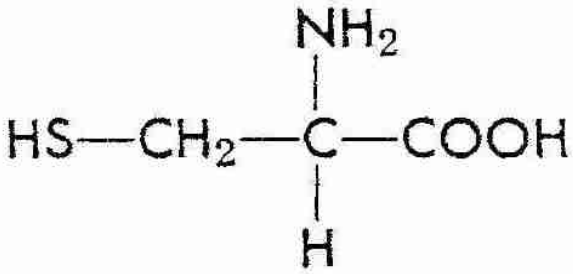
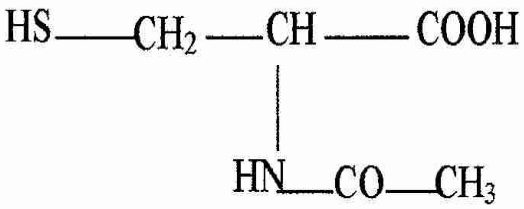
N-Acetyl Cysteine (NAC)

by Ben Best

http://www.benbest.com/nutrceut/NAC.html

Cysteine	N-AcetylCysteine (NAC)
	

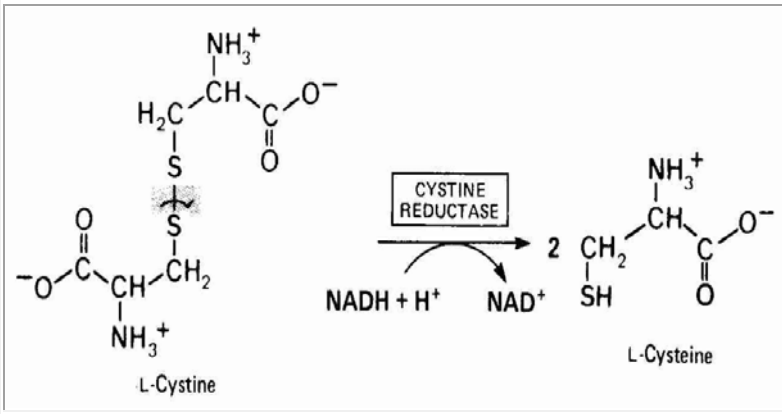
N-Acetyl Cysteine (**NAC**, N-Acetyl-L-Cysteine) is the amino acid **L-Cysteine** plus an **acetyl** (-CO-CH_3) group attached to the amino (NH_2) group. The acetyl group functions to speed absorption and distribution on orally ingested cysteine. Amino acids which contain a sulfur group have antioxidant properties.

The hydrogen atom in the **thiol** (ie, -SH) group of many sulfur-containing anti-oxidants can act as an electron for neutralizing free-radicals. Lipoic acid, the tripeptide glutathione, the amino acids cysteine & methionine and the organosulfur compounds of garlic oil are all thiol containing anti-oxidants. Even albumin can have an anti-oxidant function in plasma as a result of its cysteine-34 residue.

Glutathione (**GSH**, L-gamma-glutamyl-L-cysteinylglycine) is the predominant anti-oxidant in the aqueous cytoplasm of cells. Virtually all cells require glutathione for viability and function. Glutathione is synthesized from three amino acids in a two-step process, beginning with the combination of glutamic acid & cysteine and ending with the addition of glycine. The liver & lungs are the primary sites of glutathione synthesis. Glycine & glutamic acid are plentiful in cells, so it is the availability of cysteine that controls the reaction rate. Neuronal overexpression of the rate-limiting enzyme for glutathione synthesis in transgenic fruit flies has been shown to increase mean and maximum lifespan by up to 50% [JOURNAL OF BIOLOGICAL CHEMISTRY; Orr,WC; 280(45):37331-37338 (2005)].

Typically blood glutathione levels for clinically healthy adults do not diminish with age before age 40, are 15% lower for the 40-59 age group, 45% lower for the 60-79 age group, but only 20% lower for the 80-99 age group. Selective death of the most GSH-deficient persons is the explanation for the relatively higher levels of GSH in the very elderly compared to the 60-79 age group. In fact, many people maintain constant GSH levels throughout life with only a subset of people who pull down the averages [JOURNAL OF ANTI-AGING MEDICINE; Lang,CA; 4(2):137-144 (2001)].

Cystine to Cysteine



L-cysteine is not very water soluble, nor is it absorbed well by the intestine. Dietary cysteine comes mainly as the breakdown product of ingested proteins & peptides. Whey protein is a particularly rich food source of cysteine. Because cysteine is so unstable, the main extracellular source of intracellular cysteine is the dipeptide **cystine** (two conjugated cysteines). Cystine competes with glutamate for transport into cells such that conditions of elevated extracellular glutamate can lead to glutathione depletion, worsened oxidative stress and cell death [JOURNAL OF BIOLOGICAL CHEMISTRY; Sato,H; 274(17):11455-11458 (1999)]. S-AdenosylMethionine (**SAMe**) can increase glutathione synthesis.

