

# A review on alcohol: from the central action mechanism to chemical dependency

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## SUMMARY

**Introduction:** alcohol is a psychotropic depressant of the central nervous system (CNS) that promotes simultaneous changes in several neuronal pathways, exerting a profound neurological impact that leads to various behavioral and biological alterations.

**Objectives:** to describe the effects of alcohol on the CNS, identifying the signaling pathways that are modified and the biological effects resulting from its consumption.

**Methods:** a literature review was conducted and articles published in different languages over the last 15 years were retrieved.

**Results:** the studies reviewed describe the direct effect of alcohol on several neurotransmitter receptors (gamma-aminobutyric acid [GABA], glutamate, endocannabinoids AEA and 2-AG, among others), the indirect effect of alcohol on the limbic and opioid systems, and the effect on calcium and potassium channels and on proteins regulated by GABA in the hippocampus.

**Discussion and conclusion:** the multiple actions of alcohol on the CNS result in a general effect of psychomotor depression, difficulties in information storage and logical reasoning and motor incoordination, in addition to stimulating the reward system, a fact that may explain the development of addiction. Knowledge on the neuronal signaling pathways that are altered by alcohol allows the identification of effectors which could reduce its central action, thus, offering new therapeutic perspectives for the rehabilitation of alcohol addicts.

**Keywords:** alcohol-induced disorders, nervous system, neurotransmitter receptors.

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## INTRODUCTION

The alcohol found in beverages such as wine and beer is chemically classified as ethanol. Ethanol consists of a chain of two carbons and a hydroxyl group (-OH). These characteristics confer a perfect hydrophilic-hydrophobic balance which, together with the low weight of the molecule,<sup>1</sup> guarantees an immense capacity for diffusion and distribution in all body fluids and tissues, favoring its partitioning in the central nervous system (CNS).<sup>2</sup>

The effects of alcohol on the individual and its capacity to alter behavior have been known since the beginning

of its consumption by different societies. Although alcohol is not classically viewed as a drug in Brazil, it is considered as a psychotropic CNS depressant and its consumption is one of the highest among all psychoactive substances, a fact that has numerous consequences.

The objective of this study was to perform an extensive, but not necessarily comprehensive, literature review of the effects of alcohol on the CNS, describing the neuronal changes induced by alcohol, as well as biological and behavioral effects that can explain the development of chemical dependency and contribute to the elaboration of new therapeutic measures.

## METHODS

For this study, books and articles published in printed and electronic journals of the PubMed, Medline and Scielo databases were searched, using the following Health Sciences Descriptors (DeCS) and Medical Subject Headings (MeSH): alcohol, receptor, and central action.

A total of 159 studies on the effect of alcohol on the CNS were reviewed and 62 were selected, with priority being given to articles published over the last 15 years. Articles investigating the systemic actions of alcohol in the organism, articles describing only alcohol-induced genetic and structural modifications in receptors, and articles not reporting interactions with specific receptors or the biological effects induced by the interaction of alcohol with the CNS were excluded.

## RESULTS

### Effects of alcohol on gabaminergic and glutamatergic transmission

Alcohol is a psychotropic depressant of the CNS.<sup>3,4</sup> This property is associated with the action of alcohol on different neurotransmitters, including the stimulation of gamma-aminobutyric acid (GABA), the main inhibitory neurotransmitter of the CNS, and the inhibition of glutamate, the main central excitatory neurotransmitter. Alcohol potentiates the effects of GABA by acting directly on its receptors, enhancing their inhibitory effects.<sup>5</sup> These inhibitory effects include sedation, loss of inhibitions and relaxation, and might be related to the production of certain neurosteroids, such as allopregnanolone. The latter may be a mediator of these effects in the brain, since neuroactive steroids are positive allosteric modulators of neurotransmitter receptors, such as GABA<sub>A</sub>.

