Prenatal stress and inhibitory neuron systems: implications for neuropsychiatric disorders

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Abstract

Prenatal stress is a risk factor for several psychiatric disorders in which inhibitory neuron pathology is implicated. A growing body of research demonstrates that inhibitory circuitry in the brain is directly and persistently affected by prenatal stress. This review synthesizes research that elucidates how this early, developmental risk factor impacts inhibitory neurons and how these findings intersect with research on risk factors and inhibitory neuron pathophysiology in schizophrenia, anxiety, autism and Tourette syndrome. The specific impact of prenatal stress on inhibitory neurons, particularly developmental mechanisms, may elucidate further the pathophysiology of these disorders.

Introduction

There is an increasing appreciation for the importance of early events in brain development for the pathophysiology of psychiatric disorders. Genetic factors previously associated with mature brain dysfunction in psychiatrically-ill patients have critical roles in the development of the brain preceding illness. Environmental changes that occur during early periods of development are also risk factors for later psychopathology. Stress is a major environmental risk factor for psychiatric illness and disrupts mature brain functioning in a variety of ways.[1, 2] Stress is also a significant risk factor during development.[1, 3, 4] Just as with genetic factors, stress during embryonic development is now recognized as equally important to psychopathology as when it interacts with the mature brain. In particular, prenatal stress is associated with atypical patterns of emotions and behavior and increased risk for psychiatric illness in offspring. [5, 6] Animal model work has demonstrated that at least some of these associations are causal, as prenatal stress in rodents, primates and other models significantly influences later neural circuitry and behavior. [7, 8]

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Along with the growing appreciation for the role of development in psychiatric disorders, the importance of inhibitory neuronal systems in mental illness has also become widely recognized. As we will discuss below, inhibitory circuitry is fundamentally altered in several neuropsychiatric disorders. The effects of prenatal stress on the brain may be mediated by its influence on this important aspect of neural signaling—critical cellular development of GABAergic systems occurs during prenatal periods when stress can have persistent effects on the brain and behavior. Prenatal stress broadly influences non-GABAergic neural systems that also develop prenatally, but the interactive nature of CNS development in which GABAergic progenitors have an influence on the formation of surrounding circuitry makes understanding the influence of prenatal stress on inhibitory neurons an imperative. GABAergic systems are also part of the circuitry that normally regulates other neural systems in the mature brain—of particular interest for prenatal stress is the GABAergic control of stress regulation, a neuronal system fundamentally altered by prenatal stress.

In this review, we focus on prenatal stress as a risk factor for psychiatric disorders in which inhibitory systems are implicated. The co-occurrence of inhibitory neuron pathophysiology and risk due to prenatal stress gives weight to pre-clinical investigations of prenatal stress and inhibitory neural circuitry. Developmental events influenced by prenatal stress impact inhibitory neurons, and animal models demonstrate fundamental alterations in this neural circuitry.

Development of Inhibitory Neuronal Systems

Animal models have been extremely valuable for examining cellular and molecular changes due to prenatal stress. In most mammals, inhibitory neurons are generated solely in the ventral telencephalon.[9] From their subcortical origins, inhibitory neurons populate subcortical nuclei and tangentially migrate to the cortex, where they play a role in organizing neuronal connections to form functional groups such as cortical columns and limbic-cortical loops.[10] Due to chloride homeostasis, GABAergic signaling changes from excitatory to inhibitory during the perinatal period, and this switch has precise timing, determining the functionality of cortical and subcortical circuits.[11] GABAergic neurons act as architects in early postnatal brain development, regulating the development and function of the cerebral cortex during critical periods.[12] In the mature brain, they act as modulators of cortical excitability and cortical-subcortical oscillations through their varied morphology, widespread locations in the circuitry and diverse electrical characteristics.[13]

Inhibitory neuronal precursors follow a regulated series of events to populate the cerebral cortical primordium. After the peak of GABAergic precursor proliferation in the ganglionic eminences, during the last embryonic week in rodents, these progeny differentiate as they migrate.[14] Some of the first molecular markers of inhibitory neurons are the transcription factors, *dlx1*, *dlx2* (distal-less homeobox) and *arx* (aristaless homeobox), which are responsible for specifying cortical inhibitory neuron fate.[15, 16] The enzymes required to synthesize GABA, GAD67 and GAD65, are also expressed early in the development of inhibitory progenitors.[17] As these neuronal precursors further differentiate into different GABAergic cell subtypes, they express a variety of calcium-binding proteins such as parvalbumin (PV), calretinin (CR), and somatostatin (SOM) and acquire different

morphologies and functions.[10] Two important factors, *lhx6* (lim homeodomain transcription factor) and *nkx2.1* (NK2 homeobox 1), are expressed in ventral telencephalic cells as they begin to migrate tangentially.[18, 19] These transcription factors are specific to different subtypes but also underlie migration. GABAergic neuronal precursors that later populate the cortex express other markers that play a significant role in the targeting of these cells to specific locations, including reelin,[20] ERBB4,[21] CXCR4[22] and neuropilin.[23] Stress that occurs while these transcription factors and cell signaling molecules are expressed may have persistent effects on brain function due to their influence on gene expression or cellular function of GABAergic cells. Understanding how early risk factors influence brain development is one avenue through which improved interventions can be developed.

