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Alcohol-Induced Neuropathy: Exploring the Impact on Molecular Channels and Pain Mechanisms

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ABSTRACT: Neuropathic pain is a severe form of pain that is brought on by dysfunction in the brain and is connected with a number of degenerative alterations in the nervous system. Hyperalgesia and allodynia are two of the main symptoms of pain. Many neurological diseases seen in chronic alcoholics are linked to dietary deficiencies, especially vitamin deficits that are crucial for healthy brain function. The brain may suffer from severe functional impairment and tissue damage, mostly neuronal and vascular, as a result of specific vitamin and nutritional shortages that develop in chronic alcoholics. Moreover, nutritional inadequacies in chronic alcoholics contribute to oxidative stress, metabolic dysfunction, ion channel dysfunction, and neurotransmitter dysfunction. There are numerous molecular mechanisms that contribute to the development of alcohol-induced neuropathy symptoms. A threonine/serine kinase protein kinase C (PKC) regulates various body functions like cell growth and differentiation, release of neurotransmitters, excitation of cellular membranes and in memory. It is necessary to investigate all connected pathways in order to create an effective therapy for neuropath disease.

KEYWORDS: Neuropathic pain, Allium sativum, Induced pain,Alcoholic neuropathy

INTRODUCTION

Neuropathic pain is a severe pain condition associated with various pathological changes in the nervous system and it is occurring due to dysfunction in the brain. The major symptoms associated with ache includes *hyperalgesia* and *allodynia*, *hyperalgesia* is an elevated response painful incentives and *allodynia* is a sore reaction towards non-noxious spurs. Data concluded over the years revealed that approximately 2-3% of the population in the world suffers from neuropathic pain (Hammi *et al.*, 2022). After nicotine and caffeine, alcohol is the third most addictive substance (Guo and Ren, 2010) and it has many chronic effects which can result in early death and increases incidences of serious illness. It had been stated by the International Classification of Disease (10^{th} revision, 1993), alcoholism is a severe medical condition accomplished by a strong and frequent need to use alcohol. Alcoholic neuropathy (AN) is chronic alcohol abuse and damage to the nervous system due to (Yerdelen *et al.*, 2008) damage in primary neurons and demyelination of secondary motor and sensitive fibers (Ludin and Tackmann, 1984).

Alcoholic neuropathy symptoms take several months and years to develop, and are more common in continuous drinkers than in episodic drinkers (Monforte *et al.*, 1995), women being more vulnerable than men (Ammendola *et al.*, 2001). Several reports concluded that approximately 90% of people drink alcohol and about 30% of them develop alcohol disease (Sher, 2006). In the United States, higher consumption of alcohol results in mortality (Mokdad *et al.*, 2000). The condition mainly involves abnormalities in sensory, motor and autonomic functions. The major symptom of alcoholic neuropathy is the sensation of pain (Koike *et al.*, 2001, Koike and Sobue, 2006). Other symptoms associated with alcoholic neuropathy are burning pain, muscle weakness, nausea with or without vomiting, numbness, and pain.

The consumption of ethanol affects the central and peripheral nervous system and other tissues (liver), indirect metabolic changes mediated by malabsorption, and some molecular mechanism (Victor, 1975, Pentney and Quackenbush, 1990, Zou *et al.*, 1993). Ethanol cleaves into acetaldehyde that disrupts the sensory signaling of the brain which result in injury to nerves or tissues leading to the misfiring of neurons that result in painful condition (Campbell and Meyer, 2006). The toxic effect of ethanol on the nervous system and other tissues depletes the proteins in the liver which results in the destruction of protein and lipid metabolism leading to metabolic changes which affect the action of the nervous system. Furthermore, alcohol consumption influences the secretion of pro-inflammatory mediators associated with the protein kinase C (PKC), microglia of the spinal cord, and that affects the nerves (Dina *et al.*, 2000, Narita *et al.*, 2007).

Chronic and Acute Neuropathic pain

Nerve tissue damage indication of neurological disorder is an emotional and unpleasant experience of perception (Merskey and Bogduk, 1994). Pain can be induced by pathological and physiological conditions. The pain initiated in an undamaged nervous system of a healthy patient on exposure to a painful stimulus is called physiological pain (McMahon *et al.*, 1995). Depending upon the severity of the disease pathological pain can be classified into two types namely chronic and acute. Based on the extent of damage in tissue the pathological pain can be further divided into neuropathic pain and inflammatory pain (Scholz and Woolf, 2007; Davis-Taber *et al.*, 2008). The pathological pathways that progress into tissue damage ultimately destruct the tissue and account for the inflammatory pain (Tracey and Walker, 1995; Serhan *et al.*, 2008). As per the International Association for the Study of Pain (IASP) the neuropathic ache is the "pains resulting from disease or damage of the peripheral or central nervous systems, and from dysfunction of the nervous system" (Merskey and Bogduk, 1994). IASP also defined the pain and associated responses (Table 1). Various injuries and disease interventions disturb the central and peripheral nervous system by fabricating the growth of lesions in the somatosensory pathways and producing neuropathic pain (NP) (Figure 1) which has been regarded to be problematic due to its continuous perception in different parts of the body. The pain is resistant to analgesics and can be chronic or severe (Gilron *et al.*, 2006).

Table 1: IASP definitions of pain and its concomitant symptoms

Pain	An unusual sensual and sensitive experience characterized by tissue impairment
Neuropathic pain	Pain instigated by impairment in brain
Allodynia	Pain due to a spurs that do not usually induce throbbing
Hyperalgesia	An unpleasant reaction to incentives stimulus
Hyperpathia	Painful condition associated with atypical pain
Dysesthesia	An irregular sensation
Parasthesia	An unpleasant skin perception such as numbness, tingling, itching or burning

