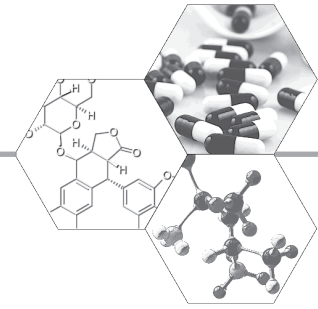

Role of IL-6 in the etiology of hyperexcitable neuropsychiatric conditions: experimental evidence and therapeutic implications

Many neuropsychiatric conditions are primed or triggered by different types of stressors. The mechanisms through which stress induces neuropsychiatric disease are complex and incompletely understood. A 'double hit' hypothesis of neuropsychiatric disease postulates that stress induces maladaptive behavior in two phases separated by a dormant period. Recent research shows that the pleiotropic cytokine IL-6 is released centrally and peripherally following physical and psychological stress. In this article, we analyze evidence from clinics and animal models suggesting that stress-induced elevation in the levels of IL-6 may play a key role in the etiology of a heterogeneous family of hyperexcitable central conditions including epilepsy, schizophrenic psychoses, anxiety and disorders of the autistic spectrum. The cellular mechanism leading to hyperexcitable conditions might be a decrease in inhibitory/excitatory synaptic balance in either or both temporal phases of the conditions. Following these observations, we discuss how they may have important implications for optimal prophylactic and therapeutic pharmacological treatment.

Stress, IL-6 & central hyperactivity

■ Hyperexcitable disease & the 'double hit' hypothesis

The pathophysiology of stress has been the target of countless studies since the pioneering studies by Selye on the role of glucocorticoids [1]. While the importance of glucocorticoids is underscored by a solid and relatively established body of work on the field, it is now clear that many other molecules are also co-released during stress, including mono- and poly-amines, and a large number of immune system-related peptides. Possible mechanism through which psychological stress may activate the immune system are the activation of the sympathetic branch of the autonomic system, which innervates numerous peripheral structures with immune functions such as the bone marrow and the thymus, but also spleen and lymph nodes [2], as well as the hypothalamus–pituitary–adrenal (HPA) axis. In spite of an acute anti-inflammatory role of the stress hormone cortisol, activation of the HPA axis actually increases the levels of **pro-inflammatory cytokines** [3], aggravating, for instance, the severity of viral infections in humans [4]. A series of peptides originally characterized by their immune function have attracted clinical and basic research interest for their potential to directly or indirectly interact with the CNS. It is now known that elevated levels of the members of a family of three peptides usually referred to as pro-inflammatory cytokines, which includes IL-1, IL-6 and TNF-α, produce central behavioral, morphological and functional effects; for example, sickness behavior [5], neurogenesis [6] and synaptic plasticity [7], which are linked to a group of apparently unrelated neuropsychiatric conditions that share neural and/or behavioral hyperexcitability and stress as triggering factor [8,9]. Schizophrenic psychoses [10,11], anxiety disorders [12–14], depression [15,16] and some types of epilepsy [14,17,18] all belong to this family of neuropsychiatric disorders, but, in a broader sense, the classification may be extended to include other conditions, such as tinnitus [19], and autistic spectrum disorders (ASDs) [20–23].

While an increase in excitability marks and defines the acute phase of these pathologies, each with a peculiar time course and distinctive behavioral phenotype (seizures in epilepsy, paranoia and hallucinations in psychoses, sudden aggression or panic attacks in anxiety disorders, sensory hypersensitivity and emotional tantrums in ASD), it has been postulated that an early phase of sensitization may 'prime' one or more particular areas of the CNS during vulnerable periods long before the appearance of an acute phase of the disease **(Figure 1)** [24]. In spite of some negative results [25], converging evidence is adding up to support a 'double hit' hypothesis, in multiple experimental contexts [26,27]. The failure to determine the efficacy of some particular 'double hit' experimental protocols should be taken as a demonstration of the biological

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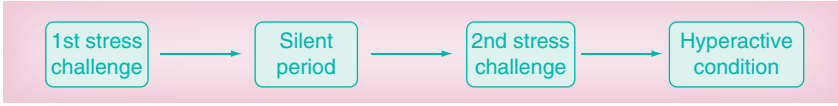

Figure 1. Double hit hypothesis. An early occurrence of a stress challenge sequence may be the first stage of the 'double hit' hypothesis. The first challenge may occur pre- or peri-natally, or even postnatally (childhood, adolescence or even adulthood), and may be followed by a silent period in which the symptoms of the condition are not evident even for a long time. The reoccurrence of a stressor challenge (of the same or of different type of the first stress challenge) may activate limbic circuits previously sensitized by the increase in neural excitability, triggering maladaptive behavior.

resilience of the organism to some types of stress, and does not decrease the strength of the 'double hit' hypothesis.

While a wealth of studies indicates a relevance of all three pro-inflammatory cytokines in the etiology of schizophrenia (reviewed in [28,29]) and other developmental disorders (reviewed in [30]), IL-6 has been proposed to have a key role in the etiology of developmental psychiatric conditions [31], particularly in ASD [32], and schizophrenia [33–35]. For this reason, this article will focus solely on the role of IL-6 in the early and late temporal phases of **hyperexcitable conditions**.

