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NMDAR Down-Regulation: Dual – Hit Molecular Target For COPD – Depression Comorbidity

Uriel Heresco-Levy[1,2], Jacob Haviv[1], Yehezkel G Caine[1]

[1]Herzog Medical Center, Jerusalem, Israel; [2]Psychiatry Department, Hadassah Medical School, Hebrew University, Jerusalem, Israel

Correspondence: Uriel Heresco-Levy, Herzog Medical Center, POBox 3900, Jerusalem, 91305, Israel, Tel +972-2-5316906, Fax +972-26075653, Email urielh@ekmd.huji.ac.il

Abstract: Chronic obstructive pulmonary disease (COPD) is a chronic lung disease characterized by sustained airflow limitation that represents one of the main causes of disability in modern society. Depression affects approximately 40% of COPD patients. Both COPD and depression are associated with chronic systemic inflammation and their comorbidity represents a critical unmet treatment need. N-methyl-D-aspartate glutamatergic receptors (NMDAR) are well characterized in the central nervous system (CNS) and widely expressed in lung tissue and inflammation-related cells. Accumulating evidence indicates that pathologic NMDAR up-regulation, leading to pro-inflammatory pathways activation and tissue damage, may play a crucial role in chronic lung injury as well as in depression. D-cycloserine, a bacteriostatic antibiotic used since the 1950's in tuberculosis, acts at therapeutic dosages also as a NMDAR functional antagonist and has antidepressant and anti-inflammatory effects. We hypothesize that NMDAR down-regulation may represent a unified molecular target for the treatment of COPD – depression comorbidity and may simultaneously alleviate both respiratory and depression symptomatology. We postulate that D-cycloserine treatment may achieve these dual – hit objectives and envisage that our hypotheses may apply to additional inflammation disorders that are frequently accompanied by depression.

Keywords: inflammation, depression, chronic obstructive pulmonary disease, N-methyl-D-aspartate receptor, D-cycloserine

Introduction

Prolonged lung disease, inflammation and respiratory dysfunction are often accompanied by depression. Chronic obstructive pulmonary disease (COPD) is a slowly-developing multicomponent incurable disorder. Estimated COPD prevalence in people aged 40 years and older ranges between 7.4% and 12.6%.[1] Depression affects about 40% of COPD patients and one in four individuals with COPD-depression comorbidity experience an unfavorable illness course.[2] The relationship between COPD and depression is likely bidirectional and is mediated in part by low-grade inflammation. Elevated levels of inflammatory biomarkers have been documented in both late-life depression and COPD and may contribute to the association of depression with pulmonary obstruction.[3]

Drugs commonly used to treat COPD, eg glucocorticoids and bronchodilators, target different receptorial systems, have significant side effects, and do not alleviate depression. Add-on selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), are employed for this indication. However, the efficacy of serotonergic antidepressants in COPD patients remains controversial. In a large cohort of older adults with validated COPD, new SSRI/SNRIs users experienced a higher risk of hospitalization, emergency care visits, COPD or pneumonia-related mortality and all-cause mortality when compared with non-users.[4] Proposed mechanisms by which serotonergic antidepressants may cause harm in COPD include induction of sleepiness leading to decreased oxygen and increased carbon dioxide levels, lowering of infection threshold by an unfavorable impact on immune cell function and reduction of apoptotic cell clearance, which could lead to COPD exacerbation.[2,5]

N-methyl-D-aspartate receptors (NMDAR) are cation channel glutamate (Glu) receptors widely expressed and well characterized in the central nervous system (CNS) that are well acknowledged to play a crucial role in brain

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physiological functions, excitotoxicity and neuropsychiatric disorders. Nevertheless, accumulating evidence suggests that Glu also acts as a signaling molecule outside the CNS, with an emerging role as an immune modulator.[6–9] In line with this concept, functional glutamatergic signaling and NMDAR expression have been found extensively in non-neuronal tissues, including lungs, kidneys, heart, pancreatic β cells, lymphocytes and inflammation-related cells. Moreover, physiological levels of NMDAR activation are of paramount importance. Under pathological conditions, extracellular Glu concentrations are increased by abnormal release and/or clearance. The resulting NMDAR over-activation triggers rapid Ca^{2+} influx in the cell that may lead to pro-inflammatory signaling pathway activation ultimately resulting in cell damage and organ dysfunction.[5,6]

