

N-acetylcysteine in Psychiatric Disorders: Possible Role of Cysteinine Deregulation

Marcos Arturo Martínez-Banaclocha^{1*}

¹Department of Pathology, Hospital Lluís Alcanyis Xàtiva, Valencia, Spain.

Mini-review Article

ABSTRACT

In the last years, several clinical studies have shown the usefulness of N-acetylcysteine (NAC) in psychiatric diseases including a role in some drug abuse disorders. Although the glutathione replenishment and the antioxidant activity of NAC have been suggested as the principal mechanisms to improve such a wide range of conditions, these actions seem to be unspecific and insufficient to explain all reported effects. The present paper proposes that cysteinine (cysteine network) may be deregulated in psychiatric diseases explaining the wide-range beneficial actions of NAC supplementation.

Keywords: N-acetylcysteine; cysteine; psychiatric diseases; psychosis; diabetes; cysteinine.

ABBREVIATIONS

NAC : N-acetylcysteine;
HIV : Human Immunodeficiency Virus;
CNS : Central Nervous System;
GSH : Glutathione;

SCCP : Sensitive Cysteine Containing Protein;
G6PD : Glucose-6-Phosphate Dehydrogenase;
NADP : Nicotinamide Adenine Dinucleotide
Phosphate;
NADPH: Nicotinamide Adenine Dinucleotide
Phosphate Hydrate;

*Corresponding author: E-mail: martinez_marben@gva.es;

NAFLD : Non-Alcoholic Fatty Liver Disease;
SirT1: Sirtuin-1.

1. INTRODUCTION

N-acetylcysteine (NAC) has been used as a mucolytic compound in chronic pulmonary diseases for a long time, showing beneficial actions in carcinogenesis [1], the treatment of acetaminophen overdose [2], and HIV-infection [3]. In the CNS, NAC has shown beneficial effects in epilepsy, traumatic brain injury and neurodegenerative diseases [4,5]. In the last years, several clinical studies have shown the usefulness of NAC in psychiatric diseases including a role in some drug abuse disorders [4,6], and post-traumatic stress disorder [7]. Preclinical investigations have shown that NAC increases the minimum effective dose of some tricyclic antidepressants [8], and some clinical trials and case reports have shown the usefulness of NAC in obsessive-compulsive disorders with minimal adverse effects [9]. In young patients suffering from obsessive-compulsive disorders, NAC was able to improve the baseline anxiety and depression scores, and the use of antidepressant medications [10]. A clinical study suggested that adjunctive NAC administration may be useful for major depressive episodes in bipolar disorder [11]. NAC has also shown beneficial effects as adjuvant treatment in schizophrenic patients [12] supporting a large-scale clinical trial in patients resistant to clozapine [13]. There is also a clinical trial suggesting that NAC can complement psychosocial treatment for cannabis dependence in adolescents [14]. NAC decreased the irritability in children and adolescents with autism spectrum disorders treated with risperidone without changing the core symptoms of autism at the doses used [15].

Although the glutathione (GSH) replenishment and the antioxidant activity of NAC have been suggested as the principal mechanisms to improve such a wide range of conditions, these actions seem to be unspecific and insufficient to explain all reported effects. In the context of ageing and some neurodegenerative diseases, a cysteine network (cysteinnet) has been proposed as a hierarchical bottom-up biochemical matrix of interconnected sensitive cysteine-containing proteins (SCCPs) that together with reactive species and the cysteine/glutathione cycles can regulate different structural, metabolic and signalling cellular pathways [5,16,17]. From this point of view, the tripeptide glutathione and other

large cysteine containing peptides form an essential part of the proposed cysteinnet paradigm. These SCCPs use the thiol groups of cysteine residues as cellular sensors that can synchronise, at very short timescale, different cellular functions under the control of the redox microenvironment. The present paper proposes that cysteinnet may be deregulated in psychiatric diseases explaining the wide-range beneficial actions of NAC supplementation.