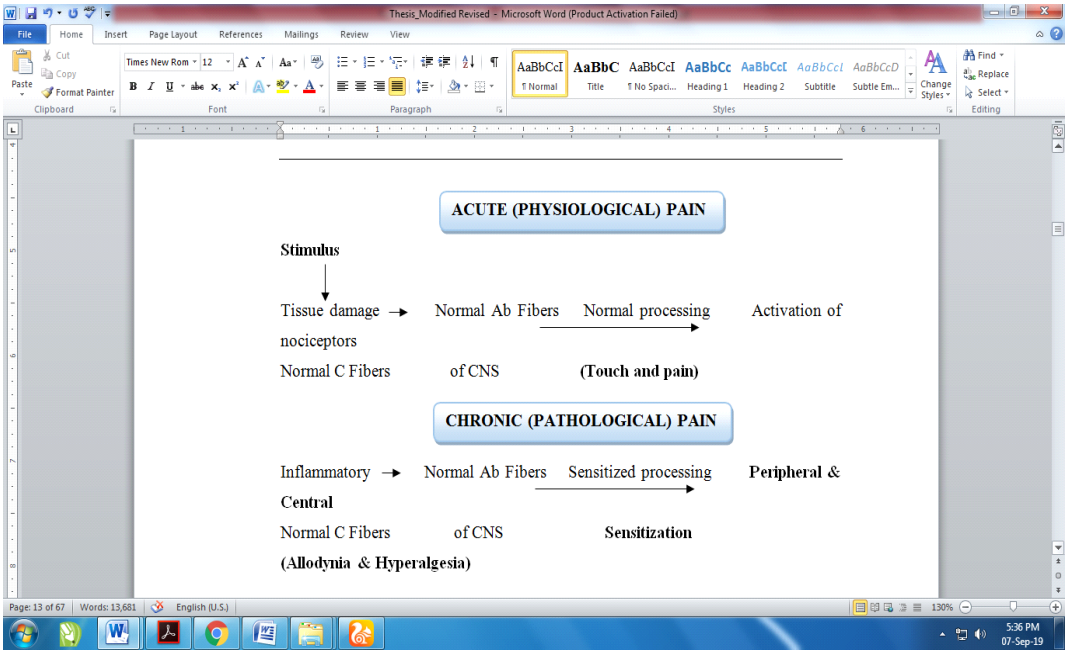

Figure 1: Mechanism of Acute and Chronic Pain

Neuropathic pain (NP) is categorized into two forms, spontaneous pain, and incentive-evoked pain. The former type of NP is long lasting and can be illustrated by dysesthesias and paresthesia's while the latter type of NP is stimulated by chemical, mechanical and thermal methods portraying signs of allodynia and hyperalgesia. Allodynia can be identified as an excruciating response to non-noxious stimuli and is evoked by peripheral stimulation whereas an augmented response to aching stimuli is termed hyperalgesia. Hyperalgesia is further categorized into primary and secondary hyperalgesia. The primary hyperalgesia begins when C-fibers produce sensitization in the injury area while secondary hyperalgesia occurs on the dorsal horn neurons induced sensitization in the surrounding undamaged area (Treede *et al.*, 1992; Campbell and Meyer, 2006).
The onset of symptoms in stimulus independent pain is unexpectedly impulsive and occurs at any moment. C fiberes, Aβ and Aδ lead to the origination of ectopic impulses which further succeed in dysesthesias and paresthesia leading to a drift towards the threshold potential due to unprompted activity of accumulated damaged sodium channels in the affected nerves (Ochoa and Torebjork, 1980; Woolf *et al.*, 1999). A decreased inhibitory input from the central nervous system may also be held accountable for the stimulus-independent pain (Woolf and Costigan, 1999). Mostly in neuropathic pain syndromes, stimulus-independent pain arises in conjunction with stimulus-evoked pain, for instance, mechanical allodynia and pain on burning in complex regional pain syndrome (CRPS) (Cline *et al.*, 1989) and is named Mixed Pain Syndrome.

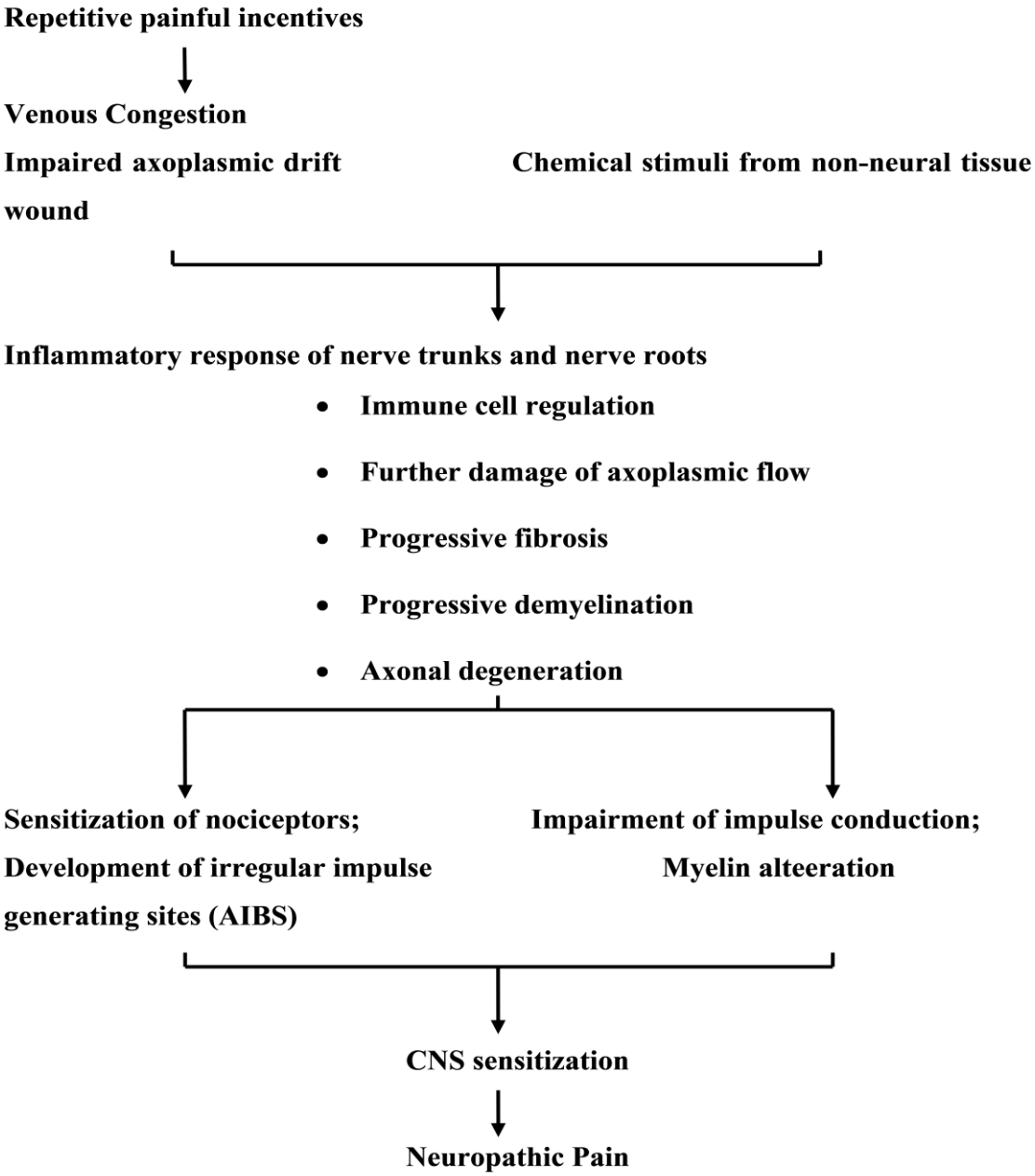

Figure 2: Brief Mechanism of Neuropathic Pain

Alcoholic Neuropathy

Alcohol is a potent cytotoxic agent with a tendency to damage neurons and is the most frequently abused drug in our society. It greatly influences the medical, psychological, economic, social and religious aspects of our life. In measured quantities, alcohol produces beneficial effects (Truelsen *et al.*, 2002; Ganguli *et al.*, 2005) but harms greatly when abused and may even lead to premature deaths and is fatal.

The chronic consumption of alcohol protrudes to a neurological complication disorder called alcoholic peripheral neuropathy characterized with dysesthesias and pain mainly in the lower regions (Ratcliff, 1979; Koike *et al.*, 2001a; Koike and Iijima, 2003). It is also accounted for the degradation of axons in neurons of brain (Yerdelen *et al.*, 2008). Alcoholic neuropathy incorporates primary damage in axons and demyelination of secondary motor and sensory nerve fibers (Ludin and Tackmann, 1984). It arises with segmental thinning or axonal demyelination in small sections for an instant while myelin loss on the peripheral ends (Mawdsley

et al., 1965). Alcoholic neuropathy can be termed nutritional peripheral nervous system (PNS) disorder or metabolic neuropathy hence making its classification lucid.

Clinical symptoms of alcoholic neuropathy

The central nervous system is encircled to produce complex toxic neurological effects on excessive consumption of alcohol (Pentney and Quackenbush, 1990; Zou *et al*., 1993). It fabricates painful neuropathy in peripheral system amidst its analgesic effect in the central system of the body. The alcoholic neuropathy symptoms may take months or years to outshine including anomalous functioning of autonomic, motor and sensory neurons. impaired gait and coordination, burning pain, weak muscles, numbness and nausea with or without vomiting are some of the symptoms expressed in alcoholic neuropathy (Hawley *et al.*, 1982). The foremost and chief symptom of alcoholic neuropathy includes painful sensations in body with burning feeling sometimes (Koike *et al.*, 2001a; Koike and Sobue, 2006). The symptoms may become dreadful with time and may impair gait (Hawley *et al.*, 1982). Certain alternations in transmission and release of neurotransmitters also occur on chronic excessive consumption of alcohol which further disturbs physiological and biochemical processes of the body (Chandler *et al.*, 1997) with modified signaling pathways (Hoek and Kholodenko, 1998).

