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HOT TOPICS

Neurotrophic effects of potentiating gaba-mediated dendritic inhibition

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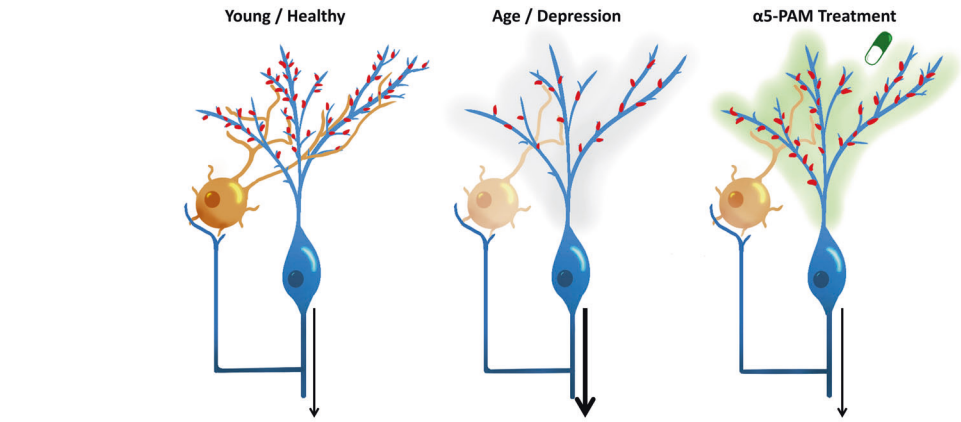
Neuropsychopharmacology (2023) 48:213–214; https://doi.org/10.1038/s41386-022-01423-0

Loss of structures mediating connections between pyramidal cells (PyC), i.e., dendrites and spines, is a hallmark of aging and stress-related disorders, such as depression. These deficits occur in frontal cortex and hippocampus, regions critical for cognition, and are widely accepted as contributing to cognitive deficits. Cognitive deficits in depression and age-related disorders are not treated by current medications, highlighting an unmet need for novel procognitive and neurotrophic therapeutics. Efforts focused on excitatory-, brain-derived neurotrophic factor- or stress-related mechanisms have not yielded breakthroughs. In contrast, despite robust evidence for deficits in aging and depression, GABAergic inhibition has received less attention, since its augmentation impairs cognition without improving cellular connectivity.

Reduced GABAergic inhibition in aging and depression spans genes, cells, neurotransmitters and neurophysiological markers of inhibition. Of the multiple GABAergic cells and receptor subtypes, dendritic inhibition is mostly mediated by somatostatin-expressing GABAergic neurons (SST-neurons) and α5-containing GABA-A receptors (α5-GABAA-R), located in PyC dendrites (Fig. 1) [1]. Dendritic inhibition gates PyC excitatory input and regulates excitatory signal-to-noise ratio for optimal signal integration [2]. Consistent with loss of cell connection in aging and diseases, SST and α5-GABAA-R gene expressions decrease by 20–40% between ages 20 and 80 [3], and in depression [4]. Rodent genetic and environmental manipulations show that reducing SST-cell function induces anxiety- and depressive-like phenotypes, and



Baseline excitatory signal gating	High	Low	Restored/High
Signal-to-Noise Ratio	High	Low	Restored/High
Information processing	Optimal	Altered	Restored/Optimal

Fig. 1 Dendritic pathology in aging and depression, and reversal by augmented GABAergic inhibition. Pyramidal cells of the frontal cortex, or principal neurons of the hippocampus (PyC; in blue) regulate dendritic excitatory signal-to-noise ratio responsible for signal integration and processing, and contributing to cognitive functions. Dendritic inhibition is mediated by GABAergic neurons such as somatostatin-expressing neurons (SST; in orange) that signal through α5-GABAA-Rs (in red) located mostly in PyCs. With age or stress-related disorders (middle panel), reduced SST-neuron function, PyC α5-GABAA-R expression and neuronal atrophy result in reduced functional connection between cells, decreased excitatory signal filtering, increased signal-to-noise ratio, reduced information processing, together underlying cognitive deficits. Interventions augmenting (and restoring) α5-GABAA-R function (right panel) reversed cognitive symptoms and neuronal atrophy in mice, representing a potential therapeutic avenue for reduced plasticity and cognitive deficits in depression and age-related disorders.

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Published online: 22 August 2022

cognitive deficits. Importantly, reducing α5-GABAA-R levels induces complex and bidirectional anxiety-like, memory and executive function changes, suggesting state-dependent contributions of α5-GABAA-R to cognitive functions [1, 4].

Reducing α5-GABAA-R function under conditions of hyper-GABAergic function has procognitive effects [1], but whether increasing α5-GABAA-R function under conditions of reduced GABAergic function was less characterized. Recently-developed molecules that preferentially activate α5-GABAA-Rs through positive allosteric modulation (α5-PAM) retain the anxiolytic effects of non-specific GABAA-R PAMs, such as benzodiazepines, and notably, show novel procognitive effects on spatial working memory deficits in aging and stress models following acute or chronic treatment, not observed with other GABAA-R PAMs, with little-to-no side effects in rodent models [5].

In addition to symptom relief, recent morphological studies showed that chronic α5-PAM treatment reverses age-related neuronal pathology (reduced spine density and dendritic complexity) in frontal cortex and hippocampus of aged mice, correlating with cognitive functions [6]. Studies also showed that a one-week treatment cessation maintained the neurotrophic, but not the procognitive effects, suggesting distinct and potentially synergistic α5-PAM effects of increasing α5-GABAA-R signaling and restoring neuronal morphology [6]. More recent studies report that these neurotrophic effects extend to chronic stress models. Chronic treatment with a racemic mixture with preferential α5-PAM activity reversed the stress-induced reduction in spine density in frontal cortex and hippocampus, correlating with cognitive functions [5].

Collectively, the procognitive and neurotrophic effects of α5-GABAA-R potentiation under conditions of reduced GABAergic function are novel and have symptomatic and disease-modifying therapeutic potential across brain disorders. The mechanisms of this unexpected neurotrophic effect may relate to neuronal "health", through improved dendritic signal-to-noise ratio and restored capacity for optimal signal integration, although the reciprocal causal links between these structural, functional and behavioral events remain to be characterized.

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AUTHOR CONTRIBUTIONS

TP and ES wrote the manuscript and prepared the figure.

FUNDING

TP and ES are supported by the Weston Brain Institute, the American Foundation for Suicide Prevention, the Discovery Fund of the Center for Addiction and Mental Health. ES is supported by CIHR. ES and TP are listed inventors on patents covering the synthesis and use of GABAergic compounds. ES is Founder, acting CEO and CSO of DAMONA Pharmaceuticals, a biopharma dedicated to bringing novel GABAergic compounds to the clinic.

COMPETING INTERESTS

The authors declare no competing interests.

ADDITIONAL INFORMATION

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