

An Insight on the Effect of Acrylamide Toxicity on Neurodegenerative Disorder via Alteration in Circadian Rythm

Saluja D and Singh A*

Department of pharmacology, ISF College of Pharmacy, India

***Corresponding author:** Arti Singh, Department of pharmacology, ISF College of Pharmacy, Moga-142001, India, Email: artiniper@gmail.com

Editorial

Volume 2 Issue 1

Received Date: September 17, 2019

Published Date: October 09, 2019

Introduction

Acrylamide (2- propenamide) is a monomer with melting point 84.5° C and boiling point 125° C. It is a colorless and odorless crystalline solid formed by acylonitrile hydration [1]. Acrylamide has molecular formula $CH_2=CH-C=O-NH_2$ with molecular weight of 71.08. It highly soluble in water (2155 g/L water at 30° C) and other polar solvents like methanol, ethanol, and acetone. It is almost insoluble in non-polar solvents such as carbon tetrachloride [2].

Acrylamide toxicity is one the most popular public health issue because it is reported to show neurotoxicity, reproductive toxicity, genotoxicity and carcinogenicity [3]. Public are directly or indirectly highly exposed to acrylamide as it is formed during roasting, frying and baking of food through the process called Millard reaction [4].

Circadian rhythm is an oscillator form that has a cycle of about 24 hours and regulates a range of physiological and metabolic processes [5]. Sleeping in the evening and being awake in the daytime is an instance of a circadian rhythm related to light. In most living things, including animals, crops, and many small microbe, circadian rhythm are discovered. Circadian clock in the brain synchronize all the biological clocks in a living thing. In vertebrate animals, including humans, the master clock is a group of about 20,000 nerve cells that form a structure called the suprachiasmatic nucleus, or SCN. The SCN is located in a part of the brain called the hypothalamus and receives direct input from the eyes [6].

Circadian rhythm disorders are caused by a chronic or periodic pattern of sleep and wake disruption owing to circadian clock dysfunction or aberrant endogenous circadian rhythm with externally imposed social and

work cycles, leading in clinically important functional impairments [7].

Through this article we want to explain the role acrylamide as a toxin which alter the circadian rhythm and alteration in circadian rhythm leads to many clinical complications.

Acrylamide Causes Reprogramming of Brain Circadian Clock

Acrylamide is the toxin produced through millard reaction during processing of food at high temperature in the foods containing asparagin and glucose [4]. Human circadian clock is at the risk through the exposure of acrylamie. Acrylamide blocked the expression of circadian proteins through the suppression of AKT phosphorylation or oxidative stress, as acrylamide therapy raises expressions of the mitochondrial dynamic genes and affected the mitochondrial morphology at night phase [5].

Circadian rhythms are regulated by key circadian genes, such as Bmal1, Clock and Pers (1-3) but the mRNA expression of Clock and Bmal1 is highest during the night and lower at light phase [8]. Acrylamide exposure resulted in a reduced expression of Bmal1 and Clock, particularly at night, suggesting the acrylamide is subjective to post- transcriptional regulation on circadian clock. These events causes mitochondrial swollen at night which leads to apoptosis, alteration in mitochondrial dynamic (fission, fusion, and mitophagy) and increase oxidative stress during night as these mitochondrial events are regulated in rhythmic manner by Bmal1 [5]. Further all the functions regulated by the circadian clock got disrupted, which further leads to several central and peripheral disorders some are discussed below.

Effect of Acrylamide on Memory Formation via Circadian Rhythm

ACR-triggered neurotoxicity related to circadian clock. Treatment with acrylamide induced suppression of circadian related protein expression which results in circadian disorders. Circadian rhythm regulates memory or cognitive functions (complex thinking and memory formation) [9]. That's why in jet lag disorder we experience memory impairment, cognitive disorder concentration difficulty and insomnia because jet lag causes alteration in circadian rhythm [10]. As circadian rhythm is not exclusive to SCN, forebrain and hippocampus also contain circadian genes and these area are responsible for memory formation. Circadian proteins (Bmal 1 and Clock) expression in prefrontal cortex and hippocampus were also blocked by acrylamide therapy [9]. This results in cognitive dysfunction due to acrylamide treatment and alteration in circadian rhythm.