The GABA<sub>A</sub> receptor-ionophore complex is widely distributed throughout the CNS and its activation causes opening of chloride channels, with consequent hyperpolarization of the membrane and production of a postsynaptic inhibitory potential.<sup>6</sup> This receptor consists of various classes of subunits (α, β, γ, δ, and ρ) that confer different pharmacological properties.<sup>7-9</sup> In studies on ethanol-dependent animals, messenger RNA (mRNA) levels of the α1 and α2 subunits of the GABA<sub>A</sub> receptor were found to be significantly reduced, whereas a significant increase was observed in mRNA levels of the α4, γ1 and γ2S subunits.<sup>10</sup> In contrast, conflicting results have been reported in other studies also using chemically dependent animals, i.e., low levels of α4 peptides and no difference in the levels of subunit γ2.<sup>10,11</sup> These results suggest that changes in the expression of GABA<sub>A</sub> receptor subunit genes lead to populations of receptors with properties

that differ from the non-ethanol-dependent state.<sup>10</sup> In this respect, molecular biology studies using *Xenopus laevis* oocytes indicate that ethanol only potentiates receptors that contain the long variant of the γ2 subunit. Since only the long, but not the short, subunit possesses a phosphorylation site, it is possible that the phosphorylation state is important for the inhibitory effect of ethanol.<sup>12</sup>

In the case of long-term alcohol use, GABA receptor down-regulation reduces the number of receptors, an event that would explain the effect of alcohol tolerance, i.e., the fact that individuals require higher doses of alcohol to achieve the same symptoms of inhibition as obtained previously with lower doses.<sup>13,14</sup> The loss of inhibitory effects and GABA receptor deficiency result in withdrawal symptoms.<sup>6</sup>

Studies also indicate that the long-term use of alcohol causes detectable memory impairments, mainly by reducing hippocampal mass mediated by GABA.<sup>13</sup> The hippocampus is related to explicit memories, i.e., memories we can talk about, such as last night's dinner or the date of a historical event. Explicit memory involves the conscious recollection of information. The hippocampus is known to be necessary for the acquisition of this type of memory, since damage to this region prevents individuals from establishing new explicit memories.<sup>15</sup> However, it is possible to recover older explicit memories that were stored before the damage had occurred. A key element in these events is a signal transduction pathway mediated by Mitogen-Activated Protein Kinases (MAPK). MAPKs are important, signaling proteins that are activated by neurotransmitters and different growth factors. One member of this family is extracellular signal-regulated kinase (ERK). The ERK cascade is used in all brain regions where synaptic plasticity occurs and its activation is needed for the formation of new memories. If ERK activity is blocked by the injection of an inhibitor into a certain brain region, such as the amygdala, the formation of all modes of learning associated with this structure will be blocked. Similarly, the blockade of ERK activity in the hippocampus prevents the hippocampal formation of explicit memories. Excessive alcohol consumption suppresses the phosphorylation of these protein kinases (ERK),<sup>15</sup> which is regulated by GABA.<sup>16</sup> Thus, ethanol abuse prevents activation of the memory circuit, in this case, the explicit memory supported by the hippocampus.<sup>14</sup>

In the case of glutamate, the loss of ionotropic (AMPA, kainate or NMDA) and metabotropic receptors (mGluR1, mGluR8) leads to a reduction in excitatory glutamatergic neurotransmission.<sup>17</sup> The activation of ionotropic receptors increases intracellular calcium (Ca<sup>2+</sup>) through different routes,

