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Review

N-Acetyl Cysteine: A Potential Adjunctive Therapy in Psychiatric Disorders

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ABSTRACT

N-acetylcysteine (NAC) is a sulfur-containing amino acid recognized for its efficacy as an antidote in cases of paracetamol overdose and its safety as a mucolytic agent. Widely accessible as a nutritional supplement across numerous countries, NAC has garnered considerable attention in psychiatric and neurological treatment strategies over the past decade. Emerging clinical research underscores its potential therapeutic utility across a spectrum of neuropsychiatric disorders, encompassing bipolar disorder, depression, obsessive-compulsive disorder, anxiety disorders, and schizophrenia. The multifaceted pharmacological actions of NAC are attributed to its modulation of various pathophysiological factors implicated in these conditions. Proposed mechanisms of action include the regulation of neurotransmitter systems, maintenance of oxidative balance, and modulation of inflammatory mediators. These findings suggest a promising role for NAC as an adjunctive therapy in the management of neuropsychiatric disorders, warranting further investigation and clinical validation. This review covers various ways NAC can help treat neuropsychiatric disorders, suggesting it needs more study to confirm its benefits.

Keywords: Cytokines, inflammatory mediators, mucolytic agent, N-acetylcysteine, neurological disorders, neurotransmitters.

N-acetylcysteine (NAC, C5H9NO3S) is an *N*-acetyl derivative of the amino acid L-cysteine. It has been used in clinical trials and practices since 1970. *N*-acetylcysteine has been extensively prescribed as a mucolytic agent and as an antitoxin to treat paracetamol overdose. The therapeutic capability of NAC has also been used to prevent liver diseases correlated with decreased glutathione (GSH) levels and/or elevated oxidative stress.[1]

It is well known that NAC is used to restore GSH levels, the main function of the primary endogenous antioxidant GSH is neutralizing reactive oxygen and nitrogen species from the cell, and it is responsible for the cell's oxidative balance.[2] Modifications in pro-and anti-inflammatory cytokines, including interleukin (IL)-6, IL-1β have been reported in populations with depression, and, bipolar disorder, and schizophrenia.[3]

These inflammatory cytokines are potential contributors to the underlying pathophysiology of these disorders. *N*-acetylcysteine has been shown to have anti-inflammatory properties that are related to oxidative pathways, which may provide another potential mechanism of action in the benefits of NAC in psychiatry.[4]

The reductions in inflammatory cytokines by NAC treatment may be a potential mechanism by which NAC modulates the symptoms of psychiatric disorders. This may be directly associated with the inflammatory pathway or working through oxidative processes linked with inflammation. More research is needed to enlighten these mechanisms besides the effects on oxidative balance diversification in cysteine levels has also been shown to modulate neurotransmitter pathways, including glutamate and dopamine (DA).[4]

In diseases such as influenza, NAC may be used to decrease the inflammation occurring in these conditions, NAC also facilitates the production of nitric oxide which is an important mechanism in the prophylaxis of nephropathy.[5]

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Moreover, NAC is used in the treatment of different diseases including human immunodeficiency virus infections, cancer, and metal toxicity. The probable direct or indirect mechanisms of action of NAC are linked to the regulation of neurotransmission by multiple oxidative homeostasis and inflammatory mediators.[5]

Aside from NAC's established efficacy as a mucolytic agent, research has revealed its ability to enhance alveolar surfactant levels due to its antimicrobial and anti-inflammatory properties. Consequently, extensive clinical trials have investigated the potential of NAC in the management of chronic pulmonary diseases. Furthermore, NAC serves a critical role as an antidote in cases of paracetamol overdose, wherein approximately 90% of paracetamol undergoes conjugation reactions, while the remainder is metabolized by cytochrome P450 2E1, leading to the formation of *N*-acetyl-p-benzoquinone imine (NAPQI).[6] After being produced cellular GSH conjugate and detoxify NAPQI. An excess production of NAPQI results in heightened oxidative stress. This oxidative stress, in turn, triggers the activation of mitogen-activated protein pathways, ultimately culminating in cellular necrosis.[4] It is also proposed that NAC acts as an antidote to other drugs including mushroom toxins, chloroform, and heavy metals, but more evidence needs to be proved.[7]

N-ACETYLCYSTEINE AND OXIDATIVE STRESS

Oxidative stress arises when oxidants outnumber antioxidant capability. Water is generated within peroxisomes through the breakdown of fatty acids, a process that yields hydrogen peroxide. Additionally, reactive oxygen species, such as hydrogen peroxide and superoxide radicals, are generated during oxidative phosphorylation within mitochondria. *N*-acetylcysteine functions as a GSH precursor, making it an antioxidant agent in addition to being a mucolytic agent that breaks disulfide bonds in mucus glycoproteins, lowering mucus viscosity.[8,7]