Prenatal Stress and Development of Inhibitory Systems

Changes in cell numbers and maturation through altered proliferation, migration and differentiation could result in persistent effects on brain functioning at distant time points. Through maternal factors interacting with the programmed sequence of developmental events, prenatal stress may have influences on a range of neuronal systems. Effects of prenatal stress may be due to activated hormone receptors that act directly on gene expression through their transcription factor properties or through the direct influence of maternal signaling proteins produced by her stress response on cellular functioning in the offspring brain, which may include epigenetic alterations. As a result of these largely unidentified molecular mechanisms, prenatal stress has effects on cerebellar and hippocampal neuronal proliferation, survival, and differentiation,[24, 25] effects initiated prenatally but persistent postnatally. The very timing of many prenatal stress models in the last week of rodent gestation, during important aspects of inhibitory neuronal development, suggests that inhibitory neuron proliferation, survival and differentiation may be affected.

Though a link between prenatal stress and dysfunction in the mature brain has been well-established, research on the developmental trajectory of this effect is still in early stages. Accordingly, there have been less than a handful of papers that discuss the relationship between prenatal stress and development of inhibitory neurons (Table 1). Work from our lab has demonstrated that, when prenatal stress occurs during the early phases of neurogenesis and migration, the migration of inhibitory neuronal progenitors is delayed during and immediately after prenatal stress, linked closely with concurrent changes in the transcription factors, *dlx2* and *nkx2.1*, that are involved in cortical interneuron migration.[26] Delays in the tangential migration of these precursors occur after even one day of prenatal stress and persist over time to result in reduced GABAergic cells in neonatal medial frontal cortex. The same group of transcription factors implicated by our work, particularly *dlx2*, was also found to be altered by prenatal maternal immune activation,[27] demonstrating that these two forms of prenatal risk, which have similar postnatal outcomes, may share a central influence on developing inhibitory neurons. Cell migration changes with prenatal stress in general, as demonstrated by delayed migration of excitatory neuronal precursors after prenatal glucocorticoids.[28, 29] Later stage maternal stress from embryonic day 15 (E15) resulted in altered distribution of late born neurons (labeled with BrdU at E15) in the cortical plate two days later, accounted for by a reduction in GABAergic cells born at E15, with no change in migration of earlier born cells.[30] These findings suggest that GABAergic cells born at

different time points are affected by prenatal stress in different ways, which could influence specific subtypes.[31]

While temporary changes in inhibitory neuron gene expression have a significant role to play in prenatal stress, there is also evidence that persistent methylation of genes expressed in GABAergic cells results from this early exposure, which may alter gene expression on a longer term basis.[32] Prenatal stress increased methylation of reelin and GAD67 and was associated with their decreased expression in frontal cortex. These results are consistent with a generalized reduction in typical inhibitory functioning after prenatal stress. Moreover, prenatal stress effects on methylation are significant as a potential mechanism by which other biological changes occur, from those of the CNS inhibitory circuits discussed here to effects in non-neural systems. [33]

Inhibitory neuron development is also affected by prenatal stress in mice with altered levels of GAD67 during development. GABA levels are dependent on, GAD67 and GAD65 which convert glutamate to GABA. GAD67 and GAD65 begin producing GABA very early in the development of inhibitory progenitors. [34, 35] This early presence of GABA plays a significant role in regulation of the very inhibitory progenitors producing it,[36] underlying the appropriate migration of progenitors. Mice with temporarily reduced levels of GAD67 during development are more sensitive to prenatal stress: total fetal corticosterone increases after prenatal stress, a change that is amplified in mice with less GAD67.[37] Whether this effect occurs through GABAergic cells or by an effect of GABA and stress together on other cells, it suggests that prenatal stress interacts with GABA during development in influencing hormonal levels.

While prenatal stress has been shown to induce cell death in some progenitors, there is little evidence that developmental processes such as cell death are part of the impact of prenatal stress on GABAergic cells or responsible for reduced inhibitory functioning across the CNS. No colocalization of caspase-3 with GAD67GFP in embryonic cortical plate[26] was found after prenatal stress or with calretinin or calbindin in early postnatal amygdala[38] after prenatal dexamethasone exposure.