Oral supplementation with **N-Acetyl Cysteine** (**NAC**) provides an alternate means of boosting intracellular glutathione via elevated intracellular cysteine. NAC is rapidly absorbed after oral administration and reaches a maximum plasma level in 2-3 hours, with a half-life of about 6 hours. NAC readily enters cells and is hydrolyzed to cysteine.

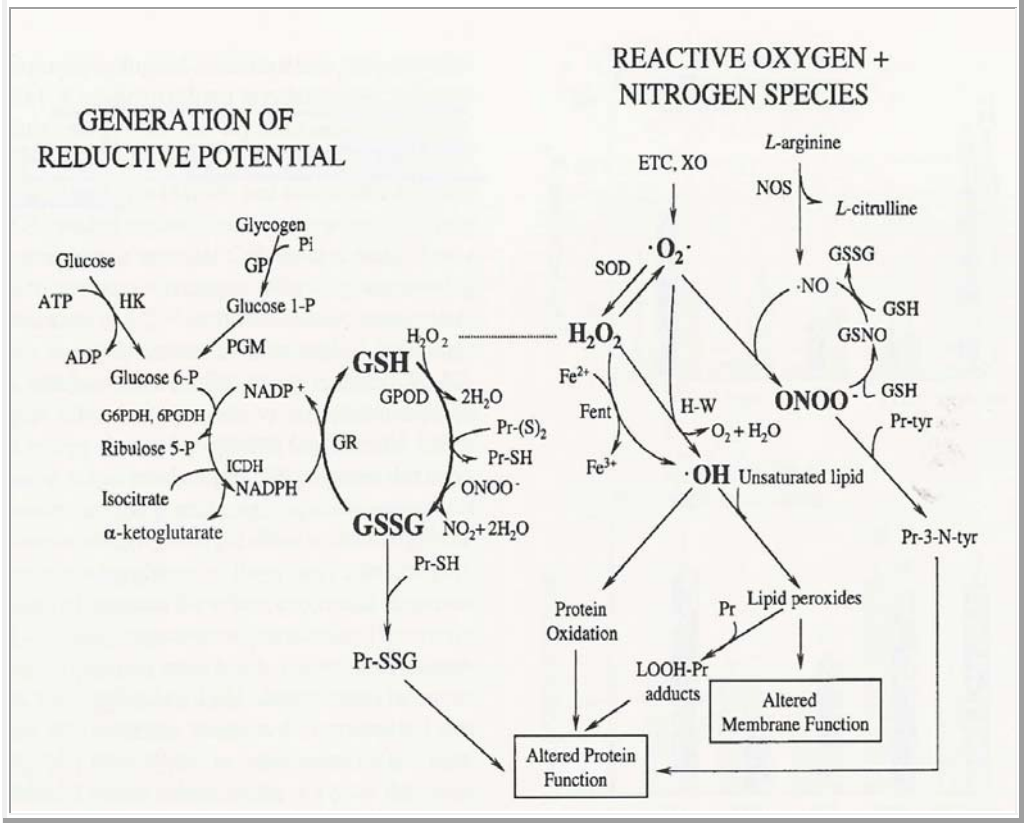
Glutathione (**GSH**) can scavenge peroxynitrite & hydroxyl radicals as well as convert hydrogen peroxide to water. Although a glutathione radical (**GS**·) is formed, it is readily neutralized by combining with another glutathione radical to produce GSSG. GSSG can be converted back to GSH by NADPH-dependent glutathione reductase enzyme (making the process dependent upon production of the NADPH energy-storing molecule). Vitamin C can regenerate a Vitamin E radical and GSH can regenerate a Vitamin C radical to its anti-oxidant Vitamin C condition -- creating a chain of anti-oxidant molecule dependency.

NAC has been shown to extend the maximum lifespan of fruit flies by nearly a quarter, but the highest doses were toxic [CELLULAR AND MOLECULAR LIFE SCIENCES; Brack,C; 53(11-12):960-966 (1997)].

NAC has been used in clinical toxicology for the treatment of acetaminophen poisoning (although the extremely high doses used for this purpose causes allergic reactions in some people -- anaphylactic shock, in extreme cases). Glutathione detoxifies acetaminophen, but once glutathione is depleted there can be significant cell death in the liver [THE AMERICAN JOURNAL OF MEDICINE; Flanagan,RJ; 91(Suppl C):131S-139S (1991)]. AIDS victims can suffer severe liver and kidney damage by using

acetaminophen or alcohol, which severely deplete glutatione [PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES (USA); Herzenberg,LA; 94(5):1967-1972 (1997)].