Acrylamide treatment itself also elevate the neurodegeneration in cortex and hippocampus area of the brain as acrylamide disrupt the blood brain barrier and blood cerebrospinal fluid barrier and reaches the brain areas. Acrylamide also induces tau- phosphorylation and p- CREB reduction that results in spatial memory impairment [11].

Effect of Acrylamide on Neuroinflammation via Circadian Rhythm

Acrylamide stimulate brain inflammation reaction via affecting the intestinal barrier integrity and increasing the level of circulating LPS which as a result increase the level of cytokines such as TNF, IL-1 AND IL-6 in liver, adipose tissue and brain [12]. The intestinal barrier is formed of epithelial cell layers and semi-permeable mucosal membrane strengthened by tight junction proteins-occludin and claudin-1. These tight junction proteins occluding and claudin-1 are the control of circadian rhythm. In day time they reach the peak and at night they drop to a nadir. A circadian protein Clock and Bmal 1 binds to the E-box in the occludin and claudin-1 promoter regions and influence their transcriptional responses. Occludin and claudin-1 protein expression are higher at ZT4 that at ZT16 [13]. Acrylamide diet suggested causing an intestinal barrier defect. Acrylamide diet reduced the expression of occludin protein, causes gut permeability and increased the content of LPS and pro-inflammatory factors in the gut and serum at night, it was noted that LPS could aggravate the neurogenic inflammation and leads to decreased concentration of BDNF [14]. This

suggest that acrylamide treatment exhibit more neurotoxicity at night. This neurotoxicity is a result of disruption of gut brain axis by acrylamide through circadian rhythm.

Circadian Rhythm and Neurodegenerative Diseases

As circadian rhythm is the physiological and behavioral cycle of around 24 hours. So therefore any interruption of this scheme may adversely impact the quality of sleep, alertness, motor control, cognitive performance, mental health and metabolism. Many of these activity become impaired in neurodegenerative disorders like Parkinson disease (PD), Alzheimer disease (AD), Huntington disease (HD), where neurodegenerative mechanism affect several brain areas, including circadian nuclei and sleep regulation [15]. Depression and schizophrenia are also reported in more than 80% of patients with sleep abnormality because circadian timing is dependent on various neurotransmitter systems [16].

Alzheimer disease is clinically defined by a gradual cognitive decrease. Circadian rhythm dysfunction is prevalent in AD patients has a significant effect on quality of life. It is also one of the most significant variables that lead to the systematization of individual to AD patient. In AD patients the circadian disturbances are similar to those seen in ordinary aged person, but are more serious and identifiable. A nocturnal sleep period delay is a typical indicator of circadian rhythm disturbance in AD, and these modifications boost with length and progression of the disease. Another clinical finding of involvement of circadian disturbances in AD is that, during the night phase, AD patients are more active than healthy checks [15].

Parkinson disease is another most prevalent neurodegenerative disorder, with cardinal characters resulting from dopaminergic neuronal degeneration within substantia nigra, includes tremor, stiffness, bradykinesia and gait deficiency [17]. Also impacted other neurotransmitter systems, which are liable for countless non- motor PD manifestation. A increasing spectrum of proof indicates changes in the circadian PD scheme. The most significant neurotransmitter i.e. dopamine is under the control of circadian system, its signaling activities and metabolism are highly affected by the circadian clock. Hindered circadian consequences in PD involves not only sleep- wake cycle dysregulation, but also cognitive, autonomic, motor and mental manifestation of the illness [15,16].

Huntington disease is a deadly autosomal neurodegenerative disease that impacts about 14-16 people per 100,000,123 and typically develops in the middle of life [18]. HD is indicated by a gradual decline in motor and non-motor dysfunctions, including cognitive defects that ultimately results in dementia, neuropsychiatric disorders, weight loss, and serious sleep and circadian rhythm disorders [15,19].