■ Mechanisms of release & action of IL-6

Il-6 is synthesized, stored and released by different types of cells including myocytes [36], cells of the immune system, microglia and astrocytes [37], and – in smaller amounts – neurons [38], in response to various internal and external stimuli. Among the stimuli that induce the release of IL-6 are physical activity, inflammation, cancer, and other types of physiological and psychological stress [39]. In the brain, the levels of IL-6 may increase due to: increased peripheral levels, through specific interleukin blood–brain barrier (BBB) transporters; leukocytes infiltrating the brain following physical trauma or metabolic or other biochemical insult to the BBB; stimulation of microglia, astrocytes and/or central neurons by synaptic stimulation or by BBB-permeable factors; or by sensory or autonomic activation of the CNS [39]. In the most studied among the molecular pathway associated with IL-6, the cytokine binds the IL-6 receptor (IL-6R), which *per se* is not associated with any transduction mechanism. On the contrary, the IL-6–IL-6R complex is one of several agonists for a distinct membrane protein, gp 130 that, in turn, activates a cascade of tyrosine kinases leading to phosphorylation of the JAK2/STAT3 pathway [40]. Two mechanisms of activation of intracellular cascades by IL-6 have been reported: the classical one, and the trans-signaling pathway. In the classical pathway, used mostly by immunocompetent cells, the IL-6R forms a membrane-bound complex with **gp130**, which is activated upon binding with IL-6 during elevations in the levels of extracellular IL-6. On the contrary, in the trans-signalling pathway, the activation of gp130 is secondary to proteolitic cleavage and release in the extracellular space of a soluble version of IL-6R from immunocompetent cells (sIL-6R 'shedding' by immune cells) [37]. The distinctive feature of 'trans-signaling' is that it allows all cell types that express gp130 in their membrane – including neurons – to respond to IL-6 regardless of whether or not they possess membrane bound IL-6R, whose expression is a prerogative of immune cells. An increase in the levels of IL-6 has been proposed to be associated with neurodegenerative disorders such as Alzheimer's disease [41]. The possible role of IL-6 in the etiology of hyperexcitable neuropsychiatric conditions will now be discussed.

Key Terms

Pro-inflammatory cytokines: Set of proteins, including IL-1, IL-6 and TNF-α, produced by, and affecting, both the immune and the nervous systems, signaling psychological or physiologic distress.

Hyperexcitable condition: Any neuropsychiatric illness associated with motor or sensory hyperactivity, including epilepsy, schizophrenia and anxiety disorders.

gp130: Membrane-bound transducer for the complex IL6–IL-6 receptor. It can be considered the real receptor for IL-6, whose 'IL-6 receptor' does not directly activate any enzymes.

Evidence of the involvement of IL-6 in central hyperactive conditions

■ Epilepsy

Epileptic seizures are characterized by uncontrolled electrical activity in the brain, which can produce a spectrum of symptoms, from minor signs to convulsions and thought disturbances. The importance of IL-6 in epilepsy is underscored by a series of genetic polymorphisms in the protein IL-6 that have been associated with increased risk of encephalopathy following hypoxic damage during birth [42] as well as of febrile seizures [43]. The elevation in IL-6 levels following an epileptic seizure has been demonstrated in several animal models, for instance, soman-induced *status epilepticus* [44]. In a cohort of patients with high frequency of refractory epilepsy where high-frequency seizures and intellectual disability were predictors of high levels of IL-6, epileptic patients showed levels of IL-6 twice as high as controls [45]. Besides the IL-6 produced by the periphery, also the IL-6 produced by immune cells infiltrating the BBB has been shown to contribute to the development of seizures [46].

Peripheral inflammation and peripherally produced cytokines can *per se* be a primary cause of epilepsy (reviewed in [47,48]), and have been proposed to be implicated in sudden unexpected deaths in epileptic patients through direct effects on cardiac function, or through propagation of epileptic activity from the CNS to the heart

through the autonomic system [49]. The complex relationship between epilepsy and cytokine elevation has been recently discussed [50]. These data are consistent with cellular studies showing that IL-6 increases neuronal excitability by impairing GABAergic function as a consequence of the decrease in the expression of β_{2-3} and γ_2 $GABA_A$ receptor subunits [51,52]. While a correlation between IL-6 and epilepsy is well accepted, the details of the cellular mechanisms and the causality of their connection are still unclear.

■ Schizophrenia

Schizophrenia is a psychiatric condition of unknown etiology associated with paranoia, disordered thought, aggression and/or hallucinations, which develops typically during adolescence or early adulthood. Current hypotheses for the origin of schizophrenia focus on the occurrence of prenatal stress, which, together with genetic factors, would increase the risk of developing the full syndrome later in life [53,54].