The Hypothesis

We hypothesize that NMDAR may represent a unified molecular target for COPD-depression comorbidity and that pharmacological NMDAR down-regulation may result in alleviation of respiratory and depression symptomatology. We further postulate that treatment with D-cycloserine, a broad-spectrum antibiotic used in tuberculosis (TB), may achieve these dual-hit objectives (Figure 1), and may be relevant in the context of additional lung disorders.

NMDAR Role in Depression

Functional neuronal NMDAR comprises two obligatory NR1 subunits, binding the co-agonists glycine and D-serine at the glycine modulatory site (GMS), and two Glu-binding NR2 (2A-D) subunits, or a combination of NR2 and NR3 (3A-B) subunits. Different subunit combinations endow NMDAR with distinct physiological and pharmacological properties. It is well established that NMDAR hypo and hyperfunction are involved in the pathogenesis of neuropsychiatric disorders including Alzheimer's disease, Huntington's disease and schizophrenia.[10–12]

Converging lines of evidence indicate that alterations in NMDAR-mediated neurotransmission are critically involved in depression pathogenesis. Building on the observation that inescapable stress exposure in animals attenuated long-term potentiation (LTP), a NMDAR-dependent process, it was found that various types of drugs that reduce NMDAR function have antidepressant-like effects in animal models of depression including a partial agonist at the GLY coagonist site of NMDAR NR1 subunit, a competitive NMDAR antagonist, an uncompetitive NMDAR antagonist, and a NMDAR NR2B subunit selective uncompetitive antagonist. Furthermore, a series of animal studies demonstrated that long-term treatment with established monoaminergic antidepressants results in adaptive changes in NMDAR signaling profile. More recently, meta-analysis of proton magnetic resonance spectroscopy (^{1}H-MRS) studies of medicated major depressive disorder (MDD) patients indicated lower levels of prefrontal cortex Glu/glutamine (Glx). Nevertheless, when medication status is considered, the data suggest that medicated MDD patients have lower Glx or Glu levels, while untreated MDD patients may have elevated levels.[13–15] Moreover, it was proposed that elevated Glu or Glx may be a marker of depressive illness severity and its reduction an indicator of antidepressant response to NMDAR antagonists.[16]

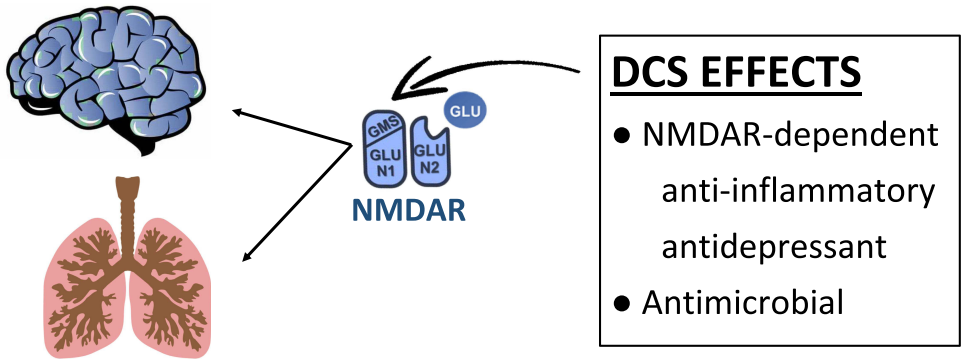

Figure 1 A schematic representation of the N-methyl-D-aspartate receptor (NMDAR) down-regulation hypothesis in chronic obstructive pulmonary disease-depression comorbidity. Simultaneous down-regulation of hyperactive NMDAR systems in brain and lungs is achieved by D-cycloserine (DCS) acting as a functional antagonist modulator at the NMDAR-associated glycine modulatory site (GMS) on NMDAR-NR1 subunit (GLUN1). Resulting DCS-induced outcomes include NMDAR- dependent anti-inflammatory and antidepressive effects and NMDAR-independent antimicrobial effects. GLU, glutamate.