References

- Friedman M (2003) Chemistry, biochemistry, and safety of acrylamide. A review. *J Agric Food Chem* 51(16): 4504-4526.
- Dearfield KL, Abernathy CO, Ottley MS, Brantner JH, Hayes PF (1988) Acrylamide: its metabolism, developmental and reproductive effects, genotoxicity, and carcinogenicity. *Mutat Res* 195(1): 45-77.
- Exon JH (2006) A Review of the Toxicology of Acrylamide: *Journal of Toxicology and Environmental Health, Part B* 9(5): 397-412.
- Zyzak DV, Sanders RA, Stojanovic M, Tallmadge DH, Eberhart BL, et al. (2003) Acrylamide formation mechanism in heated foods. *J Agric Food Chem* 51(16): 4782-4787.
- Tan, X, Zhao T, Wang Z, Wang J, Wang Y, et al. (2018) Acrylamide defects the expression pattern of the circadian clock and mitochondrial dynamics in C57BL/6J mice liver and HepG2 cells. *J Agric Food Chem* 66(39): 10252-10266.
- (2017) *Circadian Rhythms*, pp: 1-2.
- Zhu L, Zee PC (2012) Circadian rhythm sleep disorders. *Neurol Clin* 30(4): 1167-1191.
- Ko CH, Takahashi JS (2006) Molecular components of the mammalian circadian clock. *Hum Mol Genet* 15: R271-R277.
- Tan X, Ye J, Liu W, Zhao B, Shi X, et al. (2019) Acrylamide aggravates cognitive deficits at night period via the gut-brain axis by reprogramming the brain circadian clock. *Arch Toxicol* 93(2): 467-486.
- (2018) Jet lag disorder - Symptoms and causes - Mayo Clinic.
- Yan D, Yao J, Liu Y, Zhang X, Wang Y, et al. (2018) Tau hyperphosphorylation and P-CREB reduction are involved in acrylamide-induced spatial memory impairment: Suppression by curcumin. *Brain Behav Immun* 71: 66-80.
- Müller VM, Zietek T, Rohm F, Fiamoncini J, Lagkouvardos I, et al. (2016) Gut barrier impairment by high-fat diet in mice depends on housing conditions. *Mol. Nutr. Food Res.* 60(4): 897-908.
- Kyoko OO, Kono H, Ishimaru K, Miyake K, Kubota T, et al. (2014) Expressions of tight junction proteins Occludin and Claudin-1 are under the circadian control in the mouse large intestine: implications in intestinal permeability and susceptibility to colitis. *PLoS One* 9(5): e98016.
- Guo J, Lin P, Zhao X, Zhang J, Wei X, et al. (2014) Etazolate abrogates the lipopolysaccharide (LPS)-induced downregulation of the cAMP/pCREB/BDNF signaling, neuroinflammatory response and depressive-like behavior in mice. *Neuroscience* 263: 1-14.
- Videnovic A, Lazar AS, Barker RA, Overeem S (2014) The clocks that time us'—circadian rhythms in neurodegenerative disorders. *Nat Rev Neurol* 10(12): 683-693.
- Wulff K, Gatti S, Wettstein JG, Foster RG (2010) Sleep and circadian rhythm disruption in psychiatric and neurodegenerative disease. *Nat Rev Neurosci* 11(8): 589-599.
- De Lau LM, Breteler MM (2006) Epidemiology of Parkinson's disease. *Lancet Neurol* 5(6): 525-535.
- Harper PS (1992) The epidemiology of Huntington's disease. *Hum Genet* 89(4): 365-376.
- Morton AJ, Wood NI, Hastings MH, Hurelbrink C, Barker RA, et al. (2005) Disintegration of the sleep-wake cycle and circadian timing in Huntington's disease. *J Neurosci* 25(1): 157-163.