N-ACETYLCYSTEINE AND BLOOD-BRAIN BARRIER

The capacity of NAC to pass the blood-brain barrier (BBB) is being debated. *N*-acetylcysteine stimulates the collapse of the BBB in the spontaneously hypertensive stroke-prone, which may hasten the failure of vascular and perivascular clearance.[9]

N-acetylcysteine has been demonstrated to modulate DA release in addition to altering glutamate levels. It has been found to increase vesicular DA release in striatal neurons at low levels after amphetamine administration and to block release at millimolar concentrations in rat striatal slices. In mouse striatal neurons, glutamate agonist-evoked DA release has also been demonstrated to be increased by glutamate.[9]

The only mechanisms for chemicals to penetrate the blood artery wall are through NAC and carrier-mediated active transport.[10] Different NAC compositions with different pathways may result in a differential usage of these processes. In mice, intraperitoneal or intravenous injections of 14C-NAC resulted in uptake by all organs except the brain and spinal cord. However, in certain investigations, intra-arterial and intravenous administration of 14C-NAC resulted in excellent BBB permeability. *N*-acetylcysteine-amide (NACA, a NAC derivative) has been measured in the brain following oral administration, but not NAC itself. When NAC was substituted with NAC ethyl ester, there was an unusual rise in NAC levels in the brain.[9,10]

Glutamate and Cysteine

N-acetylcysteine is a cysteine active metabolite and GSH precursor, that has also been utilized in medical therapeutic procedures for several decades as a mucolytic agent and to treat illnesses linked with GSH insufficiency. *N*-acetylcysteine's other therapeutic properties include the suppression of inflammation/nuclear factor kappa B signaling and the production of proinflammatory cytokines.[11]

N-acetylcysteine is a nonantibiotic molecule with antibacterial properties that is also anticarcinogenic and antimutagenic against some forms of cancer. Cysteine aids in the control of glutamate intra- and extracellular exchange in neurons via the cystine-glutamate antiporter. While this antiporter is found in all cell types, it is preferentially found in glial cells in the brain. Astrocytes take up the dimer, cystine, and exchange it for glutamate, which is discharged into the extracellular space. This free glutamate seems to activate inhibitory metabotropic glutamate receptors on glutamatergic nerve terminals, reducing glutamate synaptic release. Given that relationship, the quantity of cysteine in the system, as well as input from neurons via GSH synthesis, may directly influence the amount of glutamate in the extracellular space.[12]

N-ACETYLCYSTEINE IN PSYCHIATRIC DISORDERS

Psychiatric disorders have a variety of causes involving mitochondrial function, apoptosis, dopamine pathway, oxidative stress, and GHS metabolism. Several clinical trials assessed NAC in the treatments of various disorders including bipolar, schizophrenia, obsessive-compulsive disorder (OCD), and cocaine addiction as it plays a role in most of the pathways mentioned above, majority of these trials and studies have evidence that NAC has a positive effect on the outcomes.[13]

A great part of preclinical evidence has reported that NAC may be involved in glutamate homeostasis modulation. Glutamate is the most abundant excitatory neurotransmitter in the central nervous system and participates in learning and memory processes. Its action enhances the influx of extracellular Ca^{2+}, which is mediated by neuronal and glial membrane transporters to maintain the homeostasis of extracellular glutamate. *N*-acetylcysteine induces the expression of glutamate transporter-1 in astrocytes, which clears synaptic and extrasynaptic glutamate and enhances the maintenance of glutamate homeostasis.[14]

Bipolar Disorders

Mutations in oxidative metabolism have also been described in populations with bipolar disorder. changes in antioxidant levels, increased markers of lipid peroxidation and protein carbonylation have all been reported.[15] A double-blind, randomized, placebo-controlled trial of NAC in 75 participants with bipolar disorder was conducted. This 6-month trial involved the addition of 2000 mg/d of NAC or placebo to treatment as usual. Over the six months, there was no difference between groups in drop-out rates, with 64% of the total sample completing the trial.[16]

Rating scores on the Montgomery-Åsberg Depression Rating Scale (MADRS) and the Bipolar Depression Rating Scale showed large decreases in depressive symptoms (about 9 points on the MADRS between NAC and placebo groups at the endpoint). to the schizophrenia trial, improvements were seen in global improvement, severity, and function scales; however, these effects were proportionally larger, with large effect sizes on most measures. Again, after discontinuation of NAC treatment, there was a convergence with scores between the NAC and placebo groups, showing a loss of benefit following washout.[15,16]

