

REVIEW ARTICLE

DOI: <http://dx.doi.org/10.15446/revfacmed.v67n3.69962>

Physiological, molecular and genetic aspects of alpha-synuclein and its correlation with high alcohol consumption

Aspectos fisiológicos, moleculares y genéticos de la α -sinucleína y su relación con el alto consumo de alcohol

Received: 23/01/2018. Accepted: 11/06/2018.

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| Abstract |

Introduction: Significant changes in the expression of α -synuclein (SNCA) can be seen in subjects with high alcohol consumption, altering neuroprotection and causing changes in the reward system.

Objective: To present state-of-the-art studies on the physiological, molecular and genetic aspects of SNCA related to high alcohol consumption.

Materials and methods: A search of records published from 2007 to 2017 in PUBMED, ScienceDirect and Cochrane was carried out using the following terms: alpha-synuclein, alcoholism, genetic polymorphism, gene expression, DNA methylation and molecular biology.

Results: The search yielded 1 331 references, of which 51 full-text studies were selected. The results describe the current evidence of the physiological and pathological aspects of α -synuclein (SNCA) and the genetic and epigenetic changes related to its expression in people with high alcohol consumption.

Conclusions: The evidence suggests that there is a differential expression of α -synuclein (SNCA) in subjects with high alcohol consumption, as a result of modifications in the genetic and epigenetic mechanisms, leading to physiopathological neuroadaptations. SNCA is a promising marker in the field of alcoholism research; therefore, more studies addressing this topic are required, taking into account the genetic heterogeneity of each population.

Keywords: Alcoholism; Genetic Polymorphism; Gene Expression; Inflammation (MeSH).

| Resumen |

Introducción. En sujetos con alto consumo de alcohol se han observado cambios importantes en la expresión de α -sinucleína (SNCA) que alteran la neuroprotección y ocasionan cambios en el sistema de recompensa.

Objetivo. Describir el estado del arte de los aspectos fisiológicos, moleculares y genéticos de SNCA relacionados con el alto consumo de alcohol.

Materiales y métodos. Se realizó una búsqueda de registros publicados entre 2007 y 2017 en las bases de datos PubMed, ScienceDirect y Cochrane con los términos alfa-sinucleína, alcoholismo, polimorfismo genético, expresión génica, metilación de ADN y biología molecular.

Resultados. La búsqueda arrojó 1 331 referencias, de las cuales se seleccionaron 51 de texto completo. Los resultados describen la evidencia actual de los aspectos fisiológicos y patológicos de SNCA y los cambios genéticos y epigenéticos relacionados con su expresión en personas con alto consumo de alcohol.

Conclusión. En sujetos con alto consumo de alcohol se encuentra una expresión diferencial de SNCA como resultado de modificaciones en los mecanismos genéticos y epigenéticos, los cuales resultan en neuroadaptaciones fisiopatológicas. La SNCA es un marcador prometedor en el campo de investigación del alcoholismo, por lo cual se requiere más investigación al respecto, teniendo en cuenta la heterogeneidad genética de cada población.

Palabras clave: Alcoholismo; Polimorfismo genético; Expresión génica; inflamación (DeCS).

Martínez-Rodríguez TY, Rey-Buitrago M. Physiological, molecular and genetic aspects of alpha-synuclein and its correlation with high alcohol consumption. Rev. Fac. Med. 2019;67(3):315-22. English. doi: <http://dx.doi.org/10.15446/revfacmed.v67n3.69962>.

Martínez-Rodríguez TY, Rey-Buitrago M. [Aspectos fisiológicos, moleculares y genéticos de la α -sinucleína y su relación con el alto consumo de alcohol]. Rev. Fac. Med. 2019;67(3):315-22. English. doi: <http://dx.doi.org/10.15446/revfacmed.v67n3.69962>.