such as influx through ionotropic receptor channels, influx through voltage-sensitive calcium channels which are activated by membrane depolarization, and the release of  $\text{Ca}^{2+}$  from endoplasmic reticulum stores. The last mechanism is controlled by the ryanodine receptor, which is activated by intracellular  $\text{Ca}^{2+}$  concentrations.<sup>18</sup> This increase in intracellular  $\text{Ca}^{2+}$  can lead to attention deficits and impaired sleep-wake regulation in the *locus coeruleus* and even to the blackout phenomenon in the hippocampus.<sup>19</sup> Recent studies have shown that  $\text{Ca}^{2+}$  increases, mediated by the activation of AMPA/kainate receptors, metabotropic receptors and K depolarization, are altered by the acute administration of ethanol to cultured cerebellar Purkinje neurons, which are known to possess abundant  $\text{Ca}^{2+}$  channels.<sup>3</sup> In this respect, it was demonstrated that the administration of an AMPA receptor agonist increases  $\text{Ca}^{2+}$  concentrations in the somatic and dendritic regions of Purkinje neurons; however, ethanol altered this response in a dose-dependent manner. No effect was observed at a dose of 10 mM, whereas doses of 33 and 66 mM caused a significant reduction. Similarly, metabotropic receptor agonists also increased  $\text{Ca}^{2+}$ -concentrations in the two regions of Purkinje neurons. However, these signals were enhanced by the administration of 10 mM ethanol, but not of 33 or 66 mM. The results of that study suggest that the components of the  $\text{Ca}^{2+}$ -signaling pathway that are sensitive to ethanol are located in Purkinje neurons. Ethanol exerts a maximum effect on AMPA receptors at a dose of 33 mM and the activation of metabotropic receptors is highly sensitive to the acute effect of ethanol. However, ethanol sensitivity related to glutamatergic transmission probably depends on the glutamate receptor subtype, since the  $\text{Ca}^{2+}$  signals related to the activation of ionotropic and metabotropic receptors vary in sensitivity and in the response to ethanol.<sup>18</sup> On the other hand, the NMDA receptor is the main receptor involved in neuronal death due to increased permeability of the  $\text{Ca}^{2+}$  channel associated with this receptor.<sup>20-22</sup> This receptor has been suggested to play an important role in the neurotoxicity observed in alcohol abuse and in alcohol withdrawal syndrome. This neurotoxicity is related to a decrease in mitochondrial membrane potential and in Na/K ATPase and Mg<sup>2+</sup>-ATPase activity.<sup>12,23,24</sup>

In contrast, the long-term use of alcohol leads to an increase in glutamatergic receptors in the hippocampus, an area that is important for memory and that is involved in seizures.<sup>5</sup> As a consequence, during alcohol withdrawal the glutamate receptors that were accustomed to the continuous presence of alcohol become hyperactive and can trigger seizures or even strokes.<sup>25</sup>

#### Effects of alcohol on opioid and dopaminergic transmission

Alcohol also exerts effects on the reward system through the opioid and dopaminergic systems.<sup>26</sup> This effect is mediated by the release of dopamine in the ventral tegmental area and in the nucleus accumbens of the limbic system.<sup>19,27-29</sup> A large number of natural opioid receptors are found around these areas. There are three classes of opioid receptors involved in opioid dependence: mu, delta and kappa.<sup>26,29</sup> Opioids activate the reward system in an indirect manner through two actions. The first consists of the binding of opioids to opioid receptors within the reward system.<sup>27,29</sup> This binding triggers a signal to release the neurotransmitter dopamine into the synaptic cleft where it binds to D-1 and D-2 receptors of the nerve cell, activating the reward system in the CNS.<sup>19,29,30</sup> The second action would be through the GABA system, which inhibits the release of dopamine. However, opioids block the action of this system. As a consequence, the effects of dopamine become more potent and long lasting.<sup>31</sup> Within this context, alcohol acts directly on these opioid receptors, with the description of a positive effect on mu opioid receptors, which is related to the feeling of pleasure and stimulation of dopamine release, and a negative effect on delta receptors, increasing alcohol addiction. Studies also report that alcohol can increase the number of beta opioid receptors, which stimulate the release of dopamine. Therefore, the opioid system acts directly on the reward system and is associated with the development of addiction.<sup>29</sup>

#### Effects of alcohol on serotonergic transmission

Serotonin (5-HT) and endorphins seem to contribute to the symptoms of well-being and mood elevation observed in alcohol intoxication.<sup>25,32-34</sup> Many studies have analyzed the effects of alcohol on serotonin neurotransmission in the brain. These studies showed that serotonin transmission is increased after the acute administration of alcohol and reduced during alcohol withdrawal.<sup>33,35</sup> Reduced neurotransmission of serotonin in dependent animals might be associated with relapse. For example, when serotonin neurotransmission was inhibited by the injection of a GABA<sub>A</sub> receptor agonist into the brainstem (which reduces serotonin activity), the consumption of alcohol by the animals was lower.<sup>36</sup> There are several serotonin receptor subtypes<sup>37</sup> and serotonin may affect alcohol consumption by the activation of specific receptors.<sup>32,33</sup> In this respect, activation of 5-HT<sub>2C</sub> or 5-HT<sub>1A</sub> receptors has been shown to reduce alcohol consumption.<sup>32,33,38,39</sup> However, controversy exists in the literature, showing that both an increase and a decrease in 5-HT<sub>1B</sub> receptor production can in-

crease ethanol consumption.<sup>32,33,40-42</sup> The overproduction of the 5-HT<sub>1B</sub> receptor is supposed to produce more significant changes. On the other hand, inhibition of the 5-HT<sub>3</sub> receptor has been shown to substantially reduce alcohol consumption.<sup>43</sup>