A number of clinical studies have demonstrated that prenatal infection is an important risk factor for schizophrenia [55]. While most bacteria or viruses do not cross the placenta, molecules produced in the inflammatory maternal response to the pathogen may cross the placenta and the developing BBB [56], increasing the probability of schizophrenia in the offspring [57]. The assessment of maternal infection as a risk factor for developmental CNS disease has been tackled with animal models using aseptic maternal immune activation (MIA), which reproduces the activation of the immune system using as immune decoys either lipopolysaccharide (LPS) from Gram-negative bacteria, or polyinosiniic:polycytidilic acid (poly[I:C]) viral-like double-stranded RNA, which are detected by Toll-like receptors type 3 and 4 and, in turn, trigger the release of pro-inflammatory cytokines [39]. Using MIA models, specific increases in IL-6 and TNF-α were reported by pregnant women who were asked to rate their subjective level of stress, which, in turn, increased the probability to contract infections during pregnancy [58]. A series of important studies on the effects of this cytokine showed that IL-6 injections in pregnant rats induce an unbalance in the ratio of *N*-methyl-D aspartate (NMDA)/GABAergic synapses in the hippocampus, increases escape latency in a water maze-task, and elevates the levels of IL-6 mRNA up to 6 months after birth, besides inducing numerous other large systemic changes [59,60]. Injection of the inflammatory challenge turpentine at gestational day 15 also produced a significant increase in locomotor behavior as well as increased sensitivity to amphetamine challenge and other schizophrenic indicators [61,62].

A specific role of IL-6 in fetal brain development was highlighted by a study in which a single injection of IL-6 at embryonal day 12.5 caused deficits in pre-pulse inhibition and latent inhibition in the adult wild-type offspring, but not in IL-6-knockout mice, while IL-6 antibodies prevented poly(I:C)-induced schizophrenia-like behavioral deficit [31]. Poly(I:C) induces the activation of STAT1, STAT3, MPAK [63] and NF-κB [64] in the placenta in an IL-6-dependent fashion, as shown by the use of antibodies against IL-6 itself. Poly(I:C) injection also induces the maturation of the pro-inflammatory T17 cells, which is known to be IL-6 dependent [65,66]. Poly(I:C) injections were used also for establishing the effect of different timing in the inflammatory challenge [67]. In this last study, by producing the immune challenge at different gestational times, it was shown that some features of the schizophrenic phenotype were associated with poly(I:C) challenge in the early gestation (decreased sensory motor gating, reduced dopamine D1 receptor density), some others in the late part of the gestation (impairment in working memory and NMDA receptor function), and yet another group of schizophrenic markers were impaired regardless of the timing of the challenge (sensitivity to amphetamine and distribution of the GABAergic interneuronal marker parvalbumin) [67].

Similar to poly(I:C), maternal injections of LPS also increase the levels of IL-6 in the pregnant mother system as well as in the placenta, as well as those of other pro-inflammatory cytokines such as TNF-α or IFN-γ [68,69], and induces anatomical and morphological neuronal damage [70]. The peculiar sensitivity of the late part of the gestation is supported also by another study in which LPS was administered to newborn rats at a time corresponding to the last trimester of human gestation [71]. LPS challenge reproduced most of the features associated with the established rodent schizophrenia model of the lesion of ventral hippocampus [71]. Patterson and colleagues observe how a plethora of unrelated factors, including birth in winter months or urban setting, maternal malnutrition or stress, and fetal hypoxia, epidemiologically correlated to schizophrenia, all share in common the increase in IL-6 levels in the pregnant mother-to

be [72]. Remarkably, in a study in which maternal LPS administration induced an altered response to inflammation in the adult, cytokine elevation in the adult was blocked by antipsychotics [73]. The peculiar role of IL-6 in the effects of prenatal LPS injections is demonstrated by the efficacy of IL-6 antibodies in the inhibition of astrocyte and microglia activation [74].

The relevance of IL-6 in 'priming' and triggering psychosis is underscored by studies showing that IL-6 not only interferes with normal CNS ontogenesis, potentially leading to the development of full-fledged schizophrenic psychosis, but also specifically elevated in schizophrenic patients [75,76]. These studies also show that neuroleptic treatment reduces IL-6 to control levels. Interesting and puzzling is the finding from a large genetic study of schizophrenic patients that showed a larger risk for schizophrenia in allelic variants of the major histocompatibility complex (MHC) type I [77], suggesting that a selection process associated with viral infections, with the associated production of pro-inflammatory cytokines, may have favored at least some allelic variants more prone to developing disorders of the schizophrenic spectrum after reaching sexual maturity. Specific allelic variations for IL-6 have also been associated with increased risk for schizophrenia, for instance in an Armenian [78] and in a Japanese cohort [79].

A series of studies by the group of Behrens deserve special mention; based on the previous finding by Reynolds and co-workers, of a deficit in parvalbumin-positive (PV+) cortical GABAergic interneurons as one of the best reproduced autoptic observation in the brain of schizophrenic patients [80,81]. The results from these studies are consistent with the hypothesis that an IL-6-driven hyperactivation of the enzyme NADPH oxidase specifically damages PV+ neurons constituting a major risk factor for schizophrenia [33–35,82].

Altogether, these data support the immune-hypothesis of schizophrenia, in agreement with the epidemiological data indicating birth in late winter and early spring as a risk factor for psychoses [83], both in the northern and the southern hemispheres [84,85], suggesting that besides the late part of gestation the first trimester may also be critical for the later development of schizophrenia. While more work will be necessary to establish a precise correlation between the timing of the early immune challenge and the type and time course of the pathology, the first and early second trimester of gestation appear to be particularly sensitive to infection that can potentially lead to schizophrenia [86]. More work will also be necessary to establish the role of cytokines in the 'second hit', and whether or not sudden increases in the cytokine levels may explain the abrupt appearance of psychoses. The difficulty in gathering non-anecdoctal information about the environmental circumstances preceding first psychotic episodes, and their heterogeneity is perhaps the reason for the paucity of information correlating specific acute stress to the psychotic trigger. In this context, it is interesting to notice that among the triggers of psychotic episode, besides disease and intense psychological stress, is the intake of stimulant drugs, such as cocaine, whose effect has been proposed to be IL-6-dependent [87]. From all these data, IL-6 emerges as a powerful molecular candidate in the etiology of psychoses and schizophrenia.