Prenatal stress and inhibition in the adult brain

Despite only a few results investigating developmental mechanisms of prenatal stress on inhibitory systems, these circuits are altered in the brains of mature prenatally-stressed animals (Table 2). Due in part to a lack of information about how prenatal stress effects proceed developmentally, it is unclear how GABAergic system changes arise—since many different neural components are altered in the mature brain of animal models of prenatal stress, the critical mediation of GABAergic system effects may be through, to name only two possibilities, altered glutamatergic or dopaminergic functioning. It is also plausible that effects are mediated in the opposite direction, with initial GABAergic changes resulting in altered consequences in other circuitry or, even more simply, a change in the balance between excitation and inhibition. Here, we will focus on GABAergic alterations, as the effects of prenatal stress across neural systems are beyond the scope of this review. Summarizing GABAergic modifications that occur with this pertinent early life event serves

not to reduce this risk to its impacts on a single system but to acknowledge the, at times overlooked, role in prenatal stress of this GABAergic neural circuitry.

One of the most consistent consequences of prenatal stress is altered hypothalamus-pituitary-adrenal (HPA) axis reactivity. In general, adult offspring that experienced prenatal stress show increased reactivity of the HPA axis[39] as well as elevations of baseline corticosterone [40-42] with some sex differences.[43] A possible mechanism by which HPA changes may occur is through decreased hippocampal mineralacorticoid and glucocorticoid receptors that occur with prenatal stress.[43, 44] However, altered inhibitory circuits in and projecting to the hypothalamus may also account for increased HPA reactivity

Complex excitatory and inhibitory circuitry controls stress responsivity through connectivity of other brains regions with the hippocampus and hypothalamus.[45] Many of these projections are GABAergic that either target the hypothalamus directly or inhibit regions that, in turn, influence the hypothalamus. In the hypothalamus, prenatal stress increases GABAergic synapses, as measured by presynaptic vGAT immunocytochemistry.[46]

Prenatal stress also causes decreased expression of inhibitory proteins in forebrain CNS regions upstream of hypothalamus. Rat offspring of "stressed" mothers, through restraint or external corticosterone administration, have fewer post-synaptic benzodiazepine binding sites and $GABA_A$ receptor subunits in the hippocampus[47, 48] and amygdala.[49, 50] The cause of these post-synaptic modifications is unclear—it may be a direct consequence of prenatal stress on receptors or a compensation due to changes in ligand activity. Decreased inhibitory functioning after prenatal stress is seen in presynaptic GABAergic neurons themselves as well as on the post-synaptic side. Neurons expressing calretinin and calbindin, calcium-binding proteins necessary for mature inhibitory neuron functioning, are reduced in lateral amygdala in female offspring after prenatal dexamethasone.[51] While these results are limited to one region—not apparent in other amygdala subregions or in the hippocampus—prenatal exposure was also limited to glucocorticoids. Generalized stress may exert different and more global effects than one hormone alone. In full prenatal stress models, inhibition across different regions is also reduced. GAD activity as measured by GABA generation with fluorimetry is lower in the hippocampus of prenatally stressed females.[52] GAD67 protein and mRNA levels are also lower after prenatal stress in frontal cortex throughout early postnatal development and into adulthood.[32, 53] These findings suggest that frontal cortex and hippocampus, both of which regulate the HPA axis through inhibitory projections to hypothalamus, may exert less inhibition after prenatal stress, at least at baseline. Studies of how the hippocampus changes in response to acute stress demonstrate that the direction of stress-reactive expression of GAD enzymes is not fundamentally changed.[48] Typically, GAD65 decreases after a single exposure to stress hormone and increases after two exposures. Prenatal stress causes only a small increase in this reactivity[48] in mRNA expression per cell, not overall expression in the region. This change may be a compensatory response to the presence of fewer GAD-expressing cells after prenatal stress.

There is some data on whether GABAergic cells are generated in the same numbers to populate various regions of the CNS after prenatal stress. In mice heterozygous for GAD67, GABAergic cells born at E15 during prenatal stress and those of the parvalbumin subtype

are deficient in dorsal, medial regions (medial frontal cortex and hippocampus).[30] This was not true of wild-type animals in the same study, suggesting that GAD67 expression may interact with prenatal stress in influencing inhibitory neuron development. Some additional insight into how inhibitory neuron number may be affected comes from the alterations in migration seen after prenatal stress[26] but also from in vitro studies. Cultured hippocampal neurons differentiate less into GAD-expressing cells after prenatal stress.[54] These results suggest that the processes contributing to GABAergic cell numbers may be disrupted by prenatal stress and may result in changes in the cell population.

These neural changes are relevant to the consistent influence of prenatal stress on anxiety-like behavior.[55, 56] Prenatally-stressed animals also show reduced social interaction,[57, 58], particularly in the setting of increased maternal susceptibility to stress.[59] Anxiety has been shown to be increased after prenatal stress in the absence of changes in GABA release in the hippocampus.[60] The circuitry of the amygdala and hippocampus that is responsible for regulating anxiety requires complex inhibitory neuronal components. However, GABAergic cells in the amygdala and hippocampus also send longer distance projections to the hypothalamus whose functioning would not be evident by GABA release in hippocampus.[45] If GABAergic cells within amygdala and hippocampus are functioning abnormally, they may disrupt prenatally stressed animals' abilities to normally regulate behavior.