2. SENSITIVE CYSTEINE-CONTAINING PROTEINS IN PSYCHIATRIC DISORDERS

2.1 Glucose-6-phosphate Dehydrogenase (G6PD)

Some well-documented reports agree with the idea that the deregulation of specific SCCPs is associated with psychotic behaviour, as it is the case of glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD is the first enzyme in the pentose phosphate pathway, which reduces nicotinamide adenine dinucleotide phosphate (NADP) to NADPH that is needed for many biosynthetic reactions including the replenishment of glutathione.¹⁷ In addition to acute hemolytic anaemia associated with G6PD deficiency [18], some studies have shown a high proportion of psychotic patients with this defect [19]. In fact, it has been reported that a 38-year-old man diagnosed with a nonspecific psychotic disorder associated with a G6PD deficiency showed minor clinical improvement after aripiprazole treatment [20]. After a year of NAC treatment, the patient showed significant clinical improvement, including the recovery of the previously reported white matter lesions in neuroimaging studies. The authors suggested that NAC effects were due to the restoration of the reduced glutathione levels associated with G6PD deficiency [20].¹⁹ However, there are others mechanisms through which NAC may improve the clinical manifestations of this patient. G6PD provides NADPH to maintain the physiological levels of reduced glutathione, but it plays a central role in the maintenance of the optimum pH and redox homeostasis [21], which is crucial for the catalytic activity of a wide range of different enzymes [22]. In fact, human G6PD exists in dimer/tetramer equilibrium depending on the pH and the ionic strength of the microenvironment [21]. Each monomer of this enzyme has eight cysteine residues in the N-terminal region that seems to play a critical role in the structural function of the protein through

the formation of disulfide bridges [21]. Besides, a decrease in glutathione concentration seems not to have a significant contribution to the oxidant sensitivity observed in G6PD deficiency. Instead, a decline in NADPH concentration showed an enhancement in G6PD deficiency oxidative sensitivity that was independent of the glutathione status [23]. Furthermore, it has been demonstrated that reactive nitrogen species may inhibit G6PD through the oxidation of specific tyrosine or cysteine residues, and also, that steric factors can determine the role of thiolic groups in the enzymatic activity [23]. The sensitivity of G6PD activity to the addition of cysteine is bi-phasic, having an inhibitory effect at high concentrations and a neutral effect at low levels, which suggests the presence of multiple binding sites for cysteine on the G6PD structure [23]. Moreover, this study showed a higher sensitivity of the defective G6PD protein to thiol-blocking agents in comparison with the normal enzyme. From this point of view, G6PD can be considered an SCCP that is regulated by the redox microenvironment. Therefore, the effects of NAC in the restoration of the psychotic symptoms associated with G6PD deficiency cannot be attributed only to the replenishment of reduced glutathione levels but also to a regulation of the enzymatic activity of the protein and other SCCPs as well as their corresponding biochemical pathways.

The mentioned data suggest that G6PD is dependent on cysteine thiolic groups for its activity and support a potential direct mechanism of NAC action on the favourable response of the patient. In agreement with this view, it has been observed a fast and irreversible inhibition of the G6PD activity with ketoprofen-CoA, suggesting the involvement of a cysteine residue in the catalytic domain of the enzyme [23]. These findings agree with the hypothesis that a complex matrix of SCCPs may be deregulated in some psychiatric disorders, explaining the significant beneficial effect associated with NAC supplementation.

2.2 Other SCCPs in Neuropsychiatric Disorders and Ageing

There are a lot of SCCPs that can be affected by the regulation of the micro-environmental redox status produced by NAC supplementation [5,16,17]. NAC was proposed as a potential treatment for neurodegenerative diseases based on preclinical studies carried out in mice synaptic mitochondria [24-28]. These experiments showed

that NAC was able to improve the specific activities of essential enzymatic complexes of the mitochondrial respiratory chain such as Complex I and IV [25,26], suggesting that NAC would have beneficial effects in the CNS [25,26]. The effects of NAC on the presynaptic mitochondrial respiratory enzymes were confirmed in vitro assays, supporting its ability to directly interact with specific amino acid residues in the enzymatic proteins, having an impact on their function as well as on their subsequent pathways [26-28]. In fact, a recent clinical trial has confirmed that NAC has therapeutic action in patients with Parkinson's disease [29]. This effect could be explained at least partially through the regulation of mitochondrial respiratory enzymatic complexes [25,26]. Other studies have shown that NAC may modulate many molecular pathways in the CNS, including apoptosis, neurogenesis, inflammatory response, as well as the glutamate cycle [4,5,6].