■ Autistic spectrum disorder

The ASDs are a large group of neuropsychiatric conditions of diverse etiology with a strong genetic component, that typically emerge in children aged between 2 and 4 years, characterized by the presence of decreased communication, decreased social interactions and exaggerated repetitive behaviors [88]. ASD displays a large degree of co-morbidity with epilepsy, hyperactivity, anxiety [89] and sleep disorders [90].

While the hypotheses on the origin of ASDs evolved since several decades ago, when, in the absence of precise anatomical or biochemical correlates, the origins of ASD were thought to be mainly psychological (e.g., having a cold or emotionally distant mother), many authors now regard ASDs as an unfortunate co-occurrence of a genetic component together with prenatal environmental factors [91]. A hypothesis on the origin of ASDs is that MIA during critical windows of prenatal CNS development may induce subtle changes in the embryo that do not necessarily produce behavioral or physical phenotypes until age 2–4 years, but jeopardizes later CNS development [32]. Developmental disruption during a critical period would produce a series of synaptic alterations that, in turn, would bring about a pathologic increase in local connectivity accompanied by a decrease in long-distance connectivity in brainstem, cerebellum, neocortex and possibly other brain areas [32]. Such pathologic synaptic rearrangement might be caused by either or both an increase in the strength of local excitatory glutamatergic synapses [92–94], and/or

by a decrease in the number or effectiveness of local GABAergic synapses [22,23,95–97]. Several studies support this view, and point towards an abnormal or untimely MIA as a trigger for impaired synaptic development, leading eventually to ASDs [70,98–100]. Toxins, heavy metals and other environmental factors producing inflammation and immune activation have also been shown to be potential triggers for ASD [101–105].

A number of maternal interleukins may cross the placenta [106] and interact with growth factors to produce abnormal neuronal growth [107]. A specific role for IL-6 in the development of the CNS has been indicated by several studies [108,109]. Dysregulation of IL-6 release has been shown to trigger a developmental course eventually leading to developmental disorders [31,32,110,111]. Remarkably, agonists for gp130 (the membrane protein transducing IL-6 signal) such as cardiotrophin, also regulate the growth and function of glia [112], which, in turn, are subject to neuronal inflammation in autistic children [113].

The cerebellum is one of the brain areas affected by ASD [114]. IL-6 levels are particularly high in the cerebellum of autistic patients, where the cytokine has been shown to alter numerous cellular and histochemical properties [115]. A study in cerebellar cultures showed that chronic treatment with IL-6 induce cellular alterations long overlasting the presence of the cytokine, disrupting cerebellar development [116]. These data suggest that a sudden increase in the levels of IL-6 triggered by inflammation may jeopardize the establishment of appropriate synaptic connections. Multiple cytokines seem to be involved in ASD: increased levels of both TNF-α and IL-6 are present in lymphoblasts from autistic children [117]. Similarly, high levels of endotoxin of bacterial origin, as well as of IL-1β and IL-6 were found in an adult cohort of ASD patients [118], suggesting a role for inflammation not just as a primary cause, but also as running consequence associated with ASD.

In spite of a wealth of data indicating a detrimental role of cytokines in the precipitation of ASD, the specific role of these molecules is yet somehow controversial, as some studies report that infections and fever are sometimes associated with temporary improvement of autistic symptoms in ASD patients [119]. Although it is difficult to reconcile IL-6 neurotrophic function with its pathogenic role in inflammation, the pleiotropy of cytokine action may imply cytokine-induced multiphasic effects and rapid shifts in cellular function, some of which might cross-regulate immune system and CNS in non-trivial fashion. The data discussed above suggest that IL-6 plays a role in the etiology and development of ASD symptoms, and that an increased sensitivity to inflammation may persist and contribute to the exacerbation of symptoms in ASD patients.

Stress & anxiety disorders

Early postnatal life (childhood and preadolescence) and even young adulthood might still belong to a critical time window in which stressful, adverse events ('first hit') can pathologically increase duration and intensity of the responses to stress at a later time ('second hit'), originating anxiety disorders. Importantly, IL-6 can be released within by vasopressin-positive neurons of the stress-sensitive hypothalamic paraventricular and supraoptic nuclei, by both psychotogenic stress (i.e., restraint) and systemic stress (i.e., hypoxia) [120,121].

In order to test the extent of IL-6 response to stress in sensitized subjects, a cohort of adults subjected to maltreatment in their early life was tested with a standardized Social Stress Test. Subjects responded with an increase in IL-6 significantly larger than the corresponding increase in non-maltreated subjects [122]. In a similar experiment, the levels of IL-6, along with those of the soluble receptor for TNF-α, are increased in an experiment of social stress in humans [123], while the levels of IL-6 and IL-6Rs are enhanced in post-traumatic stress disorder patients compared with control volunteers [124]. Another study did not find an increase in IL-6 or in other pro-inflammatory cytokines, but still detected an increase in corticosteroids levels following social stressors in rats [125]. Species-specific effects may perhaps account for these discrepancies in the response to different types of stress [126].

