N-acetylcysteine in psychiatric disorders: possible role of cysteinet deregulation

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 cysteinet (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, cysteinet

1. INTRODUCTION

N-acetylcysteine (NAC) has been used as a mucolytic compound in chronic pulmonary diseases for a long time, showing beneficial actions in carcinogenesis1, 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.6 Specifically, preclinical investigations have shown that NAC increases the minimum effective dose of some tricyclic antidepressants,7 and some clinical trials and case reports have shown the usefulness of NAC in obsessive-compulsive disorders with minimal adverse effects.8 Indeed, in young patients suffering from obsessive-compulsive disorders, NAC improved the baseline anxiety and depression scores, as well as the use of antidepressant medications.9 A clinical study suggested that adjunctive NAC administration may be useful for major depressive episodes in bipolar disorder.10 NAC has also shown beneficial effects in schizophrenia11 supporting a large-scale clinical trial in patients resistant to clozapine.12 There is also a clinical trial suggesting that NAC can complement psychosocial treatment for cannabis dependence in adolescents.13 Finally, 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. 14

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 aging and some neurodegenerative diseases, a cysteine network (cysteinet) 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 signaling cellular pathways.6,15,16 From this point of view, the tripeptide glutathione and other large cysteine containing peptides form an essential part of the proposed cysteinet paradigm. These SCCPs use the thiol groups of cysteine residues as cellular sensors that can synchronize, at very short timescale, different cellular functions under the control of the redox microenvironment. The present paper proposes that cysteinet 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 anemia associated with G6PD deficiency,17 some studies have shown a high proportion of psychotic patients with this defect.18 In fact, it has been reported a 38-year-old man diagnosed with a nonspecific psychotic disorder associated with a G6PD deficiency that showed minor clinical improvement after aripiprazole treatment.19 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.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,20 which is crucial for the catalytic activity of a wide range of different enzymes.21 In fact, human G6PD exists in dimer/tetramer equilibrium depending on the pH and the ionic strength of the microenvironment.20 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.20 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.22 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.22 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.22 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 favorable 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.22 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 aging

There are a lot of SCCPs that can be affected by the regulation of the micro-environmental redox status produced by NAC supplementation.5,15,16 NAC was proposed as a potential treatment for neurodegenerative diseases based on preclinical studies carried out in mice synaptic mitochondria.23-27 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.24,25 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.25-27 In fact, a recent clinical trial has confirmed that NAC has therapeutic action in patients with Parkinson's disease.28 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

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. 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.29 In regard to G6PD, it has been implicated in the deregulation of lipid metabolism, and insulin resistance in different models.30 It seems that the overexpression of G6PD impairs insulin signaling and insulin-dependent glucose uptake in adipocytes and potentially in other cells. Therefore, the proposed cysteinet deregulation may link G6PD disruption in psychiatric disorders, diabetes and chronic neurodegenerative diseases,31 and may explain some of the beneficial therapeutic effect 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.32 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.33 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.32

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.5 Although, some clinical studies have shown controversial results of the effects of NAC in patients with type 2 diabetes,34,35 NAC has shown beneficial action in experimental models of diabetes 36 and can also attenuate the progression of liver pathology in non-alcoholic fatty liver disease (NAFLD) rat models.37 Moreover, NAC can ameliorate the liver function in patients with NAFLD.38 Therefore, NAC actions may be mediated, at least partially, by the proposed cysteinet regulation, but it is crucial to identify the optimal doses of NAC for inhibiting the development of glucose intolerance and related metabolic disturbances.39

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.40 In addition, AD has been recently related to NAFLD, which may induce insulin resistance and other chronic age-related human diseases.41 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.42 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.42 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.43 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 cysteinet deregulation may link G6PD disruption in psychiatric disorders, diabetes and chronic neurodegenerative diseases,31 and may explain the beneficial therapeutic effect of NAC in those diseases.

3. CONCLUSION

The present manuscript proposes that cysteinet 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.

REFERENCES

1. De Flora S, Izzotti A, D'Agostini F, et al. Mechanisms of N-acetylcysteine in the prevention of DNA damage and cancer, with special reference to smoking-related end-points. Carcinogenesis 2001;22:999-1013.

2. Green JL, Heard KJ, Reynolds KM, et al. Oral and intravenous acetyl-cysteine for treatment of acetaminophen toxicity: a systematic review and meta-analysis. West J Emerg Med 2013;14: 218-26.

