Review

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Somatostatin-Positive Gamma-Aminobutyric Acid Interneuron Deficits in Depression: Cortical Microcircuit and Therapeutic Perspectives

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ABSTRACT

The functional integration of external and internal signals forms the basis of information processing and is essential for higher cognitive functions. This occurs in finely tuned cortical microcircuits whose functions are balanced at the cellular level by excitatory glutamatergic pyramidal neurons and inhibitory gamma-aminobutyric acidergic (GABAergic) interneurons. The balance of excitation and inhibition, from cellular processes to neural network activity, is characteristically disrupted in multiple neuropsychiatric disorders, including major depressive disorder (MDD), bipolar disorder, anxiety disorders, and schizophrenia. Specifically, nearly 3 decades of research demonstrate a role for reduced inhibitory GABA level and function across disorders. In MDD, recent evidence from human postmortem and animal studies suggests a selective vulnerability of GABAergic interneurons that coexpress the neuropeptide somatostatin (SST). Advances in cell type–specific molecular genetics have now helped to elucidate several important roles for SST interneurons in cortical processing (regulation of pyramidal cell excitatory input) and behavioral control (mood and cognition). Here, we review evidence for altered inhibitory function arising from GABAergic deficits across disorders and specifically in MDD. We then focus on properties of the cortical microcircuit, where SST-positive GABAergic interneuron deficits may disrupt functioning in several ways. Finally, we discuss the putative origins of SST cell deficits, as informed by recent research, and implications for therapeutic approaches. We conclude that deficits in SST interneurons represent a contributing cellular pathology and therefore a promising target for normalizing altered inhibitory function in MDD and other disorders with reduced SST cell and GABA functions.

Keywords: Depression, Dimensional, GABA, Microcircuit, Pathology, Somatostatin

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COGNITIVE-EMOTIONAL DISRUPTION AND EXCITATION–INHIBITION BALANCE IN DEPRESSION

Major depressive disorder (MDD) is characterized by low mood, anhedonia, and cognitive deficits relating to negative biases in attention, sensory processing, and memory (1). Several mechanisms have been hypothesized, including low monoamine levels (2), reduced neuroplasticity through altered glutamate or growth factor signaling (3), impaired neuroendocrine stress response regulation (4), and, more recently, altered activity of corticolimbic brain regions driven by altered excitatory and inhibitory neuron function (5,6). Although interesting insight has emerged from these hypotheses, limited progress has been made in drug development, whereby current treatments remain ineffective in half of treated patients (7).

Maintaining the balance between excitation and inhibition is a fundamental attribute of brain function that is necessary for information processing and higher cognitive functions. At a reductionist level, neural information consists of excitatory signals originating from principal glutamatergic neurons that are matched by proportional gamma-aminobutyric acidergic (GABAergic) interneuron inhibition. Changes in cellular components underlying excitation–inhibition balance may affect the detection and propagation of information across cortical microcircuits, brain regions, and neural networks. Initially adaptive, chronic changes in the excitation–inhibition balance, as hypothesized to occur in psychiatric disorders, can become maladaptive and support the emergence of clinical symptoms. For instance, human and animal studies have demonstrated altered GABA-related inhibitory function in neurodevelopmental disorders and associated these changes with cognitive deficits in information processing (8,9). Reduced GABA levels and function may similarly account for disrupted cognitive-emotional processes in MDD (10,11). For instance, functional neuroimaging identified MDD-related hyperactivity in the default mode network (DMN), a set of brain regions including the dorsolateral prefrontal cortex (PFC), posterior cingulate cortex, anterior cingulate cortex (ACC), amygdala, and hippocampus (12,13). In healthy individuals, the DMN is active during internal focus (e.g., attending to personal thoughts) and deactivated during externally oriented events (e.g., goal-directed behavior) (14); hence, a failure to suppress DMN activity during external tasks may contribute to negative self-referential processes (e.g., rumination) in MDD (15). Studies have now identified reduced molecular markers of GABA function in DMN

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regions (16–21) and correlated GABA content with functional connectivity (22–25), together suggesting GABA-related inhibitory deficits contributing to altered activity in DMN regions and, ultimately, symptom emergence in MDD.

GABA LEVELS AND RELATED NEUROPHYSIOLOGICAL MEASURES IN DEPRESSION

Studies in human live and postmortem subjects suggest a predominant role for altered GABA function underlying inhibitory deficits across multiple psychiatric disorders, including MDD (26–28), bipolar disorder (BPD), schizophrenia (SCZ) (29), and other stress-related disorders (30). Reduced cerebrospinal fluid GABA levels were first reported in MDD and SCZ more than 35 years ago (31) and have been consistently found in MDD and BPD (32–34) and extended to plasma levels correlating with illness severity, use of medication, and genetic risk (34–36).