Particularly interesting in the context of the 'double hit' theory of stress, are two studies by Audet and colleagues, in which an early social defeat induced a desensitization in the later increases in IL-6 levels, but not IL-1β or TNF-α levels, in response to either social defeat itself, or in response to LPS challenge, demonstrating that social defeat – at least in rats – has long-term consequences well overlasting the experience itself [127,128]. These studies highlight the role of adolescence as critical postnatal period for the formation of proper central responses.

An important study suggesting a peculiar role of IL-6 in anxiety has compared the basal

levels and phasic levels in corticosterone, adrenocorticotropin hormone, and IL-6 before and after LPS challenge in a high- and low-anxiety strain of rats [129]. These experiments showed that, because of a high basal level and lower response of IL-6 in low-anxiety rats compared with high anxiety ones, the two strains differed greatly in the ratio between stress-evoked/baseline levels of IL-6, whereby the low-anxiety rats displayed a lower IL-6 evoked/basal ratio compared with the high-anxiety rats. Histochemical data also support the involvement of IL-6 in stress-induced brain alterations. For example, mRNA levels of IL-6, synthesized in pyramidal neurons of the cortex [44] and of the hippocampus [130] are greatly increased by psychological stress [131,132].

■ Other neuropsychiatric conditions

It is of interest in this context that several other neuropsychiatric conditions including depression and obsessive compulsive disorder might be correlated to pathologic elevation in IL-6 levels (reviewed in [133]). The hypothesis of the involvement of inflammation in the etiology of depression derives from the early observation that cancer patients treated with anti-inflammatory agonists develop depressive symptoms within weeks from inception of treatment [134]. Supporting the hypothesis of the immune origin of depression, animals subjected to different types of stress display an increment in pro-inflammatory cytokines [135]. Remarkably, an animal model of depression based on light deprivation showed a specific increase in IL-6, while the levels of the other pro-inflammatory cytokines IL-1β or TNF-γ did not undergo any changes [136]. Similar to depression in humans, the incidence of inflammation-induced changes in mood is sex dependent [137] and may be induced by impairment in the activity of the limbic cortex [138].

Catalepsy is a medical condition characterized by high muscular tone and fixed or stereotyped posture. The hyperexcitable nature of catalepsy is suggested by the successful treatment with $GABA_A$ receptor enhancers [139]. An interesting study converted a catalepsy-resistant strain of mice into a catalepsy-prone strain by inserting in the former the cassette gene corresponding to the IL-6 transducer gp130 [140], consistent with an IL-6 involvement. Intoxication by some xenobiotics, such as methylmercury, also causes specific systemic increases in IL-6 that can reach the brain through the BBB transporters [141] and can cause neurological symptoms such as emotional instability [142]. In a rare study finding no association between inflammation markers and schizophrenia, IL-6 was actually inversely correlated with negative mood [143]. The same study however, reported that inflammatory markers were predictive of bipolar disorder. A temporary or long-term hyperexcitability of the temporal cortex is hypothesized to underlie the onset of tinnitus and hyperacusia, which positively correlated with increased levels of IL-6 [144]. While a clear causal relation is missing, all these data suggest that a variety of neuropsychiatric conditions other than those discussed above may be at associated with increases in the levels of IL-6 and the development of neural hyperexcitability.

Targets of IL-6 in the brain

■ Anatomy of IL-6 release & action

An alteration in limbic function is a trait shared by the heterogeneous group of neuropsychiatric conditions falling under the general umbrella that we denominated 'hyperexcitable', including schizophrenia, ASDs, anxiety, but also temporal lobe epilepsy. Because of this link, it is relevant to determine whether limbic areas contain IL-6 and its receptors and examine whether they are subject to IL-6 modulation.

A correlation between IL-6 and limbic cortex is consistent with an fMRI study showing that systemic inflammation increases IL-6 and functionally impairs limbic cortex function [138]. Among the key components of the limbic circuit under scrutiny as possible sources in the etiology of neuropsychiatric disease are the hypothalamus, the amygdala and the prefrontal cortex. A growing number of studies link IL-6 to dysfunction of these brain areas. It has long been known that hypothalamic glia, as well as stress-sensitive neurons in the paraventricular and supraoptic nuclei of the hypothalamus projecting to the posterior pituitary are IL-6 positive [145]. Remarkably, some of the IL-6-positive neurons co-localize with vasopressin, another stress-related hormone, but not with oxytocin [120].

The involvement of the prefrontal cortex in IL-6 pathophysiology is suggested by a more than twofold increase following a social defeat protocol in rat [127], and by the reversion of memantine block of the acquisition of a cocaine-induced conditioned place preference task following the injection of IL-6 in the prefrontal cortex [87]. A connection between IL-6 and amygdala is suggested by the increase in

IL-6 mRNA levels in this brain areas, following systemic injection of LPS (also linked to an increased level of extracellular norepinephrine) [146], as well as by the disruption in forced swim performance following intra-amygdala IL-6 injections [147].