Low-grade inflammation may represent, partly via NMDAR activation, a potential pathophysiological mechanism in depression. NMDAR is expressed in immune cells that may release GLU endogenously.[6,8] C-reactive protein (CRP), various cytokines and TNF-α are increased in patients with depression. Elevated levels of cytokines in adolescence have been associated with increased susceptibility to depression in adulthood. Some studies point to a role for increased inflammation specifically in patients with treatment-resistant depression. In MDD patients who attempted suicide, increased plasma kynurenine, IL-1, IL-6 and CRP levels correlating with brain Glu levels were reported.[17,18]

Accumulating data indicate that inflammation effects on glia initially lead to an increased release and "spillover" of Glu into the extra synaptic space by decreasing the capacity of glial transporters to buffer and clear Glu. This Glu spillover in combination with Glu released by activated or primed glial and immune cells can activate extra-synaptic NMDAR and lead to atrophy and regression of dendritic spines and processes and loss of synaptic integrity, ultimately resulting in neuronal loss.[19]

Ketamine, a non-competitive NMDAR channel blocker and dissociative anesthetic, is presently the first glutamatergic antidepressant approved for use, under precautionary conditions, for refractory MDD and suicidality. Ketamine is one of the longest used and best-known NMDAR antagonist drugs. Although it was shown to cause neuronal apoptotic lesions under experimental conditions, in usual clinical practice associated with single episodes of anesthesia it does not induce neurotoxicity.[20] Numerous studies confirmed rapid and robust ketamine efficiency upon core depression symptoms in treatment-refractory unipolar and bipolar depression when administered at sub-anesthetic doses. Reduction in Glx in the ventromedial prefrontal cortex/anterior cingulate cortex (vmPFC/ACC), measured by ^{1}H-MRS during ketamine infusion, may mediate the relationship of ketamine dose and blood level to improvement in depression.[21] However, from a practical perspective, ketamine potential for widespread clinical use is limited due to its side-effects, mainly dissociative states, cognitive impairment with repeated use and abuse liability.[14,20]

NMDAR Role in Lung Injury and Inflammation

Glu signaling and NMDAR expression have been reported in various lung regions and cell types including alveolar type II cells, trachea and airways.[9,22] NMDA/NR2 receptor subunits were reported in rat lung, with mRNA for the NR1 and NR2D subunits constitutively expressed in the peripheral lung, mid-lung and central lung regions, as well as in alveolar macrophages.[23] Functional NMDAR are expressed in immune cells (ie mononuclear leukocytes, neutrophils, dendritic cells, macrophages and platelets) that may release GLU endogenously.[8,9] NMDAR activation by Glu released from damaged lung and immune competent cells could play a role in oxidant lung injury, resulting in increased nitric-oxide (NO) production and caspase-3 activation.[6,24] Furthermore, NMDAR activation may lead to increased recruitment of leukocytes, neutrophils and macrophages, highlighting NMDAR role in chemotactic migration and T cells adhesion and activation.

In vitro and in vivo observations strongly indicate an involvement of Glu toxicity and NMDAR hyperactivation in lung injury and inflammation. The release of endogenous Glu mediates the newborn rat lung damage, which is induced by hyperoxia through NMDAR activation. NMDAR activation by NMDA, a synthetic agonist that selectively activates NMDAR, provokes acute edematous lung injury and this injury was reversed by MK-801, a noncompetitive channel antagonist of NMDAR. MK-801 also has protective effects in oxidant lung injury induced by paraquat or xanthine oxidase and acute lung injury induced by hyperoxia. Memantine, a non-competitive, low-affinity voltage-dependent NMDAR antagonist, used in dementia but with little clinical success in depression,[25] attenuates bleomycin-induced acute lung injury. NMDAR expression was also evidenced in human airway smooth muscle (HASM) cells that exhibit enhanced contractility in asthma, and it was shown that activation of these NMDAR leads to increased Ca^{2+} influx, directly induces HASM cell contractility, and triggers physiologically relevant degrees of airway narrowing ex-vivo.[9,22,23,26]