The effects of ethanol on the dopaminergic system indirectly activate serotonergic pathways as demonstrated by the observation that these effects can be attenuated by 5-HT<sub>3</sub> receptor antagonists.<sup>44</sup> The relationship between ethanol and 5-HT<sub>3</sub> receptors has also been demonstrated in studies focusing on the theory that low 5-HT levels in the brain are a risk factor for alcoholism.<sup>45</sup> Some active ingredients of drugs, such as ondansetron, a 5-HT<sub>3</sub> antagonist, are successful in reducing alcohol consumption.<sup>46-48</sup> Buspirone, a partial 5-HT<sub>1A</sub> receptor agonist, also exerts a reducing effect on alcohol consumption.<sup>49</sup> Taken together, these studies show that the function and localization of different types of serotonin receptors determine their role in the modulation of alcohol consumption.<sup>25</sup>

#### Effects of alcohol on the endocannabinoid system

Alcohol tolerance and addiction are associated with the endocannabinoid system. This system consists of cannabinoid receptors coupled to G proteins and endogenous cannabinoids (arachidonyl ethanolamine and 2-arachidonyl glycerol).<sup>40,50-52</sup> The best known receptors are CB<sub>1</sub> and CB<sub>2</sub>. The CB<sub>1</sub> receptor is widely distributed in the brain and is located in the presynaptic terminal. This receptor is responsible for the main psychoactive effects of cannabinoids. The CB<sub>2</sub> receptor mainly mediates peripheral effects and its expression plays an important role in the immune system.<sup>50</sup> New therapeutic agonists of this receptor have shown a great potential in the treatment of alcoholic liver diseases.<sup>53</sup>

The higher density of CB<sub>1</sub> receptors in certain brain regions may explain the involvement of this neurotransmission system in the main effects of ethanol. The high concentration of this receptor in basal ganglia and in the cerebellum may be responsible for alcohol-induced motor incoordination. The presence of the CB<sub>1</sub> receptor in the hippocampus and in different regions of the cerebral cortex may explain cognitive deficits and recent amnesia.<sup>50</sup>

This relationship occurs by the understanding of the relationship between endocannabinoids and ethanol, based on the observation of independent studies that the chronic administration of ethanol increased the concentrations of fatty acid esters in the brain.<sup>54,55</sup> The latter are used for the production of arachidonyl ethanolamine, whose degradation was inhibited by ethanol through blockade of the microsomal transporter.<sup>56</sup> Other studies

demonstrated increased levels of the endocannabinoid 2-arachidonyl glycerol after chronic exposure to ethanol.<sup>57</sup> With respect to the effects of alcohol on CB<sub>1</sub> receptors, it is known that chronic ethanol consumption or administration reduces the expression of these receptors in different brain regions,<sup>58,59</sup> in addition to compromising signal transduction by decreasing the affinity of this receptor for its G protein.<sup>60</sup>

#### Effects of alcohol on voltage-dependent Ca<sup>2</sup> channels

Another central action of alcohol related to motor coordination is its effect on voltage-dependent Ca<sup>2</sup> channels. These channels play an important role in cell depolarization and repolarization. In addition, they regulate a series of cellular activities, including the release of neurotransmitters. Alcohol mainly acts on L-type calcium channels, inhibiting the opening of these channels. The lower influx of positively charged ions into the cell renders it less excitable, in addition to inhibiting the release of neurotransmitters. A larger number of these channels are found in cerebellum. Therefore, the action of alcohol in this region may explain the motor incoordination such as unsteady gait, attention deficits, and impaired sleep-wake regulation.<sup>29</sup>

#### Effects of alcohol on GIRK channels

Another important effect of alcohol on the nervous system involves the activation of a specific type of potassium (K) channel, called G protein-coupled inwardly-rectifying K (GIRK) channels. However, the molecular mechanism underlying this activation is not fully understood. GIRK channels possess specific structures that permit binding to the alcohol molecule. These structures mediate the alcohol-induced activation of GIRK channels, but do not influence the inhibition of these channels.<sup>2</sup> Since they are proteins present on the plasma membrane of nerve cells that form K-selective pores, a neuron frequently expresses multiple types of K channels, which exert different functions in cell signaling. Many ion channels, such as those mediated by neurotransmitters (e.g., serotonin), are sensitive to ethanol and other alcohols. It can, therefore, be speculated that the excitation of these channels is associated with increased alcohol consumption.<sup>61</sup>