■ IL-6 & the GABAergic synapse

During recent decades an important role of the immune system in the regulation of synaptic transmission has been slowly emerging [7]. Among the synaptic processes affected by immune molecules, the enhancement of glutamatergic signaling induced by TNF-α on AMPA receptor trafficking has been studied in detail [148]. In the hippocampus, IL-6 has been found to interfere with the expression of numerous synaptic proteins [149] and synaptic function [116], besides contributing to neuronal regeneration in organotypic cultures [150]. It is important to observe that the trafficking of $GABA_A$ receptors is subject to a dynamic regulation [151], likely because of an interference of IL-6 with the mechanisms of internalization and/or receptor trafficking for the $GABA_A$ receptor, a family of membrane proteins to be subject to regulation by receptor tyrosine kinase agonists, to which IL-6 belongs [152]. Supporting this view, other activators of gp130 such as the membrane transducer for IL-6 leukemia-inhibiting factor (LIF) also interfere with proper synaptic development in other areas of the CNS [153]. Work from the Moss laboratory has shown the importance of post-translational modification, dynamin-dependent processes [154,155], and tyrosine receptor modulation, for instance by BDNF [156], in the regulation of trafficking, and presumably assembly of $GABA_A$ receptor subunits.

Clinical studies also corroborate the vulnerability of the GABAergic synapse in hyperexcitable conditions. A positron emission tomography study has shown a decreased benzodiazepine $GABA_A$ receptor binding in a group of soldiers affected by post-traumatic stress disorder (PTSD), compared with a group of soldiers without PTSD [157], supporting the hypothesis of a decrease in GABAergic function in PTSD. Interestingly, autistic patients display increased levels of IL-6 and other cytokines in response to LPS [158], as well as a significantly higher co-morbidity with epilepsy [159], which is often caused by a GABAergic deficit.

These data converge to indicate that the GABAergic system is an important target for stress in physiologic as well as in stressful conditions, which makes it a good candidate as priary trigger for many stress-related neuropsychiatric disorders [8,160]. IL-6 might be a previously overlooked key molecule to be added to corticosteroids, sex hormones, ethanol, benzodiazepines and several other drugs of use and abuse that affect $GABA_A$ receptors function. Its intense and volatile modulation of the $GABA_A$ receptor and GABAergic function in general makes IL-6 a critical factor in neuronal excitability and, hence, for an even more important global phenomena such as synaptic plasticity and the synchronization of neural activity between distant areas of the brain, such as γ-oscillations [161]. In conclusion, an unbalance between synaptic inhibition and excitation induced by stress through IL-6 might link a large and heterogeneous group of neuropsychiatric hyperexcitable conditions suggesting new avenues for their pharmacological and cognitive treatment, substituting or complementing $GABA_A$R enhancers and anti-glutamatergics largely prescribed in the early treatment of patients suffering from stress-related conditions.

Together, these data suggest that IL-6 may have a key role in increasing neural excitability during the stress challenge, perhaps both in the first and the second 'hit' **(Figure 2)**. **Table 1** lists candidate times and types of stressors in relation with the possible clinical outcomes.

The IL-6 cascade as a target for treatment of neuropsychiatric disorders

For most systemic diseases, prophylaxis is always preferable to therapy. This is all the more true for neuropsychiatric diseases, as their more profound consequences are not necessarily the direct effects of immediate cellular or biochemical damage,

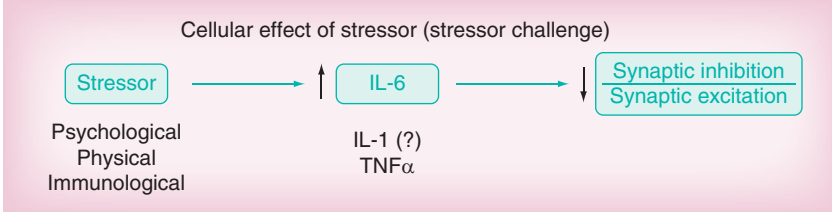

Figure 2. Link between stress, IL-6 and ratio between synaptic inhibition and excitation. Different types of stressors, such as physical work, psychologic stress or inflammatory challenge, increase the levels of pro-inflammatory cytokines including IL-6, which, in turn, increase neural excitability by decreasing the ratio between synaptic inhibition and excitation. In genetically predisposed individuals and, depending on the extent of the challenge even in individuals non-genetically predisposed, the body initiates a maladaptive series of plastic changes affecting later responses of the system. The whole temporal sequence as stress challenge is indicated.

Table 1. Combinations of types and timing of stressors and possible clinical outcomes†.

Time of first stress challenge	Time of second stress challenge	Possible outcome
Prenatal (first or third trimester)	Adolescence/early adulthood	Psychotic episode
Prenatal	Prenatal/early postnatal	Autistic regression
Adulthood	Months/years after first stress challenge	Anxiety or post traumatic stress disorder
Any time (prenatal, perinatal, stress or trauma in adulthood)	Sensory hyper-stimulation. Sometimes unnecessary, for example, sleep seizures	Epileptic seizures

†The clinic outcomes of the sequence following the events of the 'double hit' hypothesis differ depending on the time and nature of the first and the second stressor challenges.

but typically are secondary to sometimes years-long chains of psychological, biochemical and synaptic modifications that may be very difficult to revert. The detrimental effects of IL-6 in the etiology of conditions triggered by concomitant genetic predisposition and unfavorable environmental factors as in autism and schizophrenia would make desirable an early identification of pregnant mothers in couples with a family history of neuropsychiatric disease within this group (epilepsy, schizophrenia and autism), aimed to minimize endogenous or external stress for the mother and the fetus. Wherever this might not be straightforward (e.g., job loss, decease of a loved one, environment prone to infections), it would be important to perform clinical trials to test the effects of compounds blocking the IL-6 cascade. Many of these substances, some of which will be discussed in the next sections, occur naturally and are already present in many human diets.