GSH/GSH Redox Pair Anti-Oxidant Defense



Rat experiments indicate that NAC can improve neuron survival in the CA1 region of the hippocampus following ischemic-reperfusion injury when given before or after the ischemia [STROKE; Knuckey,NW; 26(2):305-311 (1995)]. NAC reduction of ischemia & reperfusion injury can accompany significantly reduced plasma levels of endothelial-cell damaging homocysteine [JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY; Sochman, J; 39(9):1422-1428 (2002)]. NAC also inhibits the expression of endothelial adhesion molecules and peroxynitite free radical damage associated with ischemia/reperfusion [CARDIOVASCULAR RESEARCH;Cuzzocrea,S; 47(3):537-548 (2000)].

Rat experiments indicate that the anti-oxidant properties of NAC can protect against endothelial dysfunction associated with hyperglycemia in diabetes mellitus [JOURNAL OF CARDIOVASCULAR PHARMACOLOGY; Pieper,GM; 32(1):101-105 (1998)].

NAC can rescue neurons from apoptotic death in the absence of growth factors by activation of the Ras-Extracellular signal Regulated Kinase (**ERK**) pathway, an effect due to direct action on transcription factors by the thiol group, rather than by anti-oxidant effects [THE JOURNAL OF NEUROSCIENCE; Yan,CY; 18(11):4042-4049

(1998)]. GSH (NAC or whey) can promote immune cell clonal expansion, restore natural killer cell activity and induce p53-dependent apoptosis in cancer cells [ANTICANCER RESEARCH; Gustavo, B; 23:1411-1416 (2003)]. NAC can prevent insulin resistance due to high blood glucose, and effect which was attributed to NAC's anti-oxidant action [AMERICIAN JOURNAL OF PHYSIOLOGY; Haber,CA; 285(4):E744-E753 (2003)]. In transgenic mice cells that are deficient in p53 protein (a protein that is mutated in half of cancer cases) increased mutation and chromosome instability was inhibited by NAC [NATURE MEDICINE; Sablina,AA; 11(12):1306-1313 (2005)].

A dose of 1200 mg daily of NAC has significantly reduced (25% versus 79%) influenza-like symptoms in elderly subjects suffering from non-respiratory diseases [EUROPEAN RESPIRATORY JOURNAL; De Flora,S; 10(7):1535-1541 (1997)]. NAC can reduce the inflammatory symptoms of chronic obstructive pulmonary disease by direct inhibition of the pro-inflammatory transcription factor NF-κB, in addition to its GSH-boosting action [EUROPEAN RESPIRATORY JOURNAL; Dekhuijzen, PNR; 23(4):629-636 (2004)]. NAC blocks the inducible form of Nitric Oxide (NO) synthetase from producing inflammatory cytokines, by inhibition of NF-κB activation [FREE RADICAL BIOLOGY & MEDICINE; Pahan,K; 24(1):39-48 (1998)].

NF-κB is normally bound to **IκB** protein in the cytoplasm, but is released to enter the nucleus when infection, oxidative stress or the pro-inflammatory cytokine Tumor Necrosis Factor−alpha (**TNF−α**) causes ubiquitination and subsequent protease degredation of IκB. NF-κB increases transcription of genes coding for TNF−α and IL−1, which can result in a positive feedback loop. NAC blocks TNF−α activation of NF-κB independently of its antioxidant activity by causing structrual changes in the TNF receptor that lower receptor affinity for TNF−α [THE EMBO JOURNAL; Hayakawa,M; 22(13):3356-3366 (2003)]. The TNF−α is so toxic in the absence of GSH that it can kill experimental animals unless NAC is rapidly given as an antidote.

NAC has been used to regenerate oxidative phosphorylation complexes in mitochondria from age-related decline in function by sulfhydryl group action, rather than antioxidant effect [EUROPEAN JOURNAL OF PHARMACOLOGY; Miquel,J; 292:333-335 (1995)]. And NAC protects against radiation damage by a direct radical scavenger action rather than by conversion to glutathione [FREE RADICAL BIOLOGY & MEDICINE; Neal,R; 34(6):689-695 (2003)].

Cysteine in blood plasma has opposing actions on LDL cholesterol. Cysteine can significantly decrease binding of copper ions (97% inhibition) to LDL-cholesterol. But cysteine can also reduce copper (Cu^{2+} to Cu^{+}) and iron -- resulting in increase free-radical damage [ATHEROSCLEROSIS; Patterson, RA; 169:87-94 (2003)]. Although this has been demonstrated in laboratory experiments, it remains to be seen what the significance of this effect could be in a person, given that extracellular cysteine is not stabile. It does raise questions about what could happen in cells in the presence of metal ions, but the evidence suggests that in most circumstances the benefits of elevated glutathione are the overriding factor, perhaps because sulfhydryl compounds like NAC can chelate heavy metal ions. (NAC has been used to treat heavy metal poisoning.) By contrast NAC added to cell culture has been shown to increase oxidative damage to DNA, an effect that can be inhibited by catalase and copper chelation [CARCINOGENESIS; Oikawa,S; 20(8):1485-1490 (1999)].

(For more on glutathione, see AntiOxidant Enzymes.)