#### Effects of alcohol on neurosteroids

Several neuroactive steroids exhibit rapid non-genomic activity in the CNS. These rapid mechanisms of action include the modulation of NMDA and GABA<sub>A</sub> receptor activity. Studies have shown that positive or negative allosteric modulators of the NMDA receptor complex bind

to distinct sites on this receptor, which differ from the binding sites of glycine, dizocilpine (MK-801), Mg<sup>2+</sup> and spermine. Furthermore, pregnenolone sulfate and dehydroepiandrosterone sulfate, which are negative allosteric modulators of the GABA<sub>A</sub> receptor, act as non-competitive antagonists to reduce the activity of GABA<sub>A</sub> and glycine receptors, whereas androsterone, progesterone, allotetrahydrodeoxycorticosterone, allopregnanolone, pregnenolone and epipregnanolone act as positive allosteric modulators of this receptor.<sup>62</sup>

Recently, interactions of neurosteroids with the effects of ethanol have been demonstrated. Allopregnanolone was shown to decrease sleep latency and to increase the ethanol-induced sleeping time, whereas pregnenolone sulfate and dehydroepiandrosterone sulfate reduced sleep duration. In addition, an increase in blood allopregnanolone levels induced by ethanol was demonstrated in rats. With respect to the motor impairment caused by ethanol, dehydroepiandrosterone sulfate exerts a stimulatory effect, whereas an inhibitory effect is observed for allotetrahydrodeoxycorticosterone.<sup>62</sup>

In view of their multiple relationships with alcohol, these neuroactive steroids are studied for the treatment of alcoholism and may be useful for the development of drugs designed to minimize the effects caused by alcohol.<sup>62</sup>

Tables 1, 2 and 3 summarize the neuronal pathways that are stimulated and inhibited by alcohol, their respective neurotransmitters and/or signaling pathways, receptors, and the effects induced by the presence of alcohol in the CNS.

## DISCUSSION AND CONCLUSION

The results of this review show the multiple actions of alcohol on numerous central neurotransmission pathways, highlighting its role as a potent “dirty drug” and a CNS disorganizer. The results were organized in Tables 1 and 2, according to the pathways activated or inhibited by alcohol, respectively. This approach permitted to associate the classical biological actions of ethanol with the mo-

lecular signaling pathways involved. Among the central actions stimulated by alcohol, its inhibitory gabaminergic effect, in conjunction with the inhibition of certain excitatory glutamatergic receptors, endocannabinoids, cerebellar calcium channels and hippocampal proteins (ERKs) which are essential for memory formation, results in sedation, loss of inhibitions, relaxation, loss of cognitive functions, attention deficit, impaired sleep-wake regulation (blackout effect), and the final state of psychomotor depression.

On the other hand, the excitatory action of alcohol on mu receptors of the opioid system and subsequent activation of the limbic system by dopamine and of 5-HT<sub>1B</sub> receptors by serotonin result in the effect of well-being and mood elevation. In addition, the down-regulation of dopamine and GABA receptors explains the increase in alcohol consumption and subsequent development of chemical dependency.

Finally, a better understanding of the effect of 5-HT<sub>3</sub> antagonists that are able to reduce alcohol consumption, as well as of neurosteroids modulating gabaminergic receptors, should lead to the identification of new therapeutic perspectives. However, since dealing with the subject exhaustively was not the objective of this review, and since many of the studies cited are very recent, it is likely that interactions of alcohol with other neuronal pathways, as well as their interrelations, will be described in the future.

## RESUMO

Uma revisão sobre o álcool: do mecanismo de ação central à dependência química

**Introdução:** o álcool é uma substância psicotrópica depressora do sistema nervoso central (SNC), que promove alteração simultânea de inúmeras vias neuronais, gerando profundo impacto neurológico e traduzindo-se em diversas alterações biológicas e comportamentais.