Neurotransmitters Released

Alcohol overstimulates glutamatergic receptors of the body and induces neurotoxicity (Fadda and Rossetti, 1998; Dodd et al., 2000, Davis and Wu, 2001) by multiple mechanisms. An overexpressed glutamatergic NMDA receptor is observed in animal models with chronic alcoholism (Hu and Ticku, 1995; Nagy, 2004). The augmented transmission of glutamatergic receptors on exposure to chronic alcohol intake causes neuronal death due to hyperexcitation (Choi, 1992; Hoffman et al., 1995). The mechanism of ethanol induced neurotoxicity stimulates glutamatergic receptors which further synthesize reactive oxygen species (ROS), generates nitric oxide and are also involved in apoptotic cell events (Fadda and Rossetti, 1998). Petty et al in a study described that GABA levels are reduced in people on chronic alcohol consumption which leads to a progression of dependence and tolerance to ethanol (Davis and Wu, 2001; Kumar et al., 2004). The functioning of NMDA glutamatergic receptors is modulated by $GABA_A$ receptors and vice versa (Isokawa, 1998; Stobbs et al., 2004). On consumption of alcohol, the transmission of $GABA_A$ receptors is reduced which enhances the transmission of glutamatergic receptors causing the death of neuronal cells on prolonged excitability (Nutt and Glue, 1990; Lovinger, 1993). The activity of voltage gated calcium channels is increased on chronic exposure to ethanol due to amplified number of binding sites in dihydropyridine (Newton et al., 2005; Walter et al., 2000). The consumption of ethanol is also regulated by these channels (Newton et al., 2005). The hyperexcitation of glutamate receptors increases the influx of calcium ions which further recruits and activates Ca-dependent enzymes (Arundine and Tymianski, 2003). Calcium blockers have been observed to diminish neuronal cell death and tend to show neuroprotective effects against NMDA receptors.

The noradrenergic neurons in both peripheral nervous system (Perec et al., 1979; Jaatinen and Hervonen, 1994) and central nervous system (Nutt and Glue, 1990; Hoffman et al., 1995) are overstimulated on prolonged contact with alcohol. Patkar et al. in year 2000 through a study on alcoholics and non-alcoholic individuals evaluated that a higher concentration of noradrenaline was observed in alcoholics as compared to non-alcoholics indicating the presence of more metabolites of norepinephrine in chronic alcoholics (Borg et al., 1983). The dopamine system in mesolimbic system mediates the ethanolic effects in the body (Kiianmaa et al., 2003). Schmidt et al in 1996 through a study depicted association between addiction of ethanol and levels of dopamine in neurotransmission. Brodie (2002) in a study administered ethanol to mouse for 21 days and observed an increased dopaminergic neuron excitation. In a study in 2001 Rothbath et al. reported that on chronic exposure to alcohol for about an year the mesostriatal system of rats showed diminished dopamine

levels. A decline in receptor density of dopamine (D2) in brain with shrunken functions in chronic alcoholics was also observed through various studies (Volkow et al., 1996).

Pathophysiology: Associated pathways

The degradation of neurons induced by ethanol is multifactorial by origin (Charness, 1993). The exact mechanism responsible for alcoholic neuropathy is not lucid though numerous pathophysiological mechanisms are being studied. Chronic consumption of alcohol may lead to deficiency of thiamine and various other nutrients which promote the genesis of neuropathy in alcoholic individuals. The levels of thiamine decrease in the liver due to its reduced absorption from the intestine on consumption of alcohol and converting it into its active form due to phosphorylation (Hoyumpa, 1980; Singleton and Martin, 2001). A dietary imbalance is also recorded in chronic alcoholics. The neurotoxic effects of alcohol have been pinpointed through various recent studies. Rats administered with alcohol showed damaged axonal neurons indicating neuropathy (Bosch, 1979). In humans, the extent of neuropathy depends upon the amount of alcohol consumed indicating a direct dose dependent relationship between neuropathy and ethanol consumption (Monforte *et al.*, 1995; Ammendola *et al.*, 2001).

The various molecular pathways that fabricate alcoholic neuropathy include protein kinase C activation mediated by release of proinflammatory cytokines (Dina *et al.*, 2000), chronic alcohol induced stimulation of spinal cord microglia (Narita *et al.*, 2007), mGlu5 receptor activation in the spinal cord (Figure 4) (Miyoshi *et al.*, 2007), opiodergic neuron induction and glutamate receptors (Narita *et al.*, 2007) induced nerve damage due to pronounced oxidative stress. The elevated oxidative stress in response to chronic consumption of alcohol leads to stimulation of protein kinase C due to genesis of proinflammatory cytokines and reduced threshold of nociception (Dina *et al.*, 2000; Dina *et al.*, 2007). Therefore, neuropathy arises due to multiple factors however the exact pathway is still lucid.

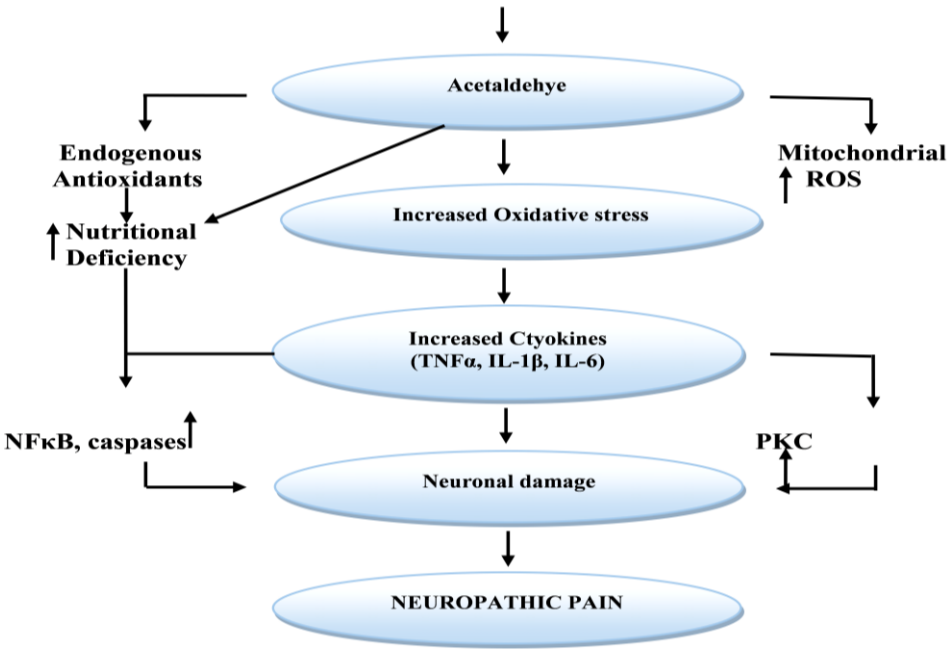

Figure 4: Pathophysiology of Alcoholic Neuropathy

Alcoholic neuropathy associated nutritional factors

The onset of alcohol induced neuropathy is intensified by several risk factors such as insufficient nutrition, thiamine deficiency, direct and indirect toxic effects of alcohol and its metabolites on nerve fibers, and genetic propensity of patients (Hamel and Logigian, 2017). The consumption of alcohol in excess produces fatal effects on different tissues of the body causing metabolic disturbances affecting nervous system the most. Demyelination of motor and sensory neurons accompanied with damage of axons are witnessed in alcoholic

neuropathy (Ludin and Tackmann, 1984). It begins with axonal demyelination of small sections initially and advances to peripheral ends with loss of myelin at later stages (Mawdsley *et al.*, 1965). The decelerated axoplasmic flow and failure of biological functions of proteins and enzymes of axons lead to demyelination and this degeneration can be portrayed as dying back. Alcohol along with its metabolites disturb the neuronal metabolism and hinder metabolic pathways of lysosomes, cytoplasm, nucleus, endoplasmic reticulum and peroxisomes (Kucera et al., 2002). Acetaldehyde dehydrogenase and ethanol dehydrogenase play major role in degrading ethanol. Ethanol in the presence of ethanol dehydrogenase is converted into acetaldehyde which is converted into acetate by a mitochondrial enzyme called acetaldehyde dehydrogenase (Figure 5). The unmetabolised acetaldehyde irreversibly binds to various proteins which further synthesizes cytotoxic proteins that have detrimental effects on our nervous system. A number of cell populations including hepatocytes are also influenced by the synthesized cytotoxic proteins causing liver cirrhosis (Achord, 1995). The proteins utilized for production of energy are depleted on chronic consumption of alcohol which disturbs protein and lipid metabolism alarming neuronal functions. The changes produced are gradual and advance to malabsorption and maldigestion.