Inhibitory neuronal function in hippocampus and amygdala that may underlie such behavior is altered at the physiological level with prenatal stress. During development and in mature animals, seizure susceptibility in a kindling model is increased by prenatal stress,[61] possibly due to a vulnerability of hippocampal inhibitory systems to secondary insults. In contrast, prenatal stress decreases the occurrence of seizures from ventral hippocampal stimulation in adult rats, concurrent with a decrease in glutamatergic release and no hippocampal GABAergic alteration.[60] The reconciliation of these results may be due to *in vivo* vs *in vitro* differences in protein measures but may also suggest that prenatal stress has effects specifically on the resilience of inhibitory neural systems.

Certainly, changes to inhibitory neurons in the forebrain occur in the context of many other changes to excitatory neurons, glial populations, monoaminergic projections and other entities.[62] These varied changes may be causally linked. Insights into how inhibitory changes may result from or lead to other neural changes in the context of prenatal stress can come from a more deep understanding of each neural system and testing how protection of one through development may rescue another. Such investigations will be helpful for clinical science in which the time course of events in disease on the cellular and molecular level is difficult to understand.

Clinical Relevance

Research on the molecular and cellular effects of prenatal stress in humans is an area for significant growth. There are no studies in humans exposed to prenatal stress examining impacts on GABAergic systems. Prenatal stress exposure has been shown to alter HPA axis functioning in children[63] and to change cortical thickness,[64] both of which could involve inhibitory neuron changes or leave them unaffected. However, the importance of prenatal

stress as a risk factor for several psychiatric disorders means that the occurrence of GABAergic abnormalities in these conditions may be related to prenatal stress exposure. Here we will review some of the critical links of prenatal stress to schizophrenia, anxiety, autism and Tourette syndrome, all disorders which are hypothesized to involve significant disruptions in CNS GABAergic circuitry.

Schizophrenia

There are multiple sources of evidence for the link of prenatal stress to risk for schizophrenia. Maternal depressed mood during pregnancy combined with parental history of psychosis elevated risk of schizophrenia in offspring.[65] Likewise, a higher incidence of schizophrenia was observed in offspring whose mothers experienced the death of a relative during the first trimester[66] or had unwanted and hence stressful pregnancies.[67] Finally, prenatal exposure to the German military invasion of the Netherlands during World War II[68] and to a devastating tornado in Massachusetts increased schizophrenia prevalence.[69]

Many lines of evidence suggest that this disorder may be related to deficits in inhibition, particularly in the dorsolateral prefrontal cortex (dlPFC). Subjects with schizophrenia show a reduction in GAD67 expression in the dlPFC.[70-72] (OR: reviewed in [73]). The reduction in GAD67 levels appears to disproportionately affect PV+ interneurons.[74] Parvalbumin mRNA expression is also decreased;[75-77] however, PV+ interneuron density is unchanged,[74, 78-80] suggesting the deficit is one of signaling rather than cell number. In addition, most studies have shown that levels of the $GABA_A$ $\alpha1$[75, 81-83] and $\beta2$[82] subunit receptors are reduced, particularly in dlPFC layers 3 and 4. Together, these data suggest a deficiency in GABA transmission, both presynaptically (in the enzymes that produce GABA) and postsynaptically (in receptor expression). There are no links between maternal stress and GABAergic deficits in schizophrenia--reconstructing prenatal exposures in postmortem studies is not feasible. The co-occurring links of psychosis with both maternal stress and inhibitory changes, however, suggests that trajectories of development similar to those seen in animal models could lead to reduced inhibitory capacity in patients with schizophrenia.

Gene associations with neuropsychiatric disorders appear, superficially, to have little significance for the environmental risk of prenatal stress. However, neural disruptions implicated by genetic deficits may demonstrate common pathways by which environment and genetics each act or may only become disrupted when genetic and environmental risk occur together. While no evidence exists for interactions of GABAergic risk alleles with prenatal stress, such candidate genes could be examined alongside retrospective data on prenatal stress. However, it is significant to the implication of inhibitory systems in schizophrenia that associated genes, even in isolation, also have roles in inhibitory neuron signaling. Genes for neuregulin-1 (NRG-1) and its receptor ErbB4, a receptor tyrosine kinase preferentially expressed in PV+ interneurons,[84-86] have both been implicated in schizophrenia.[87-90] Signaling by Nrg1 and ErbB4 controls connectivity between GABAergic interneurons[84] and tangential migration of interneurons into the cortex.[21]DISC1, a gene associated with schizophrenia[91] may also affect PV neurons[92] and the migration of cortical interneurons.[93] Mouse modeling of 22q11.2 syndrome, which carries a strong risk for schizophrenia shows disrupted interneuron migration as well.[94]

