

# Central Nervous System Neurotoxicity of Chronic Alcohol Abuse

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**How to cite this article:** Kwok CL. Central Nervous System Neurotoxicity of Chronic Alcohol Abuse. *Asia Pac J Med Toxicol* 2016;2:70-1.

Alcohol has been a popular recreational beverage since early human history. It undoubtedly plays a significant role in the social scene of many different cultures around the world today. For most people, drinking does not lead to dependence or abuse. However, a significant contingent of the population at large inevitably is afflicted by chronic alcoholism. In the United States alone, approximately 14 million Americans meet the diagnostic criteria for alcohol abuse (1). One of the major organs that chronic alcohol intoxication can damage is the brain (2).

Clinical manifestation of neurotoxicity caused by chronic alcohol abuse can vary considerably. Symptoms could vary from mild memory loss, depression, hallucination to full-blown psychosis and development of focal neurological signs. In general, persistence in alcohol abuse leads to gradual deterioration of mental status (as evidenced by increasing severity of dementia and characterized by enlargement of cerebral ventricles) (3). This is then followed by Wernicke's encephalopathy and Korsakoff's psychosis (4).

Oxidative stress is one of the mechanisms, suggested by numerous studies based on rodents, in which alcohol abuse could lead to neurodegeneration. Two transcription factors play a major role in the generation of free radicals in chronic alcohol consumption. They are respectively, nuclear factor kappa-B (known commonly as NFkB) and cAMP responsive element-binding protein (abbreviated as CREB) (5). Initially, when there is elevated concentration of alcohol, adenylyl cyclase activity is enhanced, leading to increased cAMP creation (6). This effect of hyper-stimulation; however, desensitizes the CREB pathway over time. As a result, neurological tissue exposed to chronically elevated alcohol levels would have decreased CREB pathway activity which meant less neuronal protective enzymes being produced (7). Hence, this meant diminished neuronal viability on a background of free radical formation.

Tumor necrosis factor alpha is a cytokine that is produced by a wide variety of cells such as macrophages and adipose tissue cells. Since a major aspect of alcohol metabolism involves the liver, TNF- $\alpha$  is predominantly produced by the

liver before it is released into the circulatory system where it eventually reaches the brain. As the role of TNF- $\alpha$  is immunomodulation (and specifically pro-inflammatory), this causes an up-regulation of the NFkB pathway leading to induction of iNOS (nitric oxide synthase), COX2 (cyclooxygenase) and NADPH oxidase (all of which increase the level of reactive oxygen species) (5, 8).

Another mechanism derived from rodent models is damage of neuronal tissue via inhibition of neural stem cell (NSC) regenerative actions. Studies have shown chronically elevated levels of alcohol causes systemic stress that leads to persistent production of adrenal steroids (such as cortisol) which down-regulates synthesis of nerve growth factor (NGF) and brain-derived neurotrophic factor (bDNF) (9). Since NSCs require these factors for the primary processes of neuronal regeneration (proliferation, differentiation, migration and survival), they either remain dormant in their present state or die (10).

The third contributing element of neuronal tissue injury caused by chronic alcohol abuse is via N-methyl-D-aspartate (NMDA) receptor excitotoxicity. Glutamate is a common neuro-transmitter in the human brain. And under normal circumstances, glutamate would activate NMDA receptors without clinical sequelae. However, with alcohol intoxication, NMDA receptors become sensitized to lower concentrations of glutamate (also known as adaptation) (11). Hence, seizures would often occur in alcoholic patients undergoing withdrawal. Through mechanisms not yet completely understood, highly sensitized NMDA receptors upon being activated by glutamate lead to excessive calcium ion accumulation as well as production of nitrous oxide radicals, both of which lethal to neurons (12).

The fourth and final component of explaining CNS neurotoxicity resulting from chronic alcohol abuse is thiamine deficiency. Thiamine deficiency can be caused by impaired GI uptake due to concomitant intake of alcohol or simply malnutrition associated with poor diet (13). It is becoming a rare clinical manifestation in recent years as a result of established clinical guidelines in the treatment of hospital-admitted alcoholics (patients are now given thiamine

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Received 23 May 2015; Accepted 15 April 2016

supplementation if alcohol abuse is suspected). Of note, alcoholics with severely uncorrected thiamine deficiency would often progress to develop a clinical syndrome called Wernicke's encephalopathy (characterized by ataxia, ophthalmoplegia, and impairment of short-term memory). Left untreated, 80-90% of these patients would then advance to Korsakoff's psychosis (characterized by retrograde/anterograde amnesia and confabulation) (14, 15). From the clinical syndromes described above, it is not surprising to find gross morphological features such as atrophy (or shrinkage) of the cerebellum in post-mortem examination of alcoholics as the cerebellum is responsible for involuntary eye movements and coordination of peripheral limbs (3, 4, 13).

On the cellular level, thiamine (also known as Vitamin B1) is an important cofactor in the catabolism of glucose. Three enzymes require Vitamin B1 to function properly: alpha-ketoglutarate dehydrogenase, transketolase and pyruvate dehydrogenase (4, 13). Transketolase, in particular, is a key enzyme in the pentose phosphate shunt which produces two molecules: ribose-5-phosphate and NADPH. On the one hand, Ribose-5-phosphate is an essential ingredient in the formation of nucleic acids (16). On the other hand, NADPH is vital to the process of replenishing the body's glutathione supply. Glutathione is an antioxidant involved in protecting cells against oxidative stress (17).

Both pyruvate dehydrogenase and alpha-ketoglutarate dehydrogenase participate in different steps of converting glucose to ATP. Decreased activity of these two enzymes due to thiamine deficiency causes lack of energy source for neuronal cells. As a result, there is an increased susceptibility to cellular damage. Alpha-ketoglutarate dehydrogenase, which is a citric acid cycle enzyme, is also involved in the synthesis of neurotransmitters such as glutamate and gamma-aminobutyric acid (GABA) (4, 13, 17). Hence, any change from the ideal rate of neurotransmitter production predisposes to excitotoxicity as mentioned above.

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