Introduction

According to the Pan American Health Organization, alcohol is the world's most widely consumed psychoactive substance and the main risk factor for death and disability in individuals between 15 and 49 years of age. (1) The harmful use of alcohol causes 2.5 million deaths per year and more than 200 diseases, and also has serious implications for public health as the economic burden of consumption is high due to adverse health effects and loss of productivity. (2)

Chromosome 4 contains genes associated with alcohol-related phenotypes, including the gene that encodes the α -synuclein (SNCA) protein. (3-5) This protein has been studied because it plays a fundamental role in the development of Parkinson's disease; however, due to its abundance in presynaptic nerve terminals and its diverse functions in dopaminergic neurons linked to the reward system, it has also been studied in subjects with high alcohol consumption, finding differential expression of messenger RNA (mRNA) and SNCA protein in animal and human experimental models. (6-13) Its level is related to the compulsive craving for consumption and the presence of polymorphisms, changes in the methylation of the gene and the expression of regulatory microRNAs.

In that context and taking into account the emerging role of SNCA in the physiopathology of alcoholism, this article seeks to answer the

question: What are the physiological, molecular and genetic aspects of SNCA related to high alcohol consumption? Understanding these mechanisms is fundamental to comprehend the potential of this protein in alcoholism research.

Materials and methods

A search for publications made from 2007 to 2017 was conducted in PubMed, ScienceDirect and Cochrane databases. Original and review articles containing the keywords "alpha-synuclein", "alcoholism", "genetic polymorphism", "gene expression", "DNA methylation" and "molecular biology" were selected.

The search yielded 1 331 references; 919 duplicates were eliminated and 412 articles were selected; articles whose title and abstract did not include the terms used in the search (n=159), articles that were not relevant to the topic (n=157), and articles that did not provide access to the full text (n=53) were excluded, finally obtaining 43 references. In addition, at the discretion of the authors, 8 researches published outside the time frame were included, as they had findings relevant to the field. In this way, a total of 51 references were included in the review, of which 49 were in English language and 44 were original researches (Figure 1).

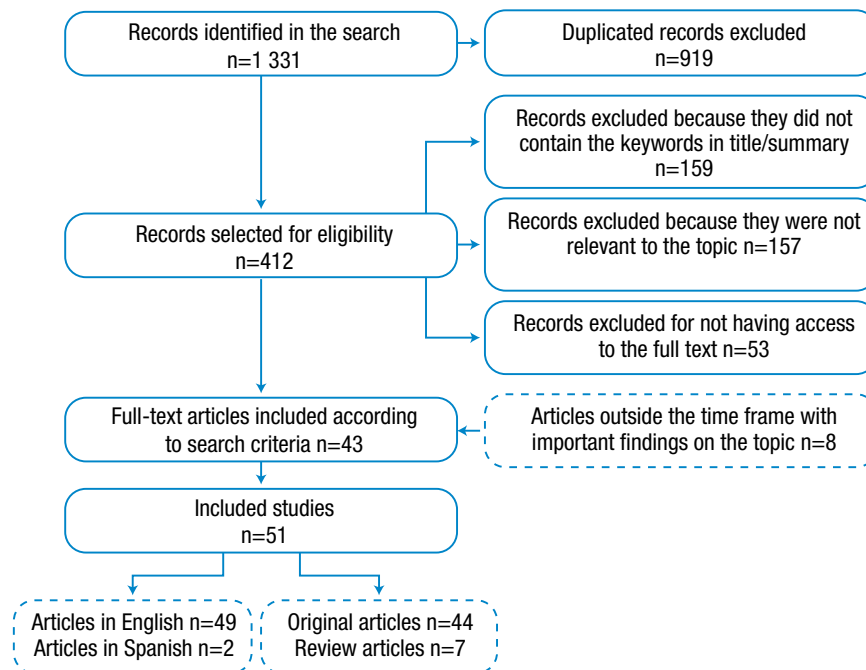


Figure 1. Search and selection flowchart of articles used to prepare the document.
Source: Own elaboration.

Results

The included studies describe the current evidence of the physiological and pathological aspects of SNCA, its usefulness as

a biological marker in peripheral tissue samples, and the genetic and epigenetic changes related to the modifications in the expression of mRNA and SNCA protein in people with high alcohol consumption (Table 1).