Autism Spectrum Disorders

As in schizophrenia, prenatal stress has been correlated with autism spectrum disorder (ASD) incidence: autistic traits in progeny are predicted by stressful events during pregnancy.[95] In particular, increased ASD risk has been associated with prenatal exposure to stressful life events,[96] family discord,[97] and hurricanes/severe tropical storms.[98]

Many studies have explored the relationship between ASD and alterations in inhibitory function. Post-mortem studies have revealed a reduction in GAD65 and GAD67 in the parietal cortex and cerebellum of patients with autism.[99, 100] Changes in $GABA_A$ and $GABA_B$ receptor expression have also been observed.[101-106] Decreased GABA concentration was observed in the frontal cortex of a small sample of children with autism via [^{1}H]MRS[107] and lower $GABA_A$ receptor levels were found in small samples of patients with autism via SPECT[108] and PET.[109] As in schizophrenia, in autism, PV+ interneurons appear to play a particularly critical role. A meta-analysis revealed that in multiple mouse models of ASD, PV+ cells are reduced[110]

Many the genes implicated in ASD play a role in inhibition. For example, contactin-associated protein 2 (CNTNAP2) plays a role in interneuron (particularly PV+ interneurons) number, neuronal migration, seizure risk, and changes in behavior—hyperactivity, less cognitive flexibility, and less social interaction-- relevant to autism..[111] Deletion of CADPS2 or MET, other ASD-associated genes, led to a reduction in cortical PV+ interneurons in mice.[112, 113]

ASDs are frequently comorbid with epilepsy, a disorder with clear impairment in CNS inhibition. Additionally, alterations in inhibition are also seen in other disorders that have social impairment like autism, Fragile X syndrome and Rett syndrome. FMR1-knockout mice (models of Fragile X) show a reduction in and abnormal morphology of cortical PV+ interneurons[114] as well as reduced expression of GABA receptor subunits.[115-119] In the amygdala, FMR1 knockouts have reduced GAD expression, smaller and less frequent inhibitory currents, and diminished GABA release.[120] Mice lacking *Mecp2* (models of Rett syndrome) display alterations in inhibition in the cortex,[121] brainstem[122] and hippocampus.[123]

While the significance of prenatal stress for GABAergic changes in autism has not been demonstrated, the same potential exists as for schizophrenia, with links between prenatal stress mechanisms and neurobiological markers advancing our understanding of overall pathophysiology. With an earlier age of onset, autism does present a possible opportunity to more accurately document retrospective prenatal stress and prospectively examine inhibitory functioning through, for example, magnetic resonance spectroscopy (MRS).

Childhood Anxiety

Anxiety disorders are arguably the most common behavioral problem of childhood[124] and have links with prenatal stress. More stressful life events during pregnancy were associated with higher assessments of fear in toddlers.[125] When mothers experienced anxiety early in pregnancy, both preschool-age and school-age children were more likely to have self-report[126] and parental report[127] of emotional problems including anxiety. And internalizing

symptoms in preschool children were related to maternal emotional problems in pregnancy.[128] While some evidence suggests that the apparent influence of prenatal stress on childhood anxiety is due only to confounds with postnatal parenting,[129] most studies have concluded that both prenatal stress and postnatal parenting exert important effects.[125-127]

There is some evidence that GABAergic systems, among others, are relevant for anxiety. While postmortem studies of anxiety disorders are limited, in vivo imaging demonstrates that cortical $GABA_A$ receptor binding is reduced in the cortex of adults with anxiety disorders[130] with $GABA_A$ receptors in prefrontal cortex implicated specifically in post-traumatic stress disorder[131] and frontal cortical $GABA_A$ receptors associated with panic disorder.[132] Genetic studies in anxiety disorders have not yielded strong findings implicating any specific neurobiological feature, including inhibitory neurons.[133, 134] Despite this paucity of clinical neurobiological findings, the well-known anxiolytic effects of GABA-acting benzodiazepines which may be one way in which a consistent neural system can be implicated in this heterogeneous group of disorders.

Tourette syndrome

Tourette syndrome (TS) is a neuropsychiatric disorder characterized by verbal and motor tics. It too has a documented relationship with prenatal stress; one study showed that in offspring with TS, the degree of stress experienced during the first trimester of pregnancy correlated with tic severity.[135] Much of the research on Tourette syndrome has focused on the role of the basal ganglia, which contain many different types of inhibitory neurons. The density of PV+ interneurons is decreased in the striatum and external segment of the globus pallidus of TS patients but increased in the internal segment of the globus pallidus; the authors suggest that this could be due to a defect in tangential migration of interneurons during development.[136, 137] Additionally, TS patients have decreased binding of $GABA_A$ receptors in the globus pallidus and ventral striatum and increased binding in the substantia nigra.[138] Lhx6, a gene necessary for the specification of cortical and striatal PV+ and SST+ interneurons,[139, 140] has a positive association with TS.[141] Genetics and neurobiology have implicated inhibitory systems in TS at least in part.