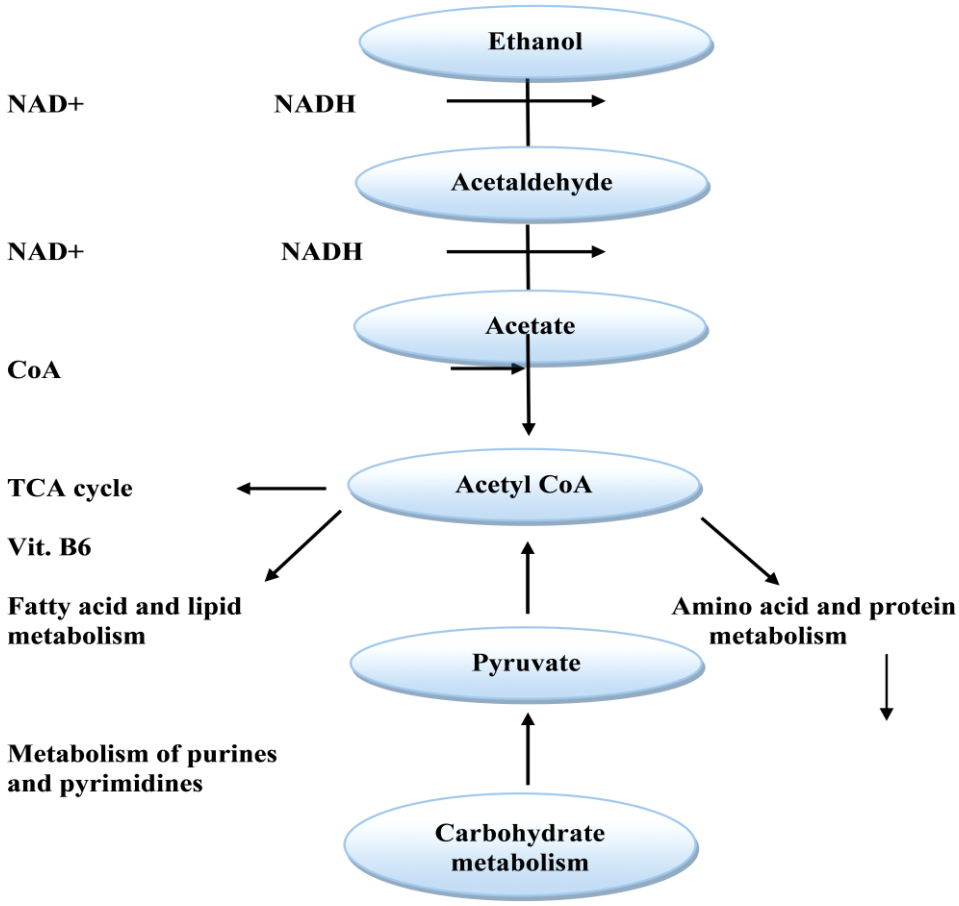

Figure 5: Metabolism of ethanol and its metabolite.

The intake of calories is an added drawback in alcoholic patients. The alcoholic beverages with high calories and low nutritional values are source of calories in these patients. Also as discussed above the energy producing proteins in liver are degraded leading to insufficient intake of proteins on chronic consumption of alcohol and deteriorates this balance. This malnourishment disrupts metabolic pathways and effects the functioning of the nervous system. The main protein that is highly impinged on is neuronal target esterase (NTE) which is very important in the functioning and proliferation of neurons (Glynn, 2000; Moretto, 2000), damage to which protrudes deflected neuronal functioning and decelerated axoplasmic flow indicating neuropathy.

Thiamine Deficiency

There is an active debate over the pathogenesis of alcoholic neuropathy. It has previously been considered in regard to nutritional deficiencies, especially thiamine, exhibited in alcoholics. Thiamine deficiency can cause neuropathy in alcoholic patients and is directly related to persistent alcoholism. The hepatic reserves of thiamine are decreased by ethanol, and it also affects the phosphorylation of thiamine, which turns it into its active form (Singleton *et al.*, 2011). The metabolic demand of thiamine is increased by alcohol. The low intake of nutrients on chronic consumption of alcohol progresses to depleted levels of thiamine. The absorption of thiamine from intestine also drops due to interference of ethanol further cutting down its levels in the body (Cornblath *et al.*, 2001). Many body reactions highly depend upon thiamine therefore deficient thiamine levels impair glycolysis and prevent neurons from maintaining a requisite adenosine triphosphate (ATP) levels and produce neuropathy.

Other Nutritional Factors

Deficiency of vitamins apart from thiamine also produces alcoholic neuropathy. Chronic alcoholism can alter the intake, absorption and utilization of various nutrients such as nicotinic acid, vitamin B2, vitamin B6, vitamin B12, folate or vitamin E. (Koike *et al.*, 2004). Alcoholics' serum levels of vitamin A were substantially lower than those of a control group of healthy individuals (Atukorala *et al.*, 1986). The severity of the liver lesions was correlated with the depression of vitamin A levels, with cirrhotic having the lowest levels. Although drinking less alcohol and for a shorter period of time than male alcoholics, female alcoholics had a more severe impact on their vitamin A levels. Some of the clinical traits include diarrhea, anorexia, hyperkeratotic dermatitis, glossitis, dermatitis and keratoconjuctivitis and vitamin B12 deficiency induced myelopathy though they are not the roots of alcoholic neuropathy (Koike *et al.*, 2004). Even with the provision of other important nutrients, prolonged alcohol use degrades the folate coenzymes and may result in the malabsorption of enterohepatically circulating folates in folate deficit (Blocker and Thenen, 1987).

Direct toxic effects

Role of acetaldehyde

The metabolites of alcohol and alcohol itself have direct fatal toxic effects on the nervous system. Acetaldehyde is the most toxic metabolite of alcohol. It prevents synthesis and depletes levels of glutathione, impairs microtubule, blocks mitochondrial electron transport chain and inhibits the repair of DNA in the liver. On decreased expression of alcohol dehydrogenase the incidence of adducts of acetaldehyde protein in organs that lack synthesis of acetaldehyde has been reported through studies (Masaki *et al.*, 2004). The presence of acetaldehyde may be explained either due to blood flow to the distant organ or microsomal ethanol oxidizing system-induced formation of acetaldehyde (Lieber, 1998). Administering anti-AAAG-specific antibodies can treat neurotoxicity induced by acetaldehyde and its fashioned advanced acetylated end products (AA-AGE) (Takeuchi and Saito, 2005). These verdicts suggest that the acetaldehyde induced neurotoxicity is linked to the progression of alcoholic neuropathy.

