Neuropharmacological aspects of chronic alcohol use and withdrawal syndrome

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Abstract

The objective of this paper is to review and describe the main neuropharmacological changes caused by the chronic use of alcohol and those observed during its withdrawal period. The results show international data referring to the involvement of monoamine systems, neurotransmitters and calcium channels in both neuroadaptation and tolerance to alcohol effects and withdrawal. Relevant studies showing the participation of other systems in those mechanisms, as opioids and other substances, are also shown. The article reinforces the importance, for both physicians and researchers, of an always growing understanding of alcohol central mechanisms of action. This understanding is necessary to new pharmacological options to alcohol harm reduction as well as to alcohol withdrawal treatment.

Keywords: Alcoholic beverages. Drug tolerance. Substance withdrawal syndrome. Neurotransmitters.

Introduction

In the last decade, clinical and pre-clinical research in the field of chemical dependence enabled a great progress in the understanding of its underlying brain mechanisms, characterizing it as a disorder of neural plasticity, responsible for the neuroadaptation to the chronic exposure to drugs.\textsuperscript{1} Neuroadaptation and other chemical alterations caused by the chronic consumption of ethanol cause cognitive impairment, tolerance and physical dependence, which in turn contribute to maintain the use of the drug.

The cessation of chronic ingestion of alcohol, or even a sudden decrease in the plasmatic levels of ethanol, may provoke symptoms of varied intensity diagnosed by the ICD-10 and by the DSM-IV as alcohol withdrawal syndrome (AWS).

The model of the neurochemical events of chronic exposure to ethanol will be AWS, which defines chemical dependence on this substance, contains common mechanisms such as the functional or pharmacodynamic tolerance and involves some of the processes which result in cognitive impairment of chronic alcoholics.

Neuroadaptation to chronic exposure to alcohol

Contrarily to other psychotropic drugs, alcohol does not produce its central effects binding itself to specific receptors to start its actions.\textsuperscript{2} It is still accepted the idea that ethanol penetrates the membrane due to an alteration in the primary arrangement of its lipidic structure, making it more fluid.\textsuperscript{3} However, there have been many studies on the participation of several neurotransmission systems in the physiologic and pharmacological actions of ethanol, such as monoamines, acetylcholine and neurotransmitter amino acids, besides calcium channels, among other mechanisms of action.

The complex mechanism of action of alcohol explains why even its ingestion in moderate doses may lead the subject with psychiatric comorbidities to have more severe consequences than those seen in the general population.\textsuperscript{4}

1 Alcohol and monoamines

It has been demonstrated that ethanol influences the release of the main neurotransmitters present in the CNS: dopamine,\textsuperscript{5} serotonin (5-HT),\textsuperscript{6} noradrenaline\textsuperscript{7} and opioid peptides.\textsuperscript{8} Ethanol activates the
dopaminergic neuronal firing in the ventral tegmental area of the mesencephalon, as well as the dopaminergic release in the nucleus accumbens, structures which are part of the mesolimbic pathway, essential for the rewarding effects of ethanol.\(^9\)

The actions of ethanol on the dopaminergic system seem to indirectly activate the serotoninergic pathways, as they are attenuated by 5-HT\(_3\) receptor antagonists.\(^10\) The relationship between ethanol and 5-HT\(_3\) receptors has been demonstrated in studies focused on the theory that low levels of brain 5-HT may be a risk factor for alcoholism.\(^11\)

### 2 Alcohol and neurotransmitter amino acids

Several authors have recently studied the actions of alcohol in neurotransmitter amino acid systems. In these studies, it has been highlighted the role of glutamate - the main excitatory neurotransmitter of the CNS of mammals, especially through the glutamatergic N-metil-D-aspartate (NMDA) receptor and the gamma-aminobutiric acid (GABA) inhibitory neurotransmitter, through GABA\(_\alpha\) and GABA\(_\beta\) receptors.\(^12\)\(^13\)

The complex NMDA receptor is controlled by several regulatory sites. To open the ionic channel of the NMDA receptor it is needed the presence of glycine, an amino acid that has its own site, acting as a co-agonist. It has been demonstrated that alcohol may act on the glycine-binding site, inhibiting the function of the NMDA receptor.\(^14\) It has been also proposed that this receptor is involved in learning and memory processes and in the phenomenon of tolerance to alcohol.\(^15\)

The modulation of the glutamatergic transmission with NMDA receptor antagonists is supposed as a new alternative for the treatment of alcoholism. Some authors propose that NMDA antagonists may have different roles in the treatment of alcoholism, including the attenuation of the effects of withdrawal.\(^16\)

### 3 Alcohol and calcium channels

Ethanol also reduces the transmembrane flow of calcium (Ca\(^{++}\)) in the intoxication period, acting on L-type calcium channels. In the period of alcohol withdrawal, there is an increase in the inflow of Ca\(^{++}\) through these channels, contributing for its symptoms. In lab animals, this compensatory effect may be reduced by the administration of antagonists of Ca\(^{++}\) channels such as nifedipine.\(^17\)

### 4 Alcohol and other mechanisms of action

Studies which assess cognitive functions associate the chronic ingestion of ethanol with the reduction in the brain concentration of acetylcholine, both in humans and mice, caused by the degeneration of brain tissues.\(^18\)

Antagonists of colcistocinines reduce the convulsant effects of alcohol withdrawal in mice\(^19\) and the opioid antagonist naltrexone has been widely used in the clinical treatment of alcoholism, helping to prevent relapses.\(^20\)

Chronic exposure to ethanol may modify the structure of the stimulatory G protein (Gs) or alter the interactions between G protein subunits. These alterations interfere in the stimulation of adenilate ciclas and in the production of AMPc, and seem to be related to the development of tolerance to alcohol.\(^21\) Nevertheless, other studies suggest that not only one, but also multiple processes may be involved in the regulation of the activities of second messengers by alcohol.\(^22\)

### Alcohol Withdrawal Syndrome (AWS)

AWS symptoms are directly related to the development of the neuroadaptation of the CNS to the chronic exposure to ethanol. Next, we will see the relationship between AWS and the main mechanisms of action of alcohol.