Suppressing inflammatory responses is considered an essential strategy for COPD treatment. In this context, the effects and mechanisms of memantine were investigated on a COPD model induced by cigarette smoke (CS) combined with lipopolysaccharide (LPS). CS and LPS stimulation caused an inflammation response, a significant increase in the release of cytokines, including TNF-α, IL-6, and INF-γ, elevated release of Glu, increased Ca^{2+} influx, and the activation of the ERP 1/2 pathway in vitro and in vivo. This inflammatory stimulation could be significantly attenuated by memantine treatment that resulted in reductions in NR1 expression, Glu release and Ca^{2+} influx.[27] Overall, these

accumulating data provide pivotal evidence that : (1) overactive Glu-NMDAR systems may contribute to COPD pathophysiology and (2) NMDAR down-regulation may represent an innovative type of treatment for this disease.

Expanded Hypothesis Relevance

NMDAR hyperstimulation has also been implicated in the pathogenesis of asthma, pulmonary fibrosis and pulmonary arterial hypertension,[22,26,28] that are also often accompanied by depression comorbidity. Post-acute COVID-19 may represent a particular target for the assessment of NMDAR antagonist dual-hit treatment. NMDAR hyperactivity has been implicated in both lung and CNS COVID-19 injury.[29] Dyspnea prevalence ranges from 42% to 66% at 60–100-day post-acute COVID-19 and clinically significant depression and anxiety were reported in 30–40% of patients.[30]

D-Cycloserine

D-cycloserine (DCS, Seromycin, Cycloserine), a structural analogue of D-alanine, is a *Streptomyces*-isolated broad spectrum antibiotic approved for TB treatment, used since the 1950's, usually at 500–1000g/day regimens, in millions of individuals. DCS blocks bacterial growth by inhibiting alanine racemase and D-alanine ligase. These molecular targets and mechanisms of action of DCS are unique among all classes of antibiotics currently known and congruently, DCS displays no cross-resistance with any other front- or second-line antitubercular drugs. Given its activity and lack of reported resistance in bacterial strains infecting humans, DCS has been labeled "the cornerstone option" for drug resistant TB treatment.[31] Recently, DCS has been recommended by WHO guidelines for treatment of multi-drug and extensively-drug resistant-TB (MDR/XDR-TB) as one of the Group B drugs and should be generally included in the starting line-up in the longer regimen for the treatment of MDR-TB.[32]

In early treatment reports, DCS had been associated with neuropsychiatric disturbances including seizures, peripheral neuropathy, headaches, anxiety, psychosis and depression. Historically this hampered widespread inclusion of DCS in anti-TB medication protocols.[33] However, many of the early side effects observations were based mainly on case reports, and more recent developments suggest that DCS may be considered a better tolerated medication with infrequent side effects. The occurrence of adverse reactions attributed to DCS, when compared to other anti-TB agents, is relatively uncommon, with a frequency of 11.1%.[34] Consistent results were found in a meta-analysis that estimated the frequencies of any DCS adverse effects at 9.1% (95%Cl: 6.4–11.7).[35] In another recent study, psychosis and/or depression were not-significantly associated with DCS exposure.[36] On the contrary, anti-depressant effects of DCS were reported as early as 1959 on symptoms such as anorexia, asthenia and insomnia in TB patients.[37]

More than three decades later it became evident that in addition to its bacteriostatic mechanisms, DCS is also a selective NMDAR NR1 partial agonist that appears to act via allosteric modulation of GMS. In vivo DCS acts like an agonist at low doses but has NMDAR antagonistic features with high doses.[38] Since the discovery of its NMDAR effects DCS has become the focus of intense research in neuropsychiatric disorders.[39] This is not surprising, given the cardinal role of NMDAR in neuroplasticity, learning, memory, thought and affect modulation. In a variety of brain injury animal models, it was shown that DCS can reverse synaptic plasticity alteration via improved LTP, restored BDNF levels and induction of higher dendritic spine density.[40–42] DCS also enhances extinction of conditioned fear, a form of learning that represents a valid preclinical model of exposure-based therapy that is dependent on NMDAR. In humans, treatment with DCS administered in conjunction with cognitive behavioral therapy (CBT) sessions enhances the efficacy of exposure therapy for various forms of maladaptive fear, including social anxiety, obsessive-compulsive disorder and panic disorder.[38,39]