Table 1. Main findings of the review.

Year	Reference	Methodology	Results
2017	McMillan <i>et al.</i> (14)	qPCR procedure for analyzing miR-7 level in rat substance nigra. miR-7T was injected with lentiviral vectors.	miR-7 plays an important role in regulating SNCA physiology, as the loss of its lentivirus-mediated function leads to an increase in SNCA expression in vitro and in vivo.
2016	Anokhin <i>et al.</i> (6)	Comparison of SNCA gene expression in the brain of rats that consumed alcohol chronically from 60 to 120 days of age. MRNA expression was evaluated with qPCR.	Animals with high alcohol consumption had lower SNCA expression in the midbrain and hypothalamus compared to the low-consumption group.

Table 1. Main findings of the review. (continued).

Year	Reference	Methodology	Results
2016	Abd-Elhadi <i>et al.</i> (15)	Determination of SNCA protein levels using immobilized lipids, such as phosphatidyl inositol, phosphatidyl serine and phosphatidyl ethanolamine.	Lipid ELISA is a sensitive method for detecting SNCA and can become a tool for determining levels of specific forms of SNCA at the pathological level.
2014	Sui <i>et al.</i> (16)	SNCA radioactively labeled with sodium was used in the animal model.	Radioactively labeled SNCA crosses the blood-brain barrier in the brain-blood direction and vice versa. Inflammation is likely to increase SNCA uptake from the blood to the brain by disrupting the blood-brain barrier, leading to increased neurotoxicity.
2013	Janeczek & Lewohl (17)	Review of the genetic and epigenetic factors involved in the regulation of SNCA expression.	SNCA expression is modulated by chronic alcohol consumption and correlates with compulsive craving in alcohol-dependent individuals. The variation of the SNCA-Rep 1 sequence is associated with alcohol-related phenotypes and correlates with expression levels. The miRN miR-7 and miR-153 of SNCA are altered by the chronic consumption of alcohol.
2013	Jangula & Murphy (18)	It was determined if SNCA expression alters the permeability in the blood-brain barrier. LPS was injected into knockout (KO) mice for SNCA and wild type (WT). In addition, Evans Blue was used and extravasation was evaluated using fluorescence spectroscopy.	WT mice showed a significant increase in blood-brain barrier permeability at 1, 3 and 6 hours after LPS injection, compared to untreated mice. In KO mice, LPS did not induce changes in permeability. Results show that SNCA expression is associated with increased opening of the blood-brain barrier in response to LPS.
2012	Janeczek <i>et al.</i> (7)	Quantification of SNCA mRNA expression in dorsolateral prefrontal cortex samples by qPCR. The sample consisted of 126 controls and 117 alcoholics.	Alcoholics had higher frequency of short allele (267 bp) associated with decreased SNCA expression. Subjects with at least one copy of the allele were more likely to show an alcohol-related phenotype.
2010	Doxakis (13)	HEK293 cell culture was used. Cells were transfected with lipofectamine and SNCA constructs. Immunocytochemistry, densitometry and bioinformatic analysis were used.	miR-7 and miR-153 show similar SNCA distribution in mRNA and protein. miR-7 and miR-153 regulate mRNA and reduce the endogenous level of the protein in neurons.
2008	Ziolkowska <i>et al.</i> (8)	Changes in SNCA expression were characterized by RT-PCR, in situ hybridization and western blotting in C57BL/6J mice with constant alcohol consumption for 32 days.	The level of SNCA protein was increased by 80% in the amygdala of mice with 24 or 48 hours of abstinence. There were no changes at the mesencephalon or striatum/accumbens level. mRNA increased in the blood of mice with 48-hour abstinence, but is not related to mRNA level at brain level.
2007	Foroud <i>et al.</i> (19)	Thirty simple nucleotide polymorphisms (SNP) were genotyped in a sample of 219 alcoholic families of American-European origin.	No association between any SNPs in SNCA and alcohol dependence was observed. Eight SNPs were associated with the alcohol craving phenotype.

