neuroprogressive mechanisms through pharmacological, nonpharmacological, or combined interventions. We view this as an emerging new priority in reversing and even preventing the chronicity of psychiatric and neuropsychiatric disorders.

Ethical statement

No subjects were included in the design and execution of this Review Article.

All articles reviewed and referred to that involved research with human subjects included statements that their research study had received approval from an institutional ethics committee.

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Conflict of interest

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