3. De Rosa SC, Zaretsky MD, Dubs JG, et al. N-acetylcysteine replenishes glutathione in HIV infection. Eu. J Clin Investig 2000;30:915-29.

4. Bavarsad Shahripour R, Harrigan MR, Alexandrov AV. N-acetylcysteine (NAC) in neurological disorders: mechanisms of action and therapeutic opportunities. Brain Behav 2014;4:108-22.

5. Martinez-Banaclocha M. Cellular cysteine network (CYSTEINET): pharmacological intervention in brain aging and neurodegenerative diseases. In: Atta-ur-Rahman, editor. Frontiers in Clinical Drug Research-Central Nervous System, Vol 2. Bentham Science Publisher, 2016;2:105-72.

6. Deepmala,D, Slattery J, Kumara N, et al. Clinical trials of N-acetylcysteine in psychiatry and neurology: A systematic review. Neurosci Biobehav Rev 2015;55:294-321.

7. Costa-Campos L, Herrmann AP, Pilz LK, et al. Interactive effects of N-acetylcysteine and antidepressants. Prog Neuropsychopharm Biol Psychiatry 2013;44:125-130.

8. Dean O, Ashley I, Bush DL, et al. Effects of N-acetyl cysteine on cognitive function in bipolar disorder. Psych Clin Neurosci 2012;66:514-17.

9. Oliver G, Dean O, Camfield D, et al. N-Acetyl Cysteine in the treatment of obsessive compulsive and related disorders: A systematic review. Clin Psychopharm Neurosci 2015;13:2-24.

10. Copolov DL, Malhi GS, Kohlmann K, et al. N-acetylcysteine for major depressive episodes in bipolar disorder. Rev Bras Psiquiatr 2011;33:374-78.

11. Berk M, Copolov D, Dean O, et al. N-acetylcysteine as a glutathione precursor for schizophrenia—a double-blind, randomized, placebo-controlled trial. Biol Psychiatry 2008;64:361-68.

12. Rossell SL, Francis PS, Galletly C, et al. N-acetylcysteine (NAC) in schizophrenia resistant to clozapine: a double blind randomised placebo controlled trial targeting negative symptoms. BMC Psychiatry 2016;16:320.

13. Gray KM, Carpenter MJ, Baker NL, et al. A double-blind randomized controlled trial of N-acetylcysteine in cannabis-dependent adolescents. Am J Psychiatry 2012;169:805-12.

14. Ghanizadeh A, Moghimi-Sarani E. A randomized double blind placebo controlled clinical trial of N-Acetylcysteine added to risperidone for treating autistic disorders. BMC Psychiatry 2013;13:196.

15. Martinez-Banaclocha M. Cysteine network (CYSTEINET) dysregulation in Parkinson's disease: role of N-acetylcysteine. Curr Drug Metab 2016;17:368-85.

16. Martinez-Banaclocha M. N-acetylcysteine: a natural antidote for Alzheimer's disease. Sci Pages Alzh Dis Dement 2016;1:e002.

17. Beutler E. Glucose-6-phosphate dehydrogenase deficiency. N Engl J Med 1991;324:169-74.

18. Bocchetta A. Psychotic mania in glucose-6-phosphate-dehydrogenase-deficient subjects. Ann Gen Hosptal Psychiatry 2003;2:6.

19. Monsivais SR, Wisdom N, Kruse JL, et al. N-acetylcysteine supplementation in an individual with glucose-6-phosphate dehydrogenase deficiency-associated psychosis. Biol Psychiatry 2016;80:71-72.

20. Au SW, Gover S, Lam VM, et al. Human glucose-6-phosphate dehydrogenase: the crystal structure reveals a structural NADP+ molecule and provides insights into enzyme deficiency. Structure 2000;8:293-303.

21. Jones DP, Go YM. Mapping the cysteine proteome: analysis of redox-sensing thiols. Curr Opin Chem Biol 2011;15:103-12.

22. Abboud MM, Al-Awaida W. Synchrony of G6PD activity and RBC fragility under oxidative stress exerted at normal and G6PD deficiency. Clin Biochem 2010;43:455-60.

23. Martinez-Banaclocha M, Hernandez AI, Martinez N. N-acetylcysteine delays age-associated memory impairment in mice: role in synaptic mitochondria. Brain Res 2000;855:100-6.