SNCA: α - synuclein; LPS: lipopolysaccharide.
Source: Own elaboration.

Discussion

General aspects of SNCA

The SNCA gene is found on chromosome 4, position 4q22.1; it is organized into 10 exons (20) —the size ranges between 42 and 110 base pairs (21)— and spans about 117 kb. (20)

SNCA is an abundant protein that represents 1% of proteins soluble in cytosol in the brain. (21) It is expressed mainly in the pre-synaptic

nerve terminals of the brain and in low concentrations in all other tissues, except the liver. (20) This protein is found in at least 4 different alternative splicing variants for functional polypeptide synthesis. (17) The predominant variant in humans is composed of 140 amino acid residues whose mRNA is synthesized from the transcription and processing of 6 exons (20); the second isoform is 126 amino acids long and is produced by the exclusion of exon 3; the third isoform is 112 amino acids long product of the exclusion of exon 5 (20,21); and the fourth isoform is 98 amino acids long with deletion of exons 3 and 5 (21,17) (Figure 2).

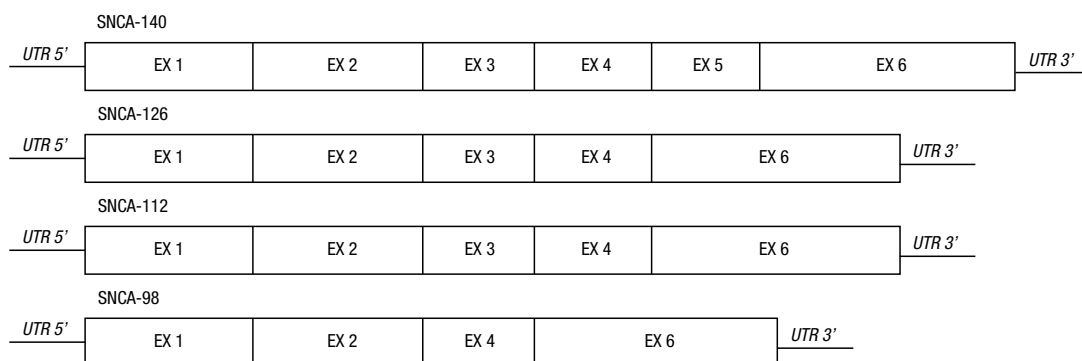


Figure 2. Structure of the four isoforms of the SNCA gene.
UTR: untranslated region of the gene; SNCA: α -synuclein; EX: exon.
Source: Own elaboration based on Janeczek *et al.* (17).

Physiological and pathological mechanisms of SNCA

SNCA has been particularly linked with synapse and plasticity processes. The high concentration in presynaptic terminals involves the protein in the recycling and maintenance of the synaptic vesicles (21); mediation functions have also been attributed to dopaminergic neurotransmission (20,22,23), including synthesis, storage, release and reabsorption of the neurotransmitter. Although the functions of SNCA have not been fully elucidated, the most relevant have been related to neuroprotection:

1. Suppression of dopaminergic neuron apoptosis by deactivation of the nuclear factor Kb (NF-kB) and reduction of protein kinase C (PKC) transcription and activity. (24)
2. Modulation of calmodulin activity, changing CaM protein from inhibitor to activator, which triggers short- and long-term memory mechanisms. (24)
3. Chaperone activity of SNCA to sustain the SNARE structure (fixation protein, important for the maintenance of cellular traffic). (24)
4. Participation in cellular differentiation, interacting with Ras kinase suppressor and activation of Ras, which trigger ERK/MAPK pathways involved in sending signals of growth factors from cellular receptors to nuclear factors. (24)
5. Regulation of tyrosine hydroxylase (TH), which modulates dopamine production and controls its levels in the cell. Thus, a low SNCA expression or aggregation leads to an increase in dopamine synthesis, leading to oxidative stress. (24)
6. Modulation of vesicle traffic from the reserves to the synapse release site. In excess, SNCA induces a decrease in dopamine reuptake and inhibits vesicular traffic, resulting in a smaller reservoir. (24)
7. Mitochondrial activity that affects membrane dynamics (25) and generates changes in mitochondrial fission and fusion. (26,27)
8. Regulation of phosphatidic acid synthesis by inhibiting phospholipase D (PLD2), which is increased in the brain of patients with neurodegenerative diseases. (21)