Inhibitory Function as a Target for Treatment

The inhibitory deficiencies outlined here suggest that drugs that enhance GABAergic function could be potential treatments for these psychiatric illnesses. BL-1020, a drug with $GABA_A$ receptor agonist activity is one such possibility.[142] In recent clinical trials, treatment of schizophrenia patients with BL-1020 changed positive and negative symptoms, cognitive functioning, and overall global improvement.[143, 144] Administration of bumetanide, which inhibits the chloride importer NKCC1 (thereby increasing levels of GABAergic inhibition), led to improvement on global measures of autism in children.[145] Similarly, the $GABA_B$ receptor agonist arbaclofen (STX209) ameliorates key Fragile X-associated synaptic impairments in FMR1-knockout mice.[146] In trials, Fragile X patients given arbaclofen showed improvement in social measures through possible direct effects on inhibitory signaling.[147] Additionally, some drugs that have been used in TS treatment target GABAergic systems, such as clonazepam (a benzodiazepine)[148] and baclofen (a $GABA_B$

receptor agonist).[149] Levetiracetam, a GABAergic anticonvulsant, has found mixed results in trials.[150-153] Clearly, inhibitory systems are a promising target for treatment of neuropsychiatric illness.

Neurodevelopmental insights from models of prenatal stress should also inform the identification of new treatments. With respect to developmental mechanisms, the clinical target is prevention, whether through blocking the primary effects of prenatal stress on the embryonic and fetal brain or facilitating recovery during early postnatal life. As more is learned about specific components of prenatal stress that impact inhibitory circuitry, factors such as physical exercise,[154] and inflammatory mediators[155] that impact these processes may become important targets for prevention and supporting endogenous compensatory mechanisms.[156]

Conclusion

Investigating the links between prenatal stress, inhibitory systems of the forebrain and behavioral/emotional consequences is important for gaining deeper insights into psychiatric pathophysiology. The mechanisms that have been shown to be significantly affected in prenatal stress animal models and related clinical populations overlap significantly with the development and functioning of inhibitory neurons. Precisely how developmental events proceed on a different course in inhibitory neuronal systems exposed to stress remains to be studied. Further understanding of these neurodevelopmental phenomena will determine possible interventions for patients and prevention of risk to the finely tuned circuitry of the brain.

Acknowledgements

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Table 1

Prenatal stress and developmental mechanisms of inhibitory neurons

Author (year)	Type of Stress	Time of Stress	Species/Strain	Timing of testing	Behavior results	Neuro-endocrine test	GABA marker	Other cellular, molecular, physiological markers
Matrisciano et al. (2013)	Restraint with bright light 2*30 min/day	E 7-21	Swiss-albino-ND4 Mice Males	PND 0, 7,14, and 60	↑ locomotor activity in OF ↑ stereotypic behavior (with PNS and/or MK-801); ↓ social in novel environment; ↓ inhibition of startle in PPI; ↑ freeze time in CFC; VPA and Clozapine reversed the above behavioral deficits		↓ GAD67 and reelin protein level in PFC at PND 60 in PNS group; ↑DNMT1, MeCP2, 5MC, and 5HMC binding to reelin and GAD67 promoter region in FC in PNS group	↑levels of DNMT1 and 3 a in FC and HP at PND 0, 7,14, and 60
Stevens et al. (2012)	Restraint with bright light 3*45 min /day	E 12-19	GAD67-GFP CD1 Mice Males	E13, 14, 15, and PND 0			Delayed GABA cell tangential and radial migration at E13-15; ↓ GAD67GFP+ progenitors at PND 0 in medial FC	↓ transcription factor *dlx2*, *nkx2.1*, and *erbb4* in PNS group at all embryonic times; No change in *bdnf, fgf2, ngn2* and *mash1*
Uchida, et al. (2011)	Restraint with bright light 3*45min/day	E 15-17.5	GAD67+/GFP & GAD67+/+ C57BL/6 mice M & F	E17.5		↑ CORT in GAD 67+/GFP mothers (PNS and CON) ↑ CORT level in GAD67+/GFP fetuses with GAD67+/+ mothers ↑ CORT level in most PNS fetuses across most maternal genotypes		↓ body weight in all PNS fetuses (across most maternal genotypes) GAD67+/+ fetuses ↓ body weight with GAD67+/GFP mothers with and without PNS Offspring of GAD67+/+ PNS mothers ↓ decreased body weight in GAD67+/GFP than GAD67+/+