Imaging studies using proton magnetic resonance spectroscopy provided evidence of central GABA deficits in MDD. A 50% reduction in occipital cortex GABA levels was first reported in medication-free patients with depression and later found to be more severe in patients with persistent melancholic depression (37). Low GABA levels were consistently identified in brain regions responsible for cognitive-emotional processes that are disrupted in mood disorders, including the PFC (16,17), amygdala (18), and ACC (19–21). These reductions were more robust in treatment-resistant depression (TRD) (19) and normalized in remitted patients (38). Imaging studies further identified a role for GABA in antidepressant response as brain levels were elevated following selective serotonin reuptake inhibitor treatment (39,40), transcranial magnetic stimulation (TMS) (41,42), electroconvulsive therapy (43), and cognitive behavioral therapy (44).

Evidence of cortical inhibitory deficits arising from GABA alterations comes from TMS studies. Using TMS, single or repetitive magnetic fields are applied to the cortex to excite or inhibit cortical activity, as measured by electromyography or electroencephalogram. TMS showed efficacy as an antidepressant treatment in patients with TRD (45) and is also used to experimentally probe cortical inhibition, including short-interval cortical inhibition (SICI), long-interval cortical inhibition (LICI), and cortical silent period (CSP). SICI is similar in duration to $GABA_A$ receptor ($GABA_AR$)-mediated inhibitory postsynaptic potentials (46,47) and is lengthened by $GABA_AR$-acting drugs (48,49) and therefore is considered to measure $GABA_AR$-mediated neurotransmission. Conversely, the slower LICI and CSP time courses resemble $GABA_B$ receptor ($GABA_BR$)-mediated postsynaptic potentials (50) and are increased by $GABA_BR$ agonists (51,52), suggesting a reflection of $GABA_BR$-mediated neurotransmission.

TMS studies in patients with MDD demonstrated reduced SICI and CSP (27,28). Although reduced cortical inhibition was not always reported (53), meta-analysis confirmed MDD-related deficits (54). Others found CSP deficits in MDD but SICI reduction only in TRD, potentially implicating $GABA_BR$ impairments in overall MDD pathophysiology and $GABA_AR$ impairments in more severe MDD (27). Reflecting findings in MDD (41,42), repetitive TMS increased cortical inhibition (55) and lengthened CSP (56) in healthy individuals, suggesting enhanced GABAergic neurotransmission.

Evidence across treatment modalities implicates cortical inhibition in antidepressant effects. For instance, electroconvulsive therapy increased SICI and CSP in nonmedicated patients with MDD (57). Pharmacological treatment with the selective serotonin reuptake inhibitor citalopram rapidly increased SICI and CSP (58), whereas the tricyclic antidepressant clomipramine increased only SICI, in patients with MDD (59). Finally, nucleus accumbens deep brain stimulation also showed antidepressant efficacy in patients with TRD (60) and increased SICI in subjects with epilepsy (61).

CORTICAL MICROCIRCUIT ORGANIZATION AND FUNCTION

How can GABA-related neurophysiological measures be linked to cellular and molecular dysfunction in depression? Here, we briefly review microcircuit roles of somatostatin (SST)-expressing GABAergic interneurons and then discuss putative functional implications.

In the neocortex, external (e.g., sensory stimuli) and internal (e.g., past representations) information is coded by excitatory activation patterns that input onto pyramidal neurons (PNs). These signals are locally integrated and, through interneuron inhibition, are transformed into PN firing patterns. This neuronal output contributes to sensory processing and cognitive function (Figure 1). Studies suggest a compartmentalized integration of excitatory signals within PNs. Thalamic feed-forward excitation terminates onto the PN soma in layers 4 and 5 (L4 and L5), whereas corticocortical feedback excitation (alongside thalamocortical afferents) impinges separately onto PN distal dendrites (Figure 1A). These signals facilitate the integration of distinct information streams and combine to drive bursts of PN activity, forming the basis of neural coding (62,63).

The input, output, and integration of excitatory signals are regulated by interconnected inhibitory GABAergic interneurons with heterogeneous morphology, distribution, electrophysiological properties, connectivity, and molecular identities. Nearly all interneurons belong to one of three nonoverlapping classes based on coexpression of markers for the calcium-binding protein parvalbumin (PV; ~40%), the neuropeptide SST (~30%), or the ionotropic serotonin receptor $5\text{-}HT_{3a}R$ (~30%), the latter of which includes vasoactive intestinal peptide (VIP)–expressing interneurons (64) (Figure 1A).

SST interneurons consist mainly of translaminar distal dendrite-targeting Martinotti cells, with low-threshold regular-spiking properties and high spontaneous activity levels, distributed throughout L2–6 (65). In the hippocampus and neocortex, SST interneurons mediate feedback and lateral inhibition, contributing to maintain sparse activity of PNs at rest (e.g., in L2/3), gate converging corticocortical and thalamic input from L1 signal streams (63,66), and regulate microcircuit gain (67). In addition, L4 non-Martinotti SST interneurons preferentially target local PV interneurons and receive thalamic afferents, thereby mostly exerting PN disinhibitory functions (68).

PV interneurons have basket or chandelier cell morphologies, target PN perisomatic regions with fast-spiking properties, and are distributed across L2–6 (65). PV interneurons regulate PN spiking output through thalamic feed-forward