While an initial lower-dose (250mg/day) study was not indicative of efficacy, high-dose (up to 1000mg/day) add-on DCS was shown to significantly and safely relieve treatment-resistant depression symptoms in MDD. Contrary to the effects of direct NMDAR channel blockers, no dissociative or psychotic symptoms were registered with DCS.[43] Subsequent clinical trials further strengthened the concept of a DCS anti-depressant potential. DCS was found beneficial for patients with treatment-resistant depression who responded to ketamine infusion but had a residual suicidal risk.[44] In bipolar disorder patients, the therapeutic effect of a single ketamine infusion was reported to be significantly maintained during 8 weeks of treatment with DCS added to ongoing medications approved for bipolar disorder.[45] Moreover, it was recently reported in animal models that, unlike ketamine, DCS has no apparent potential for abuse[46] or neurotoxicity.[47]

Surprisingly, the potential of DCS NMDAR antagonism in the context of non-CNS inflammation has not yet been assessed. NMDAR down-regulation may counteract Glu excess and excitotoxicity and alleviate inflammation and cell death. Such investigations are warranted given the proven DCS effects at NMDAR and in view of recently reported specific anti-inflammatory mechanisms of DCS. Kang et al[48] recently examined the ability of DCS to inhibit the inflammatory responses in LPS-induced RAW 264.6 macrophage cell lines. DCS inhibited NO production in a concentration-dependent manner and to some extent, inhibited the production of prostaglandin E_2. Consistent with these findings, DCS suppressed the expression of pro-inflammatory cytokines such as interleukin IL-1β and IL-6 and inhibited NO synthetase and cyclooxygenase type-2 (cox-2) expression.

Interestingly, in the context of COPD novel treatment targets, antibiotics have been recently recognized to have anti-inflammatory effects beyond their antimicrobial activity. Immunomodulatory properties were reported with the macrolide erythromycin in diffuse panbronchiolitis[49] and with azithromycin in COPD.[50] Currently, there is a scarcity of data concerning anti-inflammatory properties of DCS or other types/classes of antibiotics and their potential role as short or long term therapeutic interventions in COPD.

Safety concerns regarding antibiotic resistance also need to be addressed and monitored before DCS use in COPD and depression. Drug resistant infections represent a major medical problem of our time.[51] Nevertheless, recent research indicates that DCS has been used for six decades without significant appearance and dissemination of antibiotic resistant strains, making it an ideal model compound to understand what drives resistance evasion.[52] Moreover, it was shown that the rate of spontaneous mutations conferring resistance to DCS (mutation rate) is ultra-low in *M. tuberculosis* (ca. 10^{-11}).[52,53]

Overall, converging lines of evidence indicate that DCS characteristics relevant to our hypotheses include NMDAR down-regulation, antimicrobial, antidepressant and anti-inflammatory effects, as well as long-standing use and efficacy in chronic lung disease. Moreover, no significant propensity for addiction, abuse or neurotoxicity has been associated with DCS.

Conclusions

Since NMDAR systems are over-activated in both COPD and depression, we hypothesize that NMDAR down-regulation and specifically DCS administration may simultaneously improve depression and COPD-related lung symptomology. Significant research is needed before these hypotheses can be retained or discarded. Both animal models work and proof-of-concept clinical trials are warranted. DCS effects on inflammation, alveolar destruction and depression-related behaviors should be assessed in murine COPD experimental models. Clinical trials should include target populations suffering from COPD-depression comorbidity and should assess DCS effects upon lung-related symptoms, depression severity and inflammation marker levels. DCS side effects, toxicity and development of drug resistance should be monitored.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

UH is an inventor and has financial interests in patents and patent applications owned by Herzog Medical Center for the use of NMDAR modulators in NMDAR autoimmunity syndromes, depression and inflammation disorders. The other authors report no competing interest.

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