On the other hand, a pathophysiological model of the possible mechanisms in which SNCA aggregation is toxic to neurons has been proposed, and is related to post-translational modifications such as phosphorylation and oxidation that influence the binding to membrane lipids; SNCA monomers form dimers that may or may not propagate. The latter generate oligomers that interact with the cytoplasmic membrane forming pores and inducing intracellular calcium flow abnormally. (28)

Amyloid fibrils formation generates accumulation of intracellular inclusions, also known as Lewy bodies, which, due to their toxicity, block the trafficking of proteins from the endoplasmic reticulum up to the Golgi apparatus and alter mitochondrial function, protein degradation and synaptic transmission, causing accumulation in the cytoplasm. (28,29)

These phenomena increase membrane conductance, activate microglia and result in dysfunctional synapses, leading to disorders known collectively as α -synucleopathies (30,31), which include Parkinson's disease, Lewy body dementia and multisystem atrophy; it is also found secondarily in Alzheimer's disease. (29) The passive release of SNCA from damaged neurons could be relevant for neurodegenerative processes, since it is known that neuron-to-neuron propagation is an important phenomenon in the progression of these pathologies and affects different brain areas and structures. (32-34)

In this context, SNCA is observed in both physiological and pathological conditions. In the first case, it has multiple functions related to cellular regulation, while in the second, the modifications caused by inflammatory processes or toxicity can contribute to the abnormal folding of the protein, leading to important pathological consequences. Research in this regard has been directed to neurodegenerative diseases and addictions, especially alcohol dependence, because SNCA alteration affects surface expression and dopamine uptake, altering the reward pathway associated with addiction during chronic alcohol consumption. (17,35)

SNCA in peripheral tissues

The flow of SNCA between the brain and peripheral tissues could have important pathophysiological implications. When the protein is radioactively labeled, passage through the blood-brain barrier in the brain-blood direction and vice versa is observed; this is the mechanism responsible for regulating the brain level, therefore, accumulation of SNCA in the brain is observed in cases of inflammatory processes that lead to increased neurotoxicity due to impaired blood flow. (16) It has been shown that the injection of a single dose of lipopolysaccharide (LPS) to induce increased vascular permeability increases SNCA expression, which is associated with increased opening of the blood-brain barrier. (18)

Total SNCA concentrations in blood cells and saliva are determined by ELISA test adapted for maximum detection. (15,36) In turn, it has been evaluated in different tissues, cells and human fluids (15,37) such as blood (38,39), erythrocytes (15,40), saliva (41) and cerebrospinal fluid (CSF). On the other hand, erythrocyte expression is regulated by post-translational mechanisms through SNCA degradation and release, and is associated with the plasma membrane of erythrocytes, being more prone for aggregation and easier for detection there than in neuronal cells. (41-43)

With all of this in mind, the detection of extracellular SNCA represents a reliable marker (44), since the neuronal protein is secreted in the cerebral environment circulating to the cerebrospinal fluid (CSF) and then to the blood. (38) In addition, studies have been conducted in alcoholic subjects and have concluded that the elevation of mRNA levels is common in humans, rodents and primates. Also, the protein has been detected in plasma and its increase has been directly related to the increase in mRNA. (45) Consequently, SNCA could be useful as a peripheral marker of alcoholism, although more studies are required. (8,10,11)