Oxidative-nitrosative stress

Oxidative stress plays an imperative part in neuropathic pain animal models. Bosch-Morell *et al*. revealed ethanol induced production of oxidative stress in peripheral nerves of rats (Bosch-Morell et al., 1998). Ethanol on metabolism induces production of reactive oxygen species (ROS) (Ekstrom and Ingelman, 1989), superoxide radical (Boveris, 1983), 1-hydroxylethyl radical (Rashba, 1993), hydroxyl radical (Ingelman and Johansson, 1984) and thiobarbituric acid reactive substances. Free radicals are generated in bulk on chronic consumption of alcohol often linked with hepatic diseases (Ishii *et al.*, 1997). Various experimental studies have demonstrated decreased glutathione levels and increased synthesis of malondialdehyde (MDA) in liver on chronic intake of ethanol (Nordmann *et al.*, 1992). The ruined antioxidant resistance besides synthesis of

oxygen derived free radicals is the key factor for alcohol induced hepatic diseases due to oxidative stress. The transformation of alcohol to acetate with the help of acetaldehyde dehydrogenase in mitochondria of liver cells results in free radical synthesis and generates reactive oxygen species (ROS) (Mayes et al., 1993; Reddy *et al.*, 1999; Charness, 1993). Cytochrome P-450 metabolises ethanol in brain cells and forms ROS (Reddy *et al.*, 1999; Somani and Hussain, 1997). Alcohol dehydrogenase mediated production of NADH and NADH dependent ROS synthesis increases on excessive alcohol administration (Kukielka *et al.*, 1994; Zima *et al.*, 2001). The ROS generated fabricates cellular damage unless neutralized by action of antioxidants system (Reddy *et al.*, 1999; Somani and Hussain, 1997; Zima *et al.*, 2001).

Neuropathic pain can also be induced by nitric oxide (Levy and Zochodne, 2004; Sung *et al.*, 2004). The spinal and central neurons of the body are sensitized by nitric oxide. A very toxic compound named peroxynitrite is produced when deficient superoxide dismutase couples with nitric oxide. Malondialdehyde, a product of lipid peroxidation amplifies in the sciatic nerves of rats administered with a diet containing alcohol. The activity of glutathione peroxidase and glutathione content also decreases in rats fed with ethanol indicating alcohol-induced oxidative stress in a state of pain post-chronic consumption of alcohol.

MOLECULAR MECHANISMS

Role of Protein Kinases

A threonine/serine kinase protein kinase C (PKC) regulates various body functions like cell growth and differentiation, release of neurotransmitters, excitation of cellular membranes and in memory and learning on phosphorylation of several proteins (Miller, 1986; Nishizuka) and subsists in 1 different isoform (Hofmann, 1997; Mochly-Rosen & Kauvar, 1998). The chronic consumption of alcohol phosphorylates and activates PKC thereby sustaining alcohol induced neuropathic pain hence indicating a sharp role of PKC in alcoholic neuropathy. The excited activation of protein kinase C epsilon (PKCε) mediates neuropathic pain in a major way (Aley and Levine, 2002). Both protein kinase A and C regulate nociceptor functions (Ahlgren and Levine, 1994; Khasar, 1999). In a study by Dina et al. mechanical hyperalgesia was induced in rats fed with alcohol by fourth week from initiation which reached its maximum by 10^{th} week (Dina *et al.*, 2007). Mechanical allodynia and thermal hyperalgesia were also present besides it. Injecting non selective or selective PKC inhibitors intradermally attenuated hyperalgesia. Through a western blot analysis it was estimated that the levels of PKC were exceptionally high in dorsal root ganglia of rats administered with high alcohol hence justifying the role of PKCs in nociception advancing to hyperalgesia post chronic alcohol intake (Dina *et al.*, 2000). The threshold of mechanical nociception significantly decreased as witnessed 5 weeks later of excessive intake of alcohol in rats according to study by Miyoshi et al (Miyoshi *et al.*, 2007).

The activation of a calcium permeable ion channel named transient receptor vanilloid potential (TRPV1) which is highly expressed in thin myelinated primary axonal neurons Aδ and unmyelinated C fibers by PKC phosphorylation leads to excitation of neurons producing neuronal toxicity and releasing proinflammatory cytokines (Fitzgerald, 1983; Sakurada *et al.*, 2003). The contribution of PKA is petite as compared to PKC in neuropathic pain.

Role of Glial Cells

The commencement and maintenance of state of pain is controlled by glial cells (DeLeo and Yezierski, 2001; Raghavendra and DeLeo, 2003). The peripheral inflammation and neuropathic pain activate astrocytes, glial cells and microglia (Raghavendra and DeLeo, 2003) by pain related compounds namely substance P, excitatory amino acids and ATP (Julius and Basbaum, 2001; Norenberg, 1994) which led to hyperexcitation of neurons producing chronic inflammation and toxicity. The macrophage antigen complex-1 (Mac-1), phagocytosis and various cytotoxic molecules such as prostaglandins, nitric oxide, ROS and other cell surface markers are up-regulated in activation of microglia (Hopkins and Rothwell, 1995) which further participate in

promoting conditions of chronic pain (DeLeo and Colburn, 1999; Raghavendra and DeLeo, 2003). Narita *et al*. in their study on alcohol-induced neuropathy in the spinal cord of rats further justified their role in decreasing nociceptive effects by treatment with activation of microglia.

Role of Opioidergic System

Narita *et al*. in a study stated that v opioid receptors are disabled on chronic intake of alcohol leading to hyperalgesia even after withdrawal of ethanol. Following excessive administration of ethanol, the PKC activated degraded μ type opioid receptors reducing sensitivity to morphine induced anti-nociception in alcoholic neuropathy.

Role of Caspases

The cysteine proteases named Caspases play fundamental function in inflammation, necrosis and apoptosis. The endogenous proteolytic enzymes systems caspases are activated on translocation of NFκb receptors to the nucleus producing apoptosis (Robbins e*t al.*, 2003; Krebs *et al.*, 1999). The apoptotic process play crucial role in inducing neuropathic pain as recommended by Joseph and Levine (Joseph and Levine, 2004). Besides peripheral neuropathies the effector and activator caspases alongwith TNFα and death receptor ligand contribute in neuropathic pain. The extent of oxidative damage increases on chronic administration of alcohol which aids activation and translocation of PKC and NFκb receptors following to fragmentation of DNA and ultimately escalating to apoptosis induced neuronal death (Jung *et al.*, 2005).

Role of Glutamate

A major excitatory amino acid neurotransmitter named Glutamate contributes highly in major physiological functions of the body. In inflammation induced pain, hyperalgesia and processing of nociception the role of metabotropic glutamate receptors (mGluRs) has been successfully proved (Meller *et al.*, 1996; Young *et al.*, 1997). The upper part of spinal cord has been detected with multiple subtypes of mGluR (Jia *et al.*, 1999; Valerio *et al.*, 1997). The introduction of mGluR agonists intrathecally in rats produced thermal hyperalgesia, nociceptive behavior (Fisher and Coderre, 1996a) and allodynia but the precise cellular mechanism responsible is not yet lucid. The glutamate receptors activate protein kinase C by releasing intracellular calcium ions from stimulation of phospholipase C. Many studies suggest that besides activation of PKC, the mGluR can also trigger various downstream kinases like extracellular signal regulated kinase (ERK) (Peavy and Conn, 1998; Ferraguti *et al.*, 1999). Post inflammation in dirsal horn neurons of rats both ERK1 and ERK2 are activated. (Thomas and Hunt, 1993; Ji *et al.*, 1999). Besides mGluR, ionotropic glutamate receptor also take part in regulation of alcohol induced neuropathic pain. On conditions of chronic alcoholism, a subunit of NMDA receptors was increased in spinal cord of rats as revealed by Narita et al. that concentration of calcium and cAMP increased on NMDA glutamate receptor phosphorylation further activating protein kinase C (PKC) (Campbell and Meyer, 2006). The generation of nitric oxide synthase is promoted by NMDA receptor which further promotes release of various other neuropeptides from the sting fibers. This signaling cascade brings about pain.