On the other hand, for patients suffering from epilepsy or anxiety disorders the use of pre-emptive strategies would be obviously more difficult and therapy vs prophylaxis would be typically the only possibility. The search of blockers to break the causal chain leading from inflammation to neuropsychiatric condition needs to look into the several domains of action of the cytokine: from the BBB transporters that can make the cytokine available to the brain, to the extracellular space where the cytokine itself meets its functional chaperones IL-6R and gp130, as well as the intracellular space where IL-6 effectors carry out their pathological and physiological actions.

Key Term

JAK/STAT pathway: Tyrosine-kinase dependent intracellular metabolic pathway activated by IL-6 and other agonists.

■ Extracellular targets

The development of antibodies against IL-6 or IL-6R has been attempted to contrast the detrimental effects of systemic IL-6 [162]. In the last decade, tocilizumab has been developed, US FDA approved and commercialized, and is successfully used in the treatment of several inflammatory conditions such as rheumatoid arthritis, Castleman's disease (a benign proliferative disease of lymph nodes) and systemic juvenile arthritis (a systemic childhood disease leading to deterioration of joints) [163]. Possible side effects of the use of tocilizumab include infection of soft tissues, increase in serum cholesterol, low neutrophil count and liver dysfunction, to extents that are usually manageable in the clinical practice [164]. So far, at least seven types of IL-6-related molecules are under scrutiny by a number of pharmaceutical companies to be used mainly in the treatment of cancers and systemic autoimmune disease [163]. This list includes anti-IL-6 chimeric and humanized antibodies, antiIL-6R antibodies and an sgp130-Fc fusion protein. At the moment, to our knowledge, none of them have received approval for human treatment, but it is likely that clinical trials will rapidly advance in the assessment of their efficacy and safety. Unfortunately, similar to most high-molecular-weight hydrophilic compounds, the potential of these molecules in the treatment of CNS disease is limited by the presence of the BBB. To our knowledge, no attempts were made yet to determine a pathway through which systemically administered tocilizumab could cross the BBB. Possible strategies might include the covalent link to molecules possessing specific BBB transporters (co-shuttling), or enhancing enzymatic lysosomal BBB transport, for instance with co-administration of peripheral epinephrine [165].

Similar limitations apply for the use in the CNS of an otherwise elegant strategy based on soluble gp130 antagonists [40,166,167]. A soluble version of gp130 (sgp130Fc) has been successfully used in several studies to block both systemic [168] and central effects of IL-6 [52] (reviewed in [169]). A further limitation to gp130 interference is in principle a possible undesirable block of the transducer activity by agonists other than IL-6–IL-6R complex [152]. Several experiments demonstrated the efficacy of intra cerebroventricular injections of a saturating concentration of the sgp130Fc antibody, which sequesters the available IL-6–IL-6R complex, in preventing LPS-induced deficit in contextual fear conditioning [170].

Related to this therapeutic approach, treatment with cholesterol synthesis inhibitors belonging to the statin family attenuates

seizure behavior in rats subject to pilocarpine-induced *status epilepticus* by interfering with IL-6 expression [171].

Different strategies use modulators of estrogen receptors and anti-oxydants permeable to the BBB in order to decrease the levels of IL-6. Tamoxifen, raloxifen, ospemifen and bazedoxifen have been successfully used in a mice preparation to reduce IL-6 levels to approximately 50% of the control levels [172], while pretreatment with the antioxydant *N*-acetylcysteine before MIA and prevents the increase in IL-6 [173,174], and reduces placenta leukocyte infiltration [175,176] as well as the detrimental effects of LPS injection on long-term potentiation and spatial tasks [177].

The biochemical nature of IGF-1 suggests that this molecule might exert its neuroprotective action by decreasing inflammation. In fact, in primary cultures from rodents brain, introduction of a viral vector harboring the *IGF-1* gene greatly decreased inflammation, expression of Toll-like 4 receptors, and the production of several cytokines including IL-6 [178]. Among other relatively unexplored therapeutic strategies in the prophylaxis of schizophrenia or autism is the inhibition of Toll-like receptors in pregnant mothers of genetically predisposed couples. A list of Toll-like receptor inhibitors includes polyunsaturated fatty acids, which prevent TLR-4 dimerization in lipid rafts [179] and synthetic cyclohexenes [180] (reviewed in [181]).

Since IL-6 crosses the BBB through a saturable transporter [39,182], in cases in which the pathological effects of IL-6 would be mediated by systemic (vs central) inflammation/increase in IL-6, it would be in principle possible to attenuate the harmful effects of the pro-inflammatory cytokine by interfering with the transport mechanism [183]. Unfortunately, no pharmacological tools are available yet targeting specifically cytokine transporters present in the BBB (or elsewhere, to our knowledge), limiting, at the moment, the potential of this approach.