Differential expression of SNCA in subjects with high alcohol consumption

SNCA gene expression has been studied in different models. In mice, results have been contradictory, since possible changes in expression were evaluated after short periods of abstinence; basically, mice had constant access to an 8% alcohol solution for 32 days, then techniques were used to quantify the gene and protein levels in brain and blood. In the brain, the results showed no changes in mRNA in any of the areas studied, but the protein level was modified by an increase in the amygdala after 24 hours of abstinence, which did not correspond to the level of mRNA transcription; the authors attributed this to a possible accumulation in synaptic boutons due to alterations in transport or degradation. On the contrary, an increase in gene expression was observed in blood at 48 hours of abstinence, which in this case was not related to brain expression. (8)

An important reduction of SNCA mRNA expression has been evidenced in the prefrontal cortex of human alcoholics with the

most common variant of SNCA-140. (6,7,9) In contrast, in animal models, SNCA expression increased in regions of the brain such as the hippocampus and the caudate, and decreased in the region of the striatum. (9)

Furthermore, in non-human primates with self-administration of alcohol for 18 months and with a diagnosis of alcoholism, a 3.21-fold increase in the levels of the SNCA gene in peripheral blood was observed. (10) In humans, mRNA expression and proteins in whole blood were evaluated in subjects with a withdrawal period of 24-72 hours, showing in both cases a significant increase in the expression of SNCA compared to control subjects. (11,44)

Polymorphisms related to the expression of the SNCA gene in alcoholism

A polymorphism is an alternative form of an allele with a frequency >1% in a given population. (46) There are several types of polymorphisms, but the most frequent are simple nucleotide (SNP) polymorphisms; most of them have two alleles that are represented by the substitution of one base for another. (46) SNPs are characterized by stability, simplicity and high frequency and are genetic markers used to determine the risk of presenting a pathology and the response to pharmacological treatment. (35)

The identification of polymorphisms in the promoter region of the SNCA gene is of particular interest in Parkinson's and Alzheimer's diseases. Research has been conducted in several countries in which

different polymorphisms associated with these diseases have been identified and reported. (9,22,47)

The SNCA gene has been studied because it is highly polymorphic. SNCA-Rep 1 is a polymorphic microsatellite that is upstream of the gene and is associated with use, abuse, dependence and compulsive craving for alcohol phenotypes. (12) Findings in human blood have revealed an association between the long alleles of the SNCA-Rep 1 polymorphism (271pb) and increased expression in dependent patients. On the other hand, there was a greater frequency of the short allele of SNCA-Rep 1 (267pb) in human brain tissue of the prefrontal cortex, which was associated with decreased expression of SNCA; this suggested that individuals with at least one copy of the 267-bp allele are more susceptible to presenting an alcohol dependence and abuse phenotype. (7)

The role of SNCA in the dependence and compulsive craving phenotypes was evaluated in 219 American families of European descent. It was found that there was no association between these polymorphisms and alcohol dependence; however, for the phenotype of compulsive craving for alcohol, it was possible to identify five polymorphisms in the gene promoter region (upstream): rs7678651, rs7687945, rs2736995, rs2619364 and rs2301134, of which two were within the eight SNPs previously associated with this phenotype (rs2736995, rs2619364, rs2583985, rs2737006, rs3561184, rs356183, rs356195 and rs3561168) (19) (Figure 3). This finding is of relevance taking into account that polymorphisms in the promoter region can influence the transcription of the gene and therefore its expression.

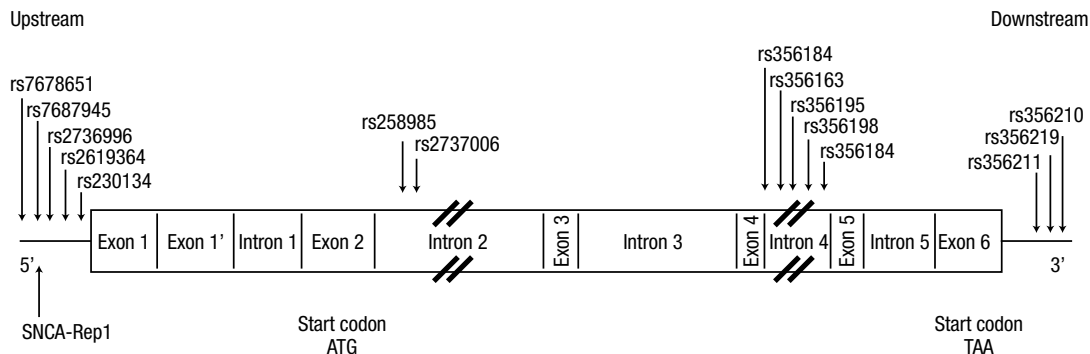


Figure 3. SNCA gene and polymorphisms related to high alcohol consumption.