Author (year)	Type of Stress	Time of Stress	Species/Strain	Timing of testing	Behavior results	Neuro-endocrine test	GABA marker	Other cellular, molecular, physiological markers
Uchida et al (in press)	Restraint with bright light 3*45min/day or DEX (1 mM) or DEX+MIFE (1 mM)	E 15-17.5	GAD67+/GFP & GAD67+/+ C57BL/6 mice	E17.5			↓ GAD67GFP+/ E15BrdU+ cells in dorsal IZ, SVZ and VZ and in ventral MGE after PS No significant difference between DEX and DEX +MIFE on MGE E15BrdU+ cells	
Zuloaga et al. (2011)	DEX 0.4 mg/kg subq injection	E18-21 or PND 4-6	SD rats M & F	PND 0 or PND 7			Caspase+ cells in AMY at PND 7 showed ↑ colocalization with calretinin and calbindin in only F following only postnatal DEX	↓ brain/body weight after pre & postnatal DEX except M with postnatal DEX ↑ caspase-3 IR in AMY in M & F at PND 0 with prenatal DEX ↑ caspase-3 IR in F central AMY after postnatal DEX ↑ *Bax* expression in AMY after prenatal or postnatal DEX with no change in *Bcl2*

Abbreviation: 5HMC = 5-hydroxymethylcytosine; 5MC = 5-methylcytosine; AMY = Amygdala; BDNF = Brain-derived neurotrophic factor; CFC = Contextual fear conditioning; CON = Control; CORT = corticosterone; DEX = Dexamethasone; DNMT = DNA-methyltransferase; E = Embryonic; F=female; FC = frontal cortex; GAD = Glutamic Acid Decarboxylase; HP= Hippocampus; IR = Immunoreactive; M=male; MeCP2 = methyl CpG binding protein 2; MIFE= mifepristone; OF= Open Field; PFC = Prefrontal Cortex; PND = Postnatal day; PNS = Prenatal stress; PPI = Prepulse inhibition; SD = Sprague-Dawley; VPA = valproic acid

Table 2

Prenatal stress and changes in adult inhibitory neuronal systems

Author (year)	Type of Stress	Time of Stress	Species/Strain	Timing of testing	Behavior results	Neuro-endocrine test	GABA marker	Other cellular, molecular, physiological markers
Barros, et al (2006)	Restraint with bright light 3*45min/day	E 14-21	W rats Males	PND 90	↓ entries/time spent in OA EPM; ↓ time in OA in EPM in NS & PNS animals reared by PNS mothers		↓ BZ receptor binding sites in CA1, CA3, DG and Ce AMY in PNS animals reared with PNS mother vs NS animals reared with PNS mother	
Fride et al. (1985)	Prenatal noise and light stress		Female	PND 4-5	↓ pup retrieval in conflict situation		↓ BZ receptor in HP of PNS group	Trend ↓ DA level in POM No difference in catecholamines in Arc.N and NA in POM
Grigoryan and Segal (2013)	20 min Forced swim, 40 min Restraint, 30 min Elevated platform 3 per day	E14-21	W rats Males	PND 30	↑time, activity and entries in open arm of EPM; ↑central squares crossing in OF; ↓ latencies to platform in Day 2, 3, 5 of MWM, ↑platform quadrant preference & ↓ latency to 1st platform quadrant crossover		↓ GAD-positive neuron and GAD fluorescence intensity in cultured PNS neuron	↑dendritic arborization in 7 and 14 DIV in cultured PNS neuron; PNS neurons mature faster but reach same density by PND 21 ↑rate of synchronous activity and ↓ rate of spontaneous miPSC activity; ↓inhibition in HP slice
Laloux, et al. (2012)	Restraint with bright light 3*45min/day	E 11-21	SD rats M & F	USV at PND 6, 10, and 14 NSF & EPM at PND 22	↑number/ duration USVs at PND 10 and 14 during UMO ↓Time in center of NSF	↓ Plasma leptin levels at PND 14 in PNS group	↓ $\gamma 2$ subunit $GABA_A$ receptor in AMY at PND 14 and 22	↓ mGlu5 receptors in PND14,22 HP ↑ mGlu5 receptors in PND22 AMY

Author (year)	Type of Stress	Time of Stress	Species/Strain	Timing of testing	Behavior results	Neuro-endocrine test	GABA marker	Other cellular, molecular, physiological markers
						↓ time spent OA in EPM time spent OA in EPM		↓mGlu2/3 in HP at PND 22
Marrocco et al 2012	Restraint with bright light 3*45min/day	E11-21	SD rats	Protein & seizures at 2mos; EPM, light dark box, and glutamate release at 3mos	↓ time in open arms of EPM; ↓ time in light		No change in synaptosome GABA release with kainite or depolarization in HP or AMY	↓ Glutamate release from ventral HP synaptosomes with kainite or depolarization ↓ Ventral HP synaptic proteins ↓ Kainate-induced seizures Correlation of anxiety with glutamate release
Matrisciano et al. (2013)	Restraint with bright 2*30min/day	E 7-19	Swiss-albino-ND4 mice Males	PND 60	↓ social interaction ↑ locomotor activity in OF mGlu2/3 receptor agonist (LY379268) reverses above behavioral deficit in PNS group		↓ GAD 67 mRNA level in FC at PND 1, 21, 60 in PNS group;	↓ BDNF and mGlu2/3 mRNA in FC at PND 1, 21, 60; ↓ mGlu3 mRNA in FC at PND 1,21 ↑ DNMT1 amount and binding to gene promoter of mGlu2/3 receptor ↑ MeCP2 binding to mGlu2 promoter in FC at PND 60, reversed by administration of mGlu2/3 receptor agonist (LY379268)
Reznikov et al. (2008)	HA 50mg/kg subq injection	E15-21	W rats M & F	PND 6mo or 8mo		↓ NA hypothalamic content and ↑ CORT plasma level in HA F group after immobilization ↑ CORT plasma level	↑ GAD activity in HP for both M and F in CON group after adult stress	↓ volume SDN-POA and SCN in F vs M; ↓ volume SCN in M HA