**TABLE 1** Neurotransmission pathways stimulated by alcohol, their respective neurotransmitter and receptor, and biological response induced in the central nervous system.

Neurotransmission pathway (neurotransmitter)	Receptor	Biological effect
Gabaminergic (GABA)	Ionotropic: GABA <sub>A</sub> and GABA <sub>C</sub> <sup>4,35,37-39</sup> Metabotropic: GABA <sub>B</sub>	Inhibition of CNS, manifesting as sedation, loss of inhibitions, and relaxation <sup>4,34,36</sup>
Opioid (dopamine)	Mu <sup>16,18-22</sup>	Pleasure, satisfaction, increased search for alcohol <sup>19,22</sup>
Serotonergic	5-HT <sub>3</sub> <sup>48,49,56</sup>	Feeling of well-being and mood elevation <sup>12,23,24,48,50</sup>

CNS: central nervous system.

**TABLE 2** Neurotransmission pathways inhibited by alcohol, their respective neurotransmitter and receptor, and biological response induced in the central nervous system.

Neurotransmission pathway (neurotransmitter)	Receptor	Biological effect
Glutamatergic (glutamate)	Ionotropic: AMPA, kainate or NMDA <sup>29</sup> Metabotropic: rM1, rM8 <sup>29</sup>	Reduced cognitive functions, attention deficit, and impaired sleep-wake regulation; blackout phenomenon <sup>21,29,40,41</sup>
Opioid (dopamine)	Delta <sup>16,22</sup>	Reduced search for alcohol <sup>19,22</sup>
Endocannabinoid (AEA, 2-AG)	CB1, CB2 <sup>26,27</sup>	Motor incoordination, difficulty in logical reasoning <sup>25</sup>
MAPK	ERKs <sup>13</sup>	Loss of explicit memory <sup>8,13</sup>
Calcium channels	L-type in the cerebellum <sup>22</sup>	Unsteady gait and loss of spatial notion <sup>22</sup>
GIRK channels	Potassium channels <sup>2,3</sup>	Altered neurotransmission <sup>2,3</sup>

AEA: arachidonyl ethanolamine; 2-AG: 2-arachidonyl glycerol.

**TABLE 3** Action of neurosteroids in the effects caused by ethanol.

Neurosteroid	Action	Biological effect
Allopregnanolone	Positive allosteric modulator of GABA <sub>A</sub> <sup>62</sup>	Reduction in sleep latency and in sleeping time <sup>62</sup>
Pregnenolone sulfate	Negative allosteric modulator of GABA <sub>A</sub> <sup>62</sup>	Reduction in sleep duration <sup>62</sup>
Dehydroepiandrosterone sulfate	Negative allosteric modulator of GABA <sub>A</sub> <sup>62</sup>	Reduction in sleep duration and motor stimulus <sup>62</sup>
Allotetrahydrodeoxycorticosterone	Positive allosteric modulator GABA <sub>A</sub> <sup>62</sup>	Motor inhibition <sup>62</sup>

**Objetivos:** descrever as ações do álcool sobre o SNC, identificando as vias de sinalização modificadas e os efeitos biológicos gerados pelo seu consumo.

**Métodos:** revisão bibliográfica, priorizando trabalhos multilinguísticos publicados nos últimos 15 anos.

**Resultados:** são descritas ação direta do álcool em inúmeros receptores de neurotransmissores (ácido gama-aminobutírico – GABA, glutamato, endocanabinoides AEA e 2-AG, entre outros), ação indireta do álcool no sistema límbico e opioide, ação sobre canais de cálcio, potássio e proteínas reguladas por GABA no hipocampo, além de ações centrais mediadas pela deficiência de vitamina B1.

**Conclusão:** a ação multifocal do álcool sobre o SNC resulta em efeito geral de depressão psicomotora, dificuldades no armazenamento de informações e no raciocínio lógico, incoordenação motora, além da estimulação do sistema de recompensa, o que pode explicar o desenvolvimento da dependência química. O conhecimento das vias de sinalização neuronais alteradas pelo álcool permite reconhecer a descrição de efeitos que possam reduzir sua ação central e, assim, vislumbrar novas perspectivas terapêuticas para a reabilitação de adictos a essa substância.

**Palavras-chave:** transtornos do sistema nervoso induzidos por álcool, neurotransmissores, receptores de neurotransmissores.

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