SNCA: α -synuclein.

Source: Own elaboration based on Foroud *et al.* (19).

Methylation of the SNCA gene and the relationship with its expression

The regulation of gene expression is affected by independent changes in the nucleotide DNA sequencing, object of study of epigenetics. In vertebrates, several phenomena of epigenetic nature occur, including methylation, perhaps the most studied. It consists of the enzymatic addition of a methyl group on carbon 5 of the cytosine; a large part of the 5-methylcytosines (5mC) is found in the CpG islands and in the complementary chain of the 3'-GpC-5' dinucleotide. These islands are located between the central region of the promoter and the transcription start site, for which a decrease in the expression is observed when they are hypermethylated. (48) Methylation in cytosine residues causes a variation in the structure of chromatin in terms of spatial disposition and temporality, with an inverse correlation between DNA methylation levels and gene expression. DNA methylation is an epigenetic marker involved in gene regulation

and is vital for maintaining normal gene silencing, genomic imprinting and inactivation of the X chromosome. (48)

The overall DNA methylation of peripheral blood mononuclear cells and, in particular, the promoter region of the SNCA gene, is altered by changes in plasma homocysteine concentrations in disorders associated with alcohol consumption. (49) Moreover, the physical interaction of SNCA with DNA-methyltransferase-1 in the nucleus seems to decrease DNA methylation by increasing the enzyme in the cytosol due to retention; this results in a significant increase in expression levels. (50)

Another study with 84 chronic alcoholics and 93 controls investigated whether DNA methylation in the promoter region of the SNCA was altered in peripheral blood mononuclear cells, both in patients intoxicated with alcohol and with early alcohol abstinence. Hypermethylation was observed in the promoter region of SNCA, which was associated with increased levels of homocysteine. (49,51)

The influence of CpG islands methylation on the expression of the SNCA gene does not seem to be limited to the promoter region

of the gene that regulates transcription, but extends to other regions such as intron 1 and exon 1 (52-54), which have been studied in α -synucleopathies; nevertheless, to date, there are no studies oriented to alcoholism. Due to the limited evidence on the changes of SNCA methylation in alcoholics, it is necessary to do more research to know the influence of methylation on mRNA expression.

MicroRNA (miRNA) in the regulation of SNCA gene expression

MiRNAs, another regulatory mechanism, are non-coding oligonucleotides that have an important role in the post-transcriptional regulation of gene expression and mRNA degradation. They are widely found in the brain, affecting its development, neuronal differentiation, synapses and neurogenesis. (55) MiRNAs intervene in adaptations after exposure to alcohol in cellular, animal and human models (16); in alcoholics, a relationship between reduced gene expression and the presence of around 35 different types of miRNA has been identified. (55)

MicroRNA-7 expressed in neurons represses α -synuclein expression through the three prime untranslated region (3'-UTR) of the mRNA, and inhibits cell death mediated by SNCA; however, in mice with

dopaminergic neurotoxicity with MPTP injections (neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) and in cells that were transfected with constructs that expressed α -synuclein, in the absence or presence of miRNA-7 and exposure to hydrogen peroxide, it was observed that the decrease of the expression of miR-7 increases the expression of SNCA. (55)

This is confirmed by recent studies in mice injected with a lentiviral vector that mediates miRNA-7 expression in complementary binding sites to induce the loss of miRNA-7 function, where there was an increase in SNCA expression in vitro and in vivo, dopaminergic neuronal death and reduction of striatal dopamine. (14)