■ Intracellular targets for the pharmacological treatment of IL-6-related conditions

IL-6 & diet

A number of studies have correlated diet and systemic inflammation (reviewed in [184]), most of them showing a definite relevance of the dietary lifestyle with tonic levels of systemic inflammation, measured by inflammatory markers including C-reactive protein and IL-6 itself [185].

An inverse correlation with systemic levels of IL-6 was determined for fiber content [186], ω-3 polyunsaturated fatty acids [187,188] and non-fried fish consumption [189]. Flavonoids are a series of tricyclic, oxygen-containing and naturally available compounds biosynthesized in a variety of plants known for their antioxidant activity. Studies comparing concentrations of pro-inflammatory cytokines in different cohorts submitted to different diets suggest that flavonoid intake reduces serum levels of IL-6, as well as those of other markers of systemic inflammation [184]. Supporting this hypothesis, an inverse correlation was found between levels of carotenoids and lutein/zeaxanthin and plasma levels of IL-6 in a 2-year long diet trial [190]. Furthermore, in a rodent model of MIA, a maternal diet with the naturally occurring flavonoids luteolin and diosmin – JAK2/STAT3 inhibitors – decreased JAK2/STAT3 phosphorylation and significantly reduced abnormal behavior and other pathological markers [191]. Another blocker of the JAK2/STAT3 cascade, resveratrol, greatly decreases the LPS-dependent increase in IL-6 levels as well as of other inflammatory markers [192].

Other intracellular targets

Additional potential targets for antagonizing the IL-6 cascade are suggested by the link between IL-6 and the ERK/MAPK pathway, which is alternative or complementary to the **JAK/STAT pathway** [163]. Accordingly, administration of the MEK inhibitor SL327 successfully inhibited the disruption in the forced swim test performance induced by intra-amygdala injections of IL-6 [147].

A recent study has identified a specific IL-6 antagonism action by the FDA-approved NMDA blocker memantine. In fact, while administration of memantine prevented conditioned place preference induced by cocaine, such effect was restored by the simultaneous administration of IL-6 [87], suggesting that memantine, in addition to its NMDA receptor antagonism, may target other sites of prophylactic or therapeutic interest in the treatment of neuropsychiatric conditions.

Because of the (incompletely known) cross talk between the STAT3 pathway and the inflammatory pathway associated with prostaglandins [193,194], non-steroid anti-inflammatory drugs such as COX2 inhibitors have been tested in schizophrenia, producing results that are yet inconclusive [29,195,196]. A study on a cohort of autistic children administered with

Key Term

Synaptic inhibitory/excitatory balance: Ratio between the strength of synaptic inhibition and excitation, characteristic for different brain areas, and sensitive to environmental and endogenous modulation.

anti-inflammatory drugs acting on cell peroxisomes showed promising results, including the decrease of irritability, lethargy, repetitive behavior and hyperactivity [197].

Future perspective

Great progress has been made in the last three decades in the establishment of a link between stress and neuropsychiatric disease. While such progress is leading to improved cognitive and behavioral therapies, more work is needed for understanding how the immune system affects neural and synaptic activity, in the search of more effective and specific pharmacological tools for the treatment of hyperexcitable central conditions. The knowledge of the molecular and cellular details of the immune–neural interactions has the potential to produce pharmacological tools targeting specific periods of human life, professional settings, and medical or psychologic conditions aimed to pre-emptive minimization of the detrimental long-term effects of the 'first hit'.

On the contrary, in cases in which minimization of the effects of the first hit is difficult or impossible (long-term unrecognized medical conditions, prenatal or genetic factors, or undisclosed abuse), it is foreseeable that IL-6 blockers or inhibitors might be administered to prevent or minimize the secondary decrease in **synaptic inhibitory/excitatory balance** associated with the 'second hit'.

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Executive summary

Mechanism of action of IL-6

- IL-6 is a pleiotropic cytokine released by multiple cell types also as a distress signal.
- Activation of the complex IL-6/IL-6R/gp130 initiates signal transduction mediating numerous effects of IL-6.

IL-6 & the 'double hit' hypothesis

- A 'double hit' hypothesis of neuropsychiatric disease proposes that several developmental or adult conditions are caused by a sequence of early insult, silent period and acute phase.
- A growing number of studies indicate that IL-6 plays a key role in both the early insult as well as the trigger of the acute phase.

IL-6 & central hyperactive conditions

- There is evidence for the involvement of IL-6 in central hyperactive conditions: epilepsy; schizophrenia; autistic spectrum disorder; stress and anxiety disorders; other neuropsychiatric conditions.

IL-6 & synaptic function

- IL-6 modulates synaptic function, particularly at inhibitory GABAergic synapses.
- IL-6 decreases the ratio between synaptic inhibition and synaptic excitation inducing cellular and behavioral hyperexcitability.
- An acute increase in excitability may sensitize limbic circuits by inducing long-term changes predisposing to neuropsychiatric disease.

The IL-6 cascade as a target for pharmacological treatment of neuropsychiatric disorders

- IL-6, IL-6R, gp130 and their soluble physiological and man-made version are potential targets and means for pharmacological intervention in the extracellular environment.
- Naturally occuring or synthetic compounds that interfere with the JAK/STAT, NF/κB or ERK/MAPK cascades are potential avenues of intracellular pharmacological intervention in the inhibition of the IL-6 effects.

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