CONCLUSION

Alcoholic Neuropathy is a chronic disease produced by ingestion of 10g/kg of 35% v/v ethanol two times a day (Tiwari *et al.*, 2009). The consumption of ethanol was responsible for the development of neuropathic pain (Narita *et al.*, 2007) and it was developed in a duration of nine weeks with estimation of biochemical parameters on 10^{th} week. Alpha-tocopherol is a vitamin help in generating neurodegenerative effect of alcohol ingestion. It has been stated that α-tocopherol inhibit the excess formation of nitric oxide in the brains of diabetic rodents (Tiwari *et al.*, 2009), thus α-tocopherol exhibit anti-nociceptive activity by increasing oxidative stress level that leads the downregulating the effect of protein kinase C (PKC). Threonine/serine

kinase PKC regulates various body functions like cell growth and differentiation, release of neurotransmitters, excitation of cellular membranes and in memory and learning on phosphorylation of several proteins (Miller, 1986; Nishizuka). It is necessary to investigate all connected pathways in order to create an effective therapy for neuropath disease.

REFERENCES

1. Adams, R.D. and Victor, M. Principles of Neurology. Fifth edition. *McGraw- Hill Inc.*, 1993, 12:1386.
2. Agar E, Demir S, Amanvermez R, Bosnak M, Ayyildiz M, Celik C. The changes in lipid peroxidation and GSH levels in the cerebellum of rats induced by ethanol consumption are prevented by vitamin E. *Neurosci Res Commun.*, 2000, 27:191–197.
3. Ahlgren SC, Levine JD. Protein kinase C inhibitors decrease hyperalgesia and C-fiber hyperexcitability in the streptozotocin-diabetic rat. *J Neurophysiol*, 1994, 72: 684–92.
4. Aley KO, Levine JD. Different peripheral mechanisms mediate enhanced nociception in metabolic/toxic and traumatic painful peripheral neuropathies in the rat. *Neuroscience*, 2002, 111:389–97.
5. Ammendola A, Tata MR, Aurilio C, Ciccone G, Gemini D, Ammendola E, Ugolini G, Argenzio F. Peripheral neuropathy in chronic alcoholism: a retrospective cross-sectional study in 76 subjects. *Alcohol Alcohol*, 2001,36:271–75.
6. Arundine M, Tymianski M. Molecular mechanisms of calcium-dependent neurodegeneration in excitotoxicity. Cell calcium. 2003;34(4-5):325-37.
7. Atukorala, T.M.S., Herath, C.A. and Ramachandran, S. Zinc and vitamin A status of alcoholics in a medical unit in Sri Lanka. *Alcohol and alcoholism*,1986, *21*(3),269-275.
8. Blocker, D.E. and Thenen, S.W. Intestinal absorption, liver uptake, and excretion of 3H-folic acid in folic acid-deficient, alcohol-consuming nonhuman primates. *The American journal of clinical nutrition*, 1987, *46*(3),503-510.
9. Bosch EP, Pelham RW, Rasool CG, Chatterjee A, Lash RW, Brown L, Munsat TL, Bradley WG. Animal models of alcoholic neuropathy: morphologic, electrophysiologic, and biochemical findings. *Muscle Nerve*, 1979, 2:133–144.
10. Bosch-Morell F,Martinez-Soriano F, Colell A, Fernandez-Checa JC, Romero FJ. Chronic ethanol feeding induces cellular antioxidants decrease and oxidative stress in rat peripheral nerves: effect of *s*-adenosyl-l-methionine and *n*-acetyl-l-cysteine. *Free Radic Biol Med* ., 1998, 25:365–68.
11. Boveris A, Fraga CG, Varsavsky AI, Koch OR. Increased chemiluminescence and superoxide production in the liver of chronically ethanol-treated rats. *Arch Biochem Biophys., 1983,* 227:534-541.
12. Campbell, J.N. and Meyer, R.A. "Mechanisms of Neuropathic Pain." *Neuron.*, 2006, 52: 77–92.
13. Chandler, L.J.; Sutton, G.; Norwood, D.; Sumners, C.; and Crews, F.T. Chronic ethanol increases NMDA-stimulated nitric oxide formation but not receptor density in cultured cortical neurons. *Mol Pharmacol* 1997, 51:733–740.
14. Charness ME .Brain lesions in alcoholics. *Alcohol Clin Exp Res.*, 1993, 17:2-11.
15. Choi D.W. Excitotoxic cell death. *J Neurobiol.*, 1992, 23:1261-1276.
16. Cline MA, Ochoa J, Torebjork HE. Chronic hyperalgesia and skin warming caused by sensitized C nociceptors. *Brain*. 1989;112:621-647.
17. Davis K.M. and Wu J.Y. Role of glutamenergic and GABAergic systems in alcoholism. *J Biomed Sci., 2001,* 8:7-19.
18. Davis-Taber, R., Baker, S., Lehto, S.G., Zhong, C., Surowy, C.S., Scott, V.E. and Honore, P. Central pituitary adenylate cyclase I receptors modulate nociceptive behaviors in both inflammatory and neuropathic pain states. *J. Pain*, 2008, 9: 449-456.

19. DeLeo JA and Colburn RW. Proinflammatory cytokines and glial cells: their role in neuropathic pain. *Cytokines and Pain* (Watkins LR and Maier SF), 1999, 159–181.
20. DeLeo JA and Yezierski RP. The role of neuroinflammation and neuroimmune activation in persistent pain. *Pain,* 2001, 90:1–6.
21. Dina OA, Barletta J, Chen X, Mutero A, Martin A, Messing RO, Levine JD. Key role for the epsilon isoform of protein kinase C in painful alcoholic neuropathy in the rat. *J Neuroscience,* 2000, 20:8614–8619.
22. Dina OA, Gear RW, Messing RO, Levine JD. Severity of alcohol-induced painful peripheral neuropathy in female rats: role of estrogen and protein kinase (A and C epsilon). *J Neuroscience*, 2007, 145: 350–6.
23. Dodd P.R., Beckmann A.M., Davidson M.S. and Wilce P.A. Glutamate mediated transmission, alcohol and alcoholism. *Neurochem Int.,* 2000, 37:509-533.
24. Ekstrom G, Ingelman-Sundberg M. Rat liver microsomal NADPH-supported oxidase activity and lipid peroxidation dependent on ethanol-inducible cytochrome P-450. *Biochem Pharmacol,* 1989, 38:1313-1319.
25. Fadda F and Rossetti ZL. Chronic ethanol consumption: from neuroadaptation to neurodegenration. *Prog Neurobiol.,* 1998, 56:385-431.
26. Ferraguti F, Baldani-Guerra B, Corsi M, Nakanishi S, Corti C. Activation of the extracellular signal-regulated kinase 2 by metabotropic glutamate receptors. *Eur J Neurosci*., 1999, 11:2073–2082.
27. Fisher K, Coderre TJ. Comparison of nociceptive effects produced by intrathecal administration of mGluR agonists. *NeuroReport*, 1996a, 7:2743–2747.
28. Fitzgerald, M. Capsaicin and sensory neurones: A review. *Pain.,* 1983, 15, 109–130.
29. Ganguli M, Vander Bilt J, Saxton JA, Shen C, Dodge HH. Alcohol consumption and cognitive function in late life: a longitudinal community study. *Neurology,* 2005, 65:1210–7.
30. Gilron, I., Watson, C.P., Cahill, C.M. and Moulin, D.E. Neuropathic pain: a practical guide for the clinician. *Canadian Medical Association Journal,* 2006, 102:1473-1479.
31. Glynn P. Neural development and neurodegeneration: two faces of neuropathy target esterase. *Prof Neurobiol,* 2000, 61 (1):61-74.
32. Guo R, Ren J. Alcohol and acetaldehyde in public health: from marvel to menace. International journal of environmental research and public health. 2010 Apr;7(4):1285-301.
33. Hamel, J., & Logigian, E. L. Acute nutritional axonal neuropathy. *Muscle & Nerve*,2018, *57*(1), 33-39.
34. Hammi C, Yeung B. Neuropathy. InStatPearls [Internet] 2022, StatPearls Publishing
35. Hammi, Claudia, and Brent Yeung. "Neuropathy." In StatPearls [Internet]. StatPearls Publishing, 2022. Achord JL. Alcohol and the liver. *Sci Amer Sci Med.*,1995, 2:16–25.
36. Hawley RJ, Kurtzke JF, Armbrustmacher VW, Saini N, Manz H. The course of alcoholic-nutritional peripheral neuropathy. *Acta Neurol Scand.,* 1982, 66:582–89.
37. Hawley, R.J., Kurtzke, J.F., Armbrustmacher, V.W., Saini, N. and Manz, H. The course of alcoholic-nutritional peripheral neuropathy. *Acta Neurologica Scandinavica,* 1982,*66*(5), pp.582-589.
38. HerHoek J B and Kholodenko B N. The intracellular signaling network as a target for ethanol. *Alcohol: Clin Exp Res*, 1998, 22:224S.
39. Hoffmann P.L., Iorio K.R., Snell L.D. and Tabakoff B. Attenuation of glutamate-induced neurotoxicity in chronically ethanol-exposed cerebellar granule cells by NMDA receptor antagonists and ganglioside. *Alcohol Clin Exp Res.,* 1995, 19:721-726.
40. Hofmann J. The potential for isoenzyme-selective modulation of protein kinase C. *Faseb J.*, 1997, 11:649-669.