After exposure of cerebral cortical neural precursors of mouse fetus to doses of alcohol equivalent to those consumed by alcoholics, suppression was observed in the expression of four miRNA: miR-21, 335, 9 and 153. (56) MiRNA-153 acts to degrade mRNA and has been identified as a regulator of the levels of SNCA expression, which, when overexpressed together with miRNA-7, significantly reduces the expression of SNCA and its reduction increases it. (13)

In short, as a result of genetic or epigenetic modifications in SNCA, the polymorphisms, the methylation status of CpG islands and miRNAs contribute to the differential expression of SNCA and to neuroadaptation (Figure 4).

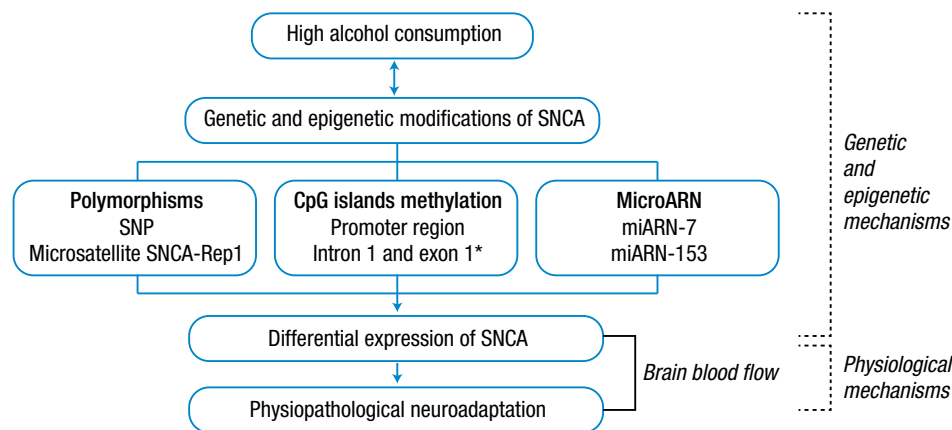


Figure 4. Effect of high alcohol consumption on the differential expression of SNCA.

SNCA: α -synuclein, SNP: 5 'simple nucleotide polymorphism.

* They seem to influence SNCA expression, but there is still no research in subjects with high alcohol consumption.

Source: Own elaboration.

Conclusions

SNCA is a protein expressed mostly in neurons, whose main research has been related to α -synucleopathies such as Parkinson's; however, research has recently emerged on its possible role in addictions.

Neuronal adaptations and alterations resulting from high alcohol consumption and the relationship of SNCA with dopaminergic neurons and the reward system make it a promising protein to understand the physiopathological and molecular mechanisms resulting from alcoholism. The measurement of SNCA in peripheral fluids, such as blood, is reliable due to regulation of the brain-blood flow of the protein through the blood-brain barrier. In animal and human models, differential expression has been demonstrated, either in the form of mRNA or protein, as well as alterations in the methylation of regulatory regions of the gene. The presence of polymorphisms related to phenotypes such as compulsive craving, the search for alcohol and the regulation of post-transcriptional expression due to the presence of miRNA turn SNCA into a potential biomarker.

However, changes in SNCA mRNA and protein expression result in different pathophysiological repercussions in people with

alcohol use problems. In addition, it is known that alcoholism is a multifactorial, polygenic pathology with great genetic and allelic heterogeneity; differences in ethnicity are crucial and each population must have their own studies according to the guidelines for selection and application of biomarkers. In this sense, more evidence on the role of SNCA in subjects with high alcohol consumption is needed to better understand the molecular and physiological mechanisms of neurotoxicity.

Conflicts of interest

None stated by the authors.

Funding

This publication is the product of the internal call for projects for the strengthening of research, creation and innovation of the Universidad Nacional de Colombia 2016-2018 through the project entitled: "Study of neuroinflammation genes, their expression and methylation state in alcohol-dependent subjects in Colombia".

Acknowledgements

To all the people who, in one way or another, contributed to the development of this work.

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