Schizophrenia

Dopaminergic disorders have traditionally been prioritized as research targets for schizophrenia, although all main neurotransmitter systems, including aminobutyric acid, serotonin, acetylcholine, glutamate, and noradrenaline, have been involved. There has been evidence of increased dopaminergic metabolism in the striatum. This hyperdopaminergic condition has been demonstrated to be inversely related to prefrontal hypodopaminergia. These modifications are thought to mediate changes in executive function as well as many of the disorder's favorable symptoms.[17] Glutamate metabolism abnormalities and reduced glutamate levels in the prefrontal cortex have been documented in schizophrenia patients. Cysteine has been demonstrated to influence glutamate levels via glutamate-cystine exchange, while GSH has been shown to modulate glutamate binding to *N*-methyl-D-aspartate (NMDA)receptors.[18]

Obsessive-Compulsive Disorder

There are similarities between brain areas involved in addiction and OCD, including the anterior cingulate cortex and the nucleus accumbens.[19] Findings indicate oxidative stress in populations with OCD, characterized by elevated lipid peroxidation. Additionally, reduced levels of vitamin E, catalase, glutathione peroxidase, and selenium have been observed. Furthermore, there is heightened superoxide dismutase activity, alongside alterations in the total oxidative state. Some of these changes have been linked to the severity of symptoms.[20]

In general, standard first-line treatments for OCD include serotonin reuptake inhibitors, and psychotherapy is used in conjunction. While this treatment regimen has some success, up to 20% of people with OCD are treatment-resistant and receive minimal relief. There is some indication that glutamatergic anomalies exist in people with OCD; however, further research is needed to establish if this is a fundamental, causative consequence.[21]

ADDICTION

The majority of the clinical studies investigating addiction have based their rationale for using NAC on the extant literature implicating glutamatergic abnormalities in addiction.[22] Glutamatergic dysfunction has been considered a central tenet of addictive disorders since the demonstration that blockade of NMDA glutamatergic receptors inhibits sensitization, and glutamate is now thought to

additionally regulate dopaminergic activity in the ventral tegmental reward area.[21,22]

The ability of NAC to regulate glutamate availability via the activity of the cystine/glutamate antiporter highlights the potential therapeutic efficacy of this drug in treating addictive disorders. In an open-label crossover imaging study of cocaine-dependent patients, NAC normalized elevated levels of glutamate, as measured by brain imaging.[22,23] However, there is now data from both clinical studies and animal models suggesting a role of oxidative stress in addiction, suggesting a further pathway whereby NAC may offer an alternate rational approach via the promotion of GSH synthesis.[18,22] In addition to the disorders, NAC is also being investigated as an adjunctive treatment for alcohol dependence, and a pilot randomized controlled trial (RCT) of NAC in combination with naltrexone has been conducted for the treatment of methamphetamine dependence, with a negative outcome.[24]

Cannabis Dependence

Cannabis is the most common illegal substance consumed by young people, and use rates are rising. A quarter of high school seniors are current cannabis users, and 7% use daily. [25] N-acetylcysteine (NAC), is a widely available over-the-counter supplement.[26]

An open-label study of NAC (1200 mg BD ("bis in die" meaning twice a day)) was conducted on 24 dependent cannabis users. After NAC treatment, users reported reductions in days per week of use, 'number of hits', compulsivity, emotionality, and purposefulness with cannabis use. Interestingly, objective urine cannabinoid measures did not significantly change with treatment and remained higher than the test's detection range. However, a recent 8-week double-blind RCT (n=116) investigated treatment with NAC (1200 mg BD) versus placebo for cannabis cessation in adolescents and found that during treatment, those receiving NAC had more than twice the odds of having negative urine cannabinoid test results than placebo, supporting its efficacy as a primary cessation therapy although in an intent-to-treat analysis.[27]

Nicotine Addiction

N-acetylcysteine has also been studied in nicotine addiction because of its potential to restore glutamate homeostasis and modulate redox balance.[28] In a placebo-controlled study of NAC (2400 mg/day) for tobacco cessation (n=29), there were no significant differences in the number of cigarettes smoked or carbon monoxide levels between NAC and placebo groups. However, post hoc analysis revealed trends toward the decreased number of cigarettes smoked in the NAC group after the removal of two outliers based on alcohol consumption, but this too did not correspond with decreased carbon monoxide levels.[29-31] There are significant active-placebo gaps in this sort of research, and because a small number of people quit smoking in cessation trials, sample sizes in the hundreds are normally required to develop efficacy.[28-32]

In conclusion, NAC offers a wide range of activities and potential benefits in a variety of settings and systems. *N*-acetylcysteine, as a medication, may just be the perfect xenobiotic (a chemical substance found within an organism that is not naturally produced or expected to be present within the organism), capable of effectively accessing endogenous metabolic systems via its metabolism. Furthermore, NAC may cross the BBB. There is potential to investigate NAC dosages and duration of therapy in neurological disorders to achieve cytoprotection. Overall, this distinctive therapeutic technique implies novel pathways as potential therapeutic targets. This serves as a stepping stone for the construction of further logical, hypothesis-based treatments. The fact that NAC claims to be safe, pleasant, and economical, as well as easily available, adds to its appeal.

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