41. Hopkins SJ and Rothwell NJ. Cytokines and the nervous system. I. Expression and recognition. *Trends Neurosci.*,1995, 18:83–88.
42. Hoyumpa AM Jr. Mechanisms of thiamin deficiency in chronic alcoholism. *Am J Clin Nutr.*, 1980, 33:2750–2761.
43. Hu X.J. and Ticku M.K. Chronic ethanol treatment upregulates the NMDA receptor function and binding in mammalian cortical neurons. *Brain Res Mol.*, 1995, 30:347-356.
44. Ingelman-Sundberg M，Johansson I. Mechanisms of hydroxyl radical formation and ethanol oxidation by ethanol-inducible and other forms of rabbit liver microsomal cytochromes P-450. *J Biol Chem.*,, 1984, 259:6447-6457.
45. Ishii H, Kurose I, Kato S. Pathogenesis of alcoholic liver disease with particular emphasis on oxidative stress. *J Gastroenterol Hepatol.*, 1997,12:S272-S282.
46. Isokawa M. Modulation of $GABA_A$ receptor-mediated inhibition by postsynaptic calcium in epileptic hippocampal neurons. *Brains Res.*, 1998, 784:347-350.
47. Ji RR, Baba H, Brenner GJ, Woolf CJ. Nociceptive-specific activation of ERK in spinal neurons contributes to pain hypersensitivity. *Nat Neurosci*., 1999, 2:1114 –1119.
48. Jia H, Rustioni A, Valtschanoff JG. Metabotropic glutamate receptors in superficial laminae of the rat dorsal horn. *J Comp Neurol.*, 1999, 410: 627–42.
49. Joseph EK, Levine JD. Caspase signalling in neuropathic and inflammatory pain in the rat. *Eur J Neurosci.*, 2004, 20:2896–902.
50. Julius D, Basbaum AI. Molecular mechanisms of nociception. Nature 2001, 413: 203–10.
51. Jung ME, Gatch MB, Simpkins JW. Estrogen neuroprotection against the neurotoxic effects of ethanol withdrawal: potential mechanisms. *Exp Biol Med.*, 2005, 230: 8–22.
52. Khasar SG, Lin YH,Martin A, Dadgar J,McMahon T,Wang D, Hundle B, Aley KO, Isenberg W,McCarter G, Green PG, Hodge CW, Levine JD,Messing RO. A novel nociceptor signaling pathway revealed in protein kinase C epsilon mutant mice. *Neuron.*,1999, 24: 253–60.
53. Koike H and Sobue G. Alcoholic neuropathy. *Curr Opin Neurol*., 2006, 19: 481–6.
54. Koike H, Iijima M, Mori K, Hattori N, Ito H, Hirayama M, Sobue G. Postgastrectomy polyneuropathy with thiamine deficiency is identical to beriberi neuropathy. *Nutrition*, 2004, 20: 961–6.
55. Koike H, Iijima M, Sugiura M,Mori K, Hattori N, Ito H, Hirayama M, Sobue G. Alcoholic neuropathy is clinicopathologically distinct from thiamine-deficiency neuropathy. *Ann Neurol.*, 2003, 54:19–29.
56. Koike H,Mori K,Misu K, Hattori N, Ito H, Hirayama M, Sobue G. Painful alcoholic polyneuropathy with predominant small-fiber loss and normal thiamine status. *Neurology.*, 2001a, 56: 1727–32.
57. Krebs JF, Armstrong RC, Srinivasan A, Aja T,Wong AM, boy A, Sayers R, Pham B, Vu T, Hoang K, Karanewsky DS, Leist C, Schmitz A,Wu JC, Tomaselli KJ, Fritz LC. Activation of membrane-associated procaspase-3 is regulated by Bcl-2. *J Cell Biol*., 1999, 144: 915–26.
58. Kucera P, Balaz M, Varsik P, Kurca E. Pathogenesis of alcoholic neuropathy. *Bratisl Lek Listy*., 2002, 103:26–9.
59. Kukielka E, Dicker E, Cederbaum AI. Increased production of reactive oxygen species by rat liver mitochondria after chronic ethanol treatment. *Archives Biochemistry Biophysics*, 1994, 309:377-86.
60. Kumar S., Fleming R.L. and Morrow A.L. Ethanol regulation of gamma-aminobutyric acid A receptors: genomic and nongenomic mechanisms. *Pharmacol Ther.*, 2004, 101:211-226.
61. Levy D, Zochodne DW. NO pain: potential roles of nitric oxide in neuropathic pain. *Pain Pract.*, 2004, 4:11–8.
62. Lieber CS. Hepatic and other medical disorders of alcoholism: from pathogenesis to treatment. *J Stud Alcohol*, 1998, 59:9–25.

63. Lovinger D.M. Excitotoxicity and alcohol related brain damage. *Alcohol Clin Exp Res.,* 1993, 17:19-27.
64. Ludin HP and Tackman W. Polyneuropathien. *Stuttgart--New York, George Thieme Verlag*, 1984, 250-255.
65. Martin, P. R. "Molecular mechanisms of thiamine utilization." *Current molecular medicine*, 2001, 1, 197-207.
66. Masaki T,Mochizuki H,Matsushita S, Yokoyama A, Kamakura K, Higuchi S. Association of aldehyde dehydrogenase-2 polymorphism with alcoholic polyneuropathy in humans. *Neurosci Lett.,* 2004, 363:288–90.
67. Mawdsley C and Mayer RF, C.; Mayer, R. F. "Nerve Conduction in Alcoholic Polyneuropathy". *Brain; a journal of neurology*, 1965, 88: 335–356.
68. McMahon, S.B., Dmitrieva, N. and Koltzenburg, M. Visceral Pian. *Br. J. Anaesth.,* 1995, 75:132-144.
69. Meller ST, Dykstra C, Gebhart GF. Acute thermal hyperalgesia in the rat is produced by activation of *N*-methyl d-aspartate receptors and protein kinase C and production of nitric oxide. *Neuroscience*, 1996, 71: 327–35.
70. Merskey H, Bogduk N, eds. *Classification of chronic pain.* Seattle: IASP Press, 1994.
71. Miller, R.J. Protein kinase C: a key regulator of neuronal excitability? *Trends Neurosci.,* 1986, 9:538-541.
72. Miyoshi K, Narita M, Takatsu M, Suzuki T. mGlu5 receptor and protein kinase C implicated in the development and induction of neuropathic pain following chronic ethanol consumption. *Eur J Pharmacol.*, 2007, 562: 208–11.
73. Mochly-Rosen D. & Kauvar L.M. Modulating protein kinase C signal transduction. *Adv. Pharmacol.*, 1998, 44:91-145.
74. Mokdad AH, Marks JS, Stroup DF, Gerberding JL. Actual causes of death in the United States, 2000. Jama. 2004 Mar 10;291(10):1238-45.
75. Monforte, R., Estruch, R. and Valls-Sole, J. Autonomic and peripheral neuropathies in patients with chronic alcoholism. A dose-related toxic effect of alcohol. *Archives of Neurology*, 1995, 52:45–51.
76. Moretto A. Promoters and promotion of axonopathies. *Toxicol Lett.,* 2000, 17:112-133.
77. Nagy J. Renaissance of NMDA receptor antagonists: do they have a role in the pharmacotherapy for alcoholism? *Idrugs.,* 2004, 7:339-350.
78. Narita M,Miyoshi K, Narita M, Suzuki T. Involvement of microglia in the ethanol-induced neuropathic pain-like state in the rat. *Neurosci Lett.,* 2007, 414: 21–5.
79. Newton PM, Tully K, McMahon T, Connolly J, Dadgar J, Treistman SN, Messing RO. Chronic ethanol exposure induces an N-type calcium channel splice variant with altered channel kinetics. FEBS letters. 2005;579(3):671-6.
80. Nordmann R, Ribiere C, Rouach H. Implication of free radical mechanisms in ethanol-induced cellular injury. *Free Radic Biol Med., 1992,* 12:219-240.
81. Norenberg ND. Astrocyte responses to CNS injury. J Neuropathol Exp Neurol., 1994; 53: 213–20.
82. Nutt D.J. and Glue P. Neuropharmacological and clinical aspects of alcohol withdrawal. *Ann Med.*, 1990, 22:275-281.
83. Ochoa J and Torebjork HE. Paraesthesiae from ectopic impulse generation in human sensory nerves. *Brain*, 1980, 103:835– 854.
84. Peavy RD, Conn PJ. Phosphorylation of mitogen-activated protein kinase in cultured rat cortical glia by stimulation of metabotropic glutamate receptors. *J Neurochem.,* 1998, 71:603– 612.