Author (year)	Type of Stress	Time of Stress	Species/Strain	Timing of testing	Behavior results	Neuro-endocrine test	GABA marker	Other cellular, molecular, physiological markers
						in HA F group 30 min after ICV infuse of GABA in HP in HA treated M group ↓ GAD activity in HP in HA treated F group	No change of GAD activity in HA F group 30 min after ICV infuse in HP in HA treated M group	group vs M CON group
Stone, et al. (2001)	CORT administration 10mg/kg	E18-22 and/or PND 48 and 60	F344 rats Males	PND 61 or 65			↓mRNA at PND 61 of GAD65 in CA1, CA2, CA4 — eliminated or reduced in group with prenatal CORT (except in DG) No change at PND 61 in GAD67 or α2 subunit GABA_A receptor with pre or postnatal CORT ↑mRNA at PND 65 of GAD67 in CA1, DG after postnatal CORT—effect slightly bigger in group also receiving prenatal CORT in CA3, DG ↓mRNA at PND 65 of γ2 subunit of GABA_A receptor in CA2, CA3 after postnatal CORT ↓mRNA of γ2 subunit of GABA_A receptor in CA2 at PND65	

Author (year)	Type of Stress	Time of Stress	Species/Strain	Timing of testing	Behavior results	Neuro-endocrine test	GABA marker	Other cellular, molecular, physiological markers
							with prenatal CORT with prenatal CORT ↓ BZ receptor in CA2 after prenatal or postnatal CORT	
Uchida et al. (in press)	Restraint with bright light 3*45min/day	E15-17.5	Cross-fostered at P0; GAD67+/GFP & GAD67+/+ C57BL/6 mice	PND 21			↓ GAD67GFP+/E15BrdU+ and PV+ cells in FC and ↓ PV+ cells in CA1 only in GAD67+/GFP mice	
Viltart et al. (2006)	Restraint with bright light 3*45min/day	E 11-21	SD rats	PND 60		delayed return to basal CORT levels after mild stress	↑ vGAT in PVN and HT surrounding area	↑Fos+ neurons in parvocellular medial PVN after mild stress in both PNS & CON group (except PNS ventral subregion) ↓Fos+ neurons in ventral med PVN in PNS vs CON after mild stress ↑Fos+ neurons CA and DG in PNS vs CON group. No change in Fos+ neurons after mild stress ↑Fos+ neuron in LC at baseline in PNS. ↑Fos +/TH+ colabeled cells in LC in PNS vs CON group after mild stress

Author (year)	Type of Stress	Time of Stress	Species/Strain	Timing of testing	Behavior results	Neuro-endocrine test	GABA marker	Other cellular, molecular, physiological markers
Zuloaga et al. (2012)	DEX 0.4 mg/kg subq injection	E18-22	SD rats	PND 60			↓ number of calretinin (not calbindin) cells in lateral AMY of adult F with no difference in BL AMY, HP CA1 or CA3	

Abbreviations: Arc.n = Arcuate nucleus; BDNF = Brain-derived neurotrophic factor; BZ = Benzodiazepine; BL/Ce AMY = Basolateral/Central amygdala; CON = Control; CORT = corticosterone; DA = dopamine; DEX = Dexamethasone; DG= dentate gyrus; DIV = day in vitro; DNMT = DNA-methyltransferase; E = Embryonic; EPM = Elevated Plus Maze; F=female; FC = frontal cortex; GAD = Glutamic Acid Decarboxylase; HA = Hydrocortisone acetate; HP= Hippocampus; HT = Hypothalamus; ICV = Intracerebroventricular; LC = locus coeruleus; M=male; MeCP2 = methyl CpG binding protein 2; mIPSC = miniature inhibitory postsynaptic current; mo = month; MWM = Morris water maze; NA = Noradrenaline; NS = non-stressed; NSF = Novelty Suppressed Feeding; OA= Open Arm; OF= Open Field; PND = Postnatal day; PNS = Prenatal stress; POM = Medial preoptic nucleus; PVN = Paraventricular nucleus; SCN = suprachiasmatic nucleus; SD = Sprague-Dawley; SDN-POA = Sexually dimorphic nucleus of pre-optic area; TH = Tyrosine hydroxylase; UMO=Unfamiliar Male Odor; USV: ultrasonic vocalization; vGAT = GABA vesicular transporter; W = Wistar