#### 1 AWS and monoamines

Regarding monoamines, AWS symptoms are mainly linked to the alteration in the noradrenaline and dopamine releasing levels. Some studies show that adrenergic hyper stimulation, which may be intense in this period, stems from a decrease in the activity of subtype (2 pre-synaptic inhibitory adrenoreceptors, a phenomenon known as down-regulation.\(^23\) These receptors control, by means of feedback, the release of monoamines in the synaptic cleft. If they do not work, the release will be excessive. These effects are responsible for a great number of physiological reactions, including cardiovascular ones, such as tachycardia through the activation of the beta-adrenergic receptors, hypertension through activation of alpha-adrenergic pathways, and increase in the contracting strength of the cardiac muscle, due to the positive inotropic adrenergic action. Other symptoms caused by adrenergic hyperactivity include: nausea and vomiting due to the decrease in the gastric emptying; piloerection, midriasis; trembling due to the facilitation of muscle neurotransmission, increase in oxygen consumption and increase of body temperature in up to 2C.

The role of serotonin in the reinforcement by alcohol is complex, due to the variety of types and subtypes of receptors for this neurotransmitter. Several of these receptors produce behavioral inhibition, explaining how the increase in its function caused by 5HT reuptake inhibitory drugs would have an inhibitory action on the drinking behavior. On the other hand, 5HT\(_2\) receptors are different as they are excitatory and seem to be involved in the increase of dopamine in the nucleus accumbens. Therefore, an agonist action in these receptors would have an inverse effect, increasing the consumption.\(^24\)

#### 2 AWS and neurotransmitter amino acids

Regarding the excitatory mechanisms of the CNS, it is known that ethanol acts as an antagonist of NMDA receptors.\(^25\) The chronic consumption of alcohol provokes an increase in the density of NMDA receptors. During withdrawal an increased response to the physiologically-released neurotransmitter will occur. Thus, hyperactivity of the glutamatergic NMDA receptors, which are responsible for the appearance of convulsive crises characteristic of the withdrawal period and possibly for neuronal death, will occur. The attenuation of this hyperexcitability would be one the main mechanisms of action of acamprosate which would prevent immediate and delayed withdrawal symptoms, the latter having less intense symptoms (irritability, anxiety), but may contribute for relapse.

The increase in the excitability of the CNS is also due to GABA-ergic hypoactivity. In the period of alcohol withdrawal, GABA stops its inhibitory activity, mainly on the GABA\(_\alpha\) receptors. This reduction seems to occur rather on functional levels, as, contrarily to what occurs with NMDA receptors, there is no evidence of alteration in the number of GABA\(_\beta\) receptors during the chronic exposure to alcohol.\(^26\)

#### 3 AWS and calcium channels

The chronic administration of ethanol leads to a compensatory increase in the density of these channels, similarly to what occurs with NMDA receptors. As these alterations persist in the withdrawal period, when there is a generalized increase in the electrical activity, the voltage-dependent calcium channels seem to have an important contribution for the AWS symptoms.\(^16\)

#### 4 AWS and other systems

The role of the corticotropin releasing factor (CRF) in alcohol and drug dependence has been recently studied. Non-hypothalamic corticotropin-releasing brain systems seem to be involved in the behavioral and physiological manifestations that occur during the withdrawal period. On the other hand, it seems that CRF, through its action on the hypothalamic-pituitary-adrenal (HPA) axis, is involved in the reinforcing effects of alcohol.\(^27\) Besides, other studies showed that the increase in cortisol levels in chronic intoxication and in the withdrawal period, through interactions with the HPA axis, contributes for a higher risk of infectious diseases in alcoholics.\(^28\)

The increase in the severity of AWS symptoms, after repeated withdrawal episodes, the kindling phenomenon, describes a sensitization in which a weak chemical or electrical stimulation, initially unable to
provoke any clinical alteration, may lead to the appearance of symp-
toms, such as seizures, being a long-term and apparently irrevers-
ible process[20]. There are also several studies about genetic altera-
tions, some of them linked to the individual vulnerability to chromosomal alter-
ations in specific neurotransmitters, such as GABA and dopamine,
in the search for genetic markers that could predict the severity of AWS
symptoms, both in pre-clinical and clinical studies with al-
coholics[29,31].

Final comments

The complexity of the mechanisms of action of ethanol and the increa-
sing interest of the scientific community in the study of the involvement
of central nervous systems lead to the rising number of new studies and theories about the relationship of these systems with
the effects of alcohol and those of cessation of its consumption, both
in animal studies and in clinical models. Being this a recent investigation field, it is difficult
to establish the most efficacious treatment for AWS, what will be only solved with the better
understanding of the functioning of the neurotransmission systems and the neuroadaptation
phenomena associated with the chronic consumption of ethanol. In this study we have pre-

tended only the main mechanisms involved in the central effects of ethanol and in the period of
alcohol withdrawal, those which arise the highest attention of researchers and which are more
directly linked to the main clinical symptoms, whose understanding is fundamental for the ade-
quate treatment of AWS.

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