2.3 SCCPs in Diabetic-Related Metabolic Disorders and Psychiatry

Diabetes is highly associated with psychiatric disorders, and several studies have shown that the prevalence of diabetes in psychiatric diseases is higher than in the general population [30]. However, the relationship between diabetes and psychiatric disorders is complex and seems bidirectional. The metabolic disturbances in diabetes may contribute to the pathogenesis of psychiatric disorders, while drugs used for the treatment of psychiatric disorders can interfere with glucose metabolism and insulin resistance. Besides, some psychiatric disorders may act as significant independent risk factors for the development of diabetes [30]. In regard to G6PD, it has been implicated in the deregulation of lipid metabolism, and insulin resistance in different models [31]. It seems that the overexpression of G6PD impairs insulin signalling and insulin-dependent glucose uptake in adipocytes and potentially in other cells. Therefore, the proposed cysteine deregulation may link G6PD disruption in psychiatric disorders, diabetes and chronic neurodegenerative diseases [32], and may explain some of the beneficial therapeutic effects of NAC. Indeed, NAC can prevent hyperglycemia-induced insulin resistance by the modulation of the redox metabolism, including the GSH intracellular concentration that is necessary as a cofactor in key enzymatic reactions [33]. In this regard, glyoxalase can be considered an SCCP because of its high content of cysteine residues that can be nitrosylated in

mammalian Schwann cells [34]. Glyoxalase plays a key role in the metabolism of reactive triose phosphate-derived 3-carbon intermediates and therefore, in the production of advanced glycation end products and diabetes complications [33].

The doses and administration periods of NAC are essential to evaluate its effects in different diseases and experimental conditions. It has been well established that NAC can cross the blood-brain barrier having effects in the CNS both in animal and human studies [5]. Although, some clinical studies have shown controversial results of the effects of NAC in patients with type 2 diabetes [35,36]. NAC has shown beneficial action in experimental models of diabetes [37] and can also attenuate the progression of liver pathology in non-alcoholic fatty liver disease (NAFLD) rat models [38]. Moreover, NAC can ameliorate the liver function in patients with NAFLD [39]. Therefore, NAC actions may be mediated, at least partially, by the proposed cysteinyl regulation, but it is crucial to identify the optimal doses of NAC for inhibiting the development of glucose intolerance and related metabolic disturbances [40].

On the other hand, Alzheimer disease (AD) has been viewed as a form of diabetes that selectively involves the brain, having metabolic features that overlap with type 1 and type 2 diabetes [41]. In addition, AD has been recently related to NAFLD, which may induce insulin resistance and other chronic age-related human diseases [42]. NAFLD may be a complication of the metabolic syndrome that can be alleviated by the activation of Sirtuin-1 (SirT1). This protein is a member of the NAD⁺-dependent class III histone deacetylase family that can be reversibly inhibited by the oxidation of three specific redox-sensitive cysteine residues [43]. The activation of this protein decreased apoptosis and improved the lipid metabolism in hepatocytes, while the oxidative modification of these specific SirT1 cysteine residues results in the inhibition of its enzymatic activity during metabolic stress [43]. Therefore, the post-translational modifications of SirT1 by the redox and nutritional status of cells is considered central in the metabolic syndrome, insulin resistance, and dyslipemia. In fact, SirT1 is inhibited by physiological levels of nitrosothiol S-nitrosoglutathione [44]. From this point of view, this protein can be considered an SCCP with a key role in the metabolic syndrome and therefore, susceptible to be regulated by NAC therapy.

As above-mentioned, the overexpression of G6PD may impair insulin signaling and insulin-dependent glucose uptake. Therefore, the proposed cysteinyl deregulation may link G6PD disruption in psychiatric disorders, diabetes and chronic neurodegenerative diseases, and may explain the beneficial therapeutic effect of NAC in those diseases.

3. CONCLUSION

The present manuscript proposes that cysteinyl deregulation may be the common pathway through which different etiologic events evolve toward a redox homeostatic disruption in metabolic, psychiatric, and neurodegenerative disorders that can be ameliorated with adequate NAC supplementation.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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