85. Pentney RJ and Quackenbush LJ. Dendritic hypertrophy in Purkinje neurons of old Fischer 344 rats after long-term ethanol treatment. *Alcohol Clin Exp Res.*, 1990, 14:878–886.
86. Raghavendra V and DeLeo JA. The role of astrocytes and microglia in persistent pain, in Non-Neuronal Cells in the Nervous System: Function and Dysfunction. *Elsevier*, Amsterdam, in press., 2003.
87. Rashba Step J, Turro NJ, Cederbaum AI. Increased NADPH- and NADH-dependent production of superoxide and hydroxyl radical by microsomes after chronic ethanol treatment. *Arch Biochem Biophys.*, 1993, 300:401-408.
88. Ratcliff EV. Alcoholic neuropathies. *Aust Fam Physician*., 1979, 8:171–7.
89. Reddy SK, Husain K, Schlorff EC, Scott RB, Somani SM. Dose response of ethanol ingestion on antioxidant defense system in rat brain subcellular fractions. *Neurotoxicology*, 1999, 20: 977-87.
90. Robbins MA,Maksumova L, Pocock E, Chantler JK. Nuclear factor-kappa B translocation mediates double-stranded ribonucleic acid-induced NIT-1 beta-cell apoptosis and up-regulates caspase-12 and tumor necrosis factor receptor-associated ligand (TRAIL). *Endocrinology*, 2003, 144: 4616–25.
91. Sakurada, T., Matsumura, T., Moriyama, T., Sakurada, C., Ueno, S. and Sakurada, S. Differential effects of intraplantar capsazepine and ruthenium red on capsaicin induced desensitization in mice . *Pharmacol. Biochem. and Behav.*, 2003, 75:115-121.
92. Scholz, J. and Woolf, C.J. The neuropathic pain triad: neurons, immune cells and glia. *Nat Neurosci.*, 2007, 10: 13631-1368.
93. Serhan. C.N., Chiang, N. and Van Dyke, T.E. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat. Rev. immunol.*, 2008, 8: 349-361.
94. Sher L. Alcohol consumption and suicide. Qjm. 2006 Jan 1;99(1):57-61.
95. Singleton CK, Martin PR. Molecular mechanisms of thiamine utilization. *Curr Mol Med*., 2001, 1:197–207.
96. Somani SM, Husain K. Interaction of exercise training and chronic ethanol ingestion on antioxidant system of rat brain regions. *JAppl Toxicol*., 1997, 7:329-36.
97. Stobbs S.H., Ohran A.J., Lassen M.B., Allison D.W., Brown J.E. and Steffensen S.C. Ethanol suppression of ventral tegmental area GABA neuron electrical transmission involves N-methyl-D-aspartate receptors. *J Pharmacol Exp Ther.*, 2004, 311:282-289.
98. Sung CS,Wen ZH, Chang WK, Ho ST, Tsai SK, Chang YC, Wong CS. Intrathecal interleukin-1beta administration induces thermal hyperalgesia by activating inducible nitric oxide synthase expression in the rat spinal cord. *Brain Res.*, 2004, 1015:145–53.
99. Takeuchi M and Saito T. Cytotoxicity of acetaldehyde-derived advanced glycation end-products (AA-AGE) in alcoholic-induced neuronal degeneration. *Alcohol Clin Exp Res*.,2005, 29:220.
100. Tiwari V, Kuhad A, Chopra K. Suppression of neuro-inflammatory signaling cascade by tocotrienol can prevent chronic alcohol-induced cognitive dysfunction in rats. *Behav Brain Res.*, 2009, 203:296–303.
101. Thomas K, Hunt S. The regional distribution of extracellularly regulated kinase-1 and kinase-2. *Neuroscience*, 1993, 56:741–757.
102. Tracey, D.J. and Walker, J.S. Pain due to nerve damage: are inflammatory mediators involved? *Inflamm. Res.*, 1995, 44: 407-411.
103. Treede, R.D., Meyer, R.A., Raja, S.N. and Campbell, J.N. Peripheral and central mechanism of cutaneous hyperalgesia. *Prog. Neurobiol*., 1992, 38: 397-421.
104. Truelsen T, Thudium D, Gronbaek M. Amount and type of alcohol and risk of dementia: the Copenhagen City Heart Study. *Neurology*, 2002, 59:1313–9.

105. Valerio A, Paterlini M, Boifava M,Memo M, Spano P. Metabotropic glutamate receptor mRNA expression in rat spinal cord. *Neuroreport*., 1997, 8:2695–9.
106. Victor, M. Polyneuropathy due to nutritional deficiency and alcoholism. *Saunders*, London, 1975.
107. Walter HJ, McMahon T, Dadgar J, Wang D, Messing RO. Ethanol regulates calcium channel subunits by protein kinase C δ-dependent and-independent mechanisms. Journal of Biological Chemistry. 2000;275(33):25717-22.
108. Woolf CJ, Costigan M. Transcriptional and posttranslational plasticity and the generation of inflammatory pain. *Proc Natl Acad Sci USA*.1999; 96:7723–7730.
109. Yerdelen D, Koc F, Uysal H. Strength-duration properties of sensory and motor axons in alcoholic polyneuropathy. *Neurol Res*. 2008.
110. Young MR, Fleetwood-Walker SM, Dickinson T, Blackburn-Munro G, Sparrow H, Birch PJ, Bountra C. Behavioural and electrophysiological evidence supporting a role for group I metabotropic glutamate receptors in the mediation of nociceptive inputs to the rat spinal cord. *Brain Res.*,1997, 777:161–9.
111. Zima T, Fialova L, Metsek O, Janebova M, Crkovska J, Malbohan I. Oxidative stress, metabolism of ethanol and alcohol-related diseases. *Journal of Biomedical Science*, 2001, 8:59-70.
112. Zou J, Rabin RA, Pentney RJ. Ethanol enhances neurite outgrowth in primary cultures of rat cerebellar macroneurons. *Brain Res Dev Brain Res*., 1993, 72:75–84.