24. Martinez-Banaclocha M, Martinez N, Hernandez AI, et al. Hypothesis: can N-acetylcysteine be beneficial in Parkinson's disease? Life Sci 1999;64:1253-1257.

25. Martinez-Banaclocha M. N-acetylcysteine elicited increase in complex I activity in synaptic mitochondria from aged mice: implications for treatment of Parkinson's disease. Brain Res 2000;859:173-5.

26. Martinez-Banaclocha M, Martinez N. N-acetylcysteine elicited increase in cytochrome c oxidase activity in mice synaptic mitochondria. Brain Res 1999;842:249-51.

27. Martinez-Banaclocha M, Hernandez AI, Martinez N, et al. N-acetylcysteine protects against age-related increase in oxidized proteins in mouse synaptic mitochondria. Brain Res 1997;762:256-8.

28. Monti DA, Zabrecky G, Kremens D, et al. N-acetylcysteine may support dopamine neurons in Parkinson's disease: preliminary clinical and cell line data. PLoS ONE 2016;11:e0157602.

29. Balhara YPS. Diabetes and psychiatric disorders. Indian J Endocrinol Metab 2011;15:274-83.

30. Park J, Rho HK, Kim KH, et al. Overexpression of glucose-6-phosphate dehydrogenase is associated with lipid dysregulation and insulin resistance in obesity. Mol Cell Biol 2005;25:5146-57.

31. Martins IJ. Nutritional and genotoxic stress contributes to diabetes and neurodegenerative diseases such as Parkinson's and Alzheimer's diseases. In: Atta-ur-Rahman, editor. Frontiers in Clinical Drug Research-CNS and Neurological Disorders. Bentham Science Publisher 2015;3:158-92.

32. Haber CA, Lam TKT, Yu Z, et al. N-acetylcysteine and taurine prevent hyperglycemia-induced insulin resistance in vivo: possible role of oxidative stress. Am J Physiol Endocrinol Metab 2003;285:E744-53.

33. Morgenstern J, Fleming T, Schumacher D, et al. Loss of Glyoxalase 1 induces compensatory mechanism to achieve dicarbonyl detoxification in mammalian Schwann cells. J Bioll Chem 2017;292:3224-38.

34. Ozkilic AC, Cengiz M, Ozaydin A, Cobanoglu A, Kanigur G. The role of N-acetylcysteine treatment on anti-oxidative status in patients with type II diabetes mellitus. J Basic Clin Physiol Pharmacol 2016;17:245-54.

35. Szkudlinska MA, von Frankenberg AD, Utzschneider KM. The antioxidant N-acetylcysteine does not improve glucose tolerance or β-cell function in type 2 diabetes. J Diabetes Complications 2016;30:618-22 .

36. Kaga AK, Barbanera PO, Lima Do Carmo NO, et al. Effect of N-acetylcysteine on dyslipidemia and carbohydrate metabolism in STZ-induced diabetic rats. Intern J Vasc Med 2018;e6428630.

37. Baumgardner JN, Shankar K, Hennings L, et al. N-acetylcysteine attenuates progression of liver pathology in a rat model of non-alcoholic steatohepatitis. J Nutrition 2008;138:1872-79.

38. Khoshbaten M, Aliasgarzadeh A, Masnadi K, et al. N-acetylcysteine improves liver function in patients with non-alcoholic fatty liver disease. Hepatitis Monthly 2010;10:12-6.

39. Falach-Malik A, Rozenfeld H, Chetboun M, et al. N-Acetyl-L-Cysteine inhibits the development of glucose intolerance and hepatic steatosis in diabetes-prone mice. Am J Transl Res 2016;8:3744-56.

40. De la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes–evidence reviewed. J Diabetes Sci Tech 2008;2:1101-13.

41. Martins IJ. Type 3 diabetes with links to NAFLD and other chronic diseases in the western World. Int J Diabetes 2016;1:1-5.

42. Shao D, Fry JL, Han J, et al. A redox-resistant Sirtuin-1 mutant protects against hepatic metabolic and oxidant stress. J Biol Chem 2014;289:7293-306.

43. Kalous KS, Wynia-Smith SL, Olp MD, Smith BC. Mechanism of Sirt1 NAD+-dependent protein deacetylase inhibition by cysteine S-nitrosation. J Biol Chem 2016;291:25398-410.

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