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Review article

Evaluation of the dopaminergic system with positron-emission tomography in alcohol abuse: A systematic review

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ABSTRACT

Objective: Performed a systematic review to evaluated the dopaminergic system in alcohol abuse in a systematic review in humans.
Method: A search of the electronic databases was proceeded, on MEDLINE, EMBASE, Cochrane Library, Insight and Gray literature (Google Scholar and the British Library) for studies published until August 2018. A search strategy was developed using the terms: "*dopamine*" and "*ethanol*" or "*"alcohol*"," and "*positron-emission tomography*" as text words and Medical Subject Headings (i.e., MeSH and EMTREE) and searched.
Results: We found 293 studies. After reading titles and abstracts 235 were considered irrelevant, as they did not meet the inclusion criteria. For the reading of the full text, 50 studies were analyzed. Of these 41 were excluded with reasons by study design, patient population, intervention and outcomes. Nine studies were included in our qualitative synthesis. Four studies have resulted in a reduction in availability only at the D2 receptor in different brain regions. Concerning the D3 receptor alone only one study reported this finding and four studies reported a decrease in both receptors.
Conclusion: Changes in D2 receptors in several brain regions in human alcoholics were found in a systematic review.

1. Introduction

Alcohol abuse is a matter of deep concern and great relevance to health agencies. Around 3.3 million people worldwide died as a result of harmful alcohol use in 2012, amounting to 5.9% of all deaths in that year (WHO, 2014). In the Americas alone, it contributed more than 300,000 deaths, of which 80,000 could have been avoided without the use of alcohol (PAHO, 2015). The death rate associated with alcohol is higher than mortality from HIV/AIDS (2.8%), violence (0.9%), and tuberculosis (1.7%). In addition, 5.1% of the global burden of diseases and injuries were attributable to alcohol, which is equivalent to 139 million Disability Adjusted Life Years (DALYs) (WHO, 2014).

Ethanol or ethyl alcohol (C_2H_5OH) is a colorless liquid found in all alcoholic beverages, and although these are classified as "drugs," their marketing is lawful and widely accepted. It is a widely used psychoactive substance whose excessive consumption entails a series of physical, social, and mental problems (Almeida and Campos, 2013).

Ethanol is a small lipid-soluble neurotrophic substance that penetrates the blood brain barrier and consequently interacts with various neurotransmitter systems in the brain, such as dopamine. Alcohol increases dopaminergic transmission and increases the firing rate of dopaminergic neurons, thereby increasing the release of dopamine (Ward et al., 2009). The reward pathway modulates the primary physiological functions related to survival, including food and water intake and sexual behavior. This pathway is also targeted by psychoactive substances, including cocaine, amphetamines, and opioids (Jones and Miller, 2008).

During abusive consumption, larger amounts of alcohol may be required to trigger the release of dopamine in order to achieve the pleasurable effects of alcohol intake. During withdrawal from alcohol, the release of dopamine will be reduced, dramatically reducing the firing of related neurons, leading to dysphoria, malaise, and depression (Boileau et al., 2003; Ward et al., 2009).

The evaluation of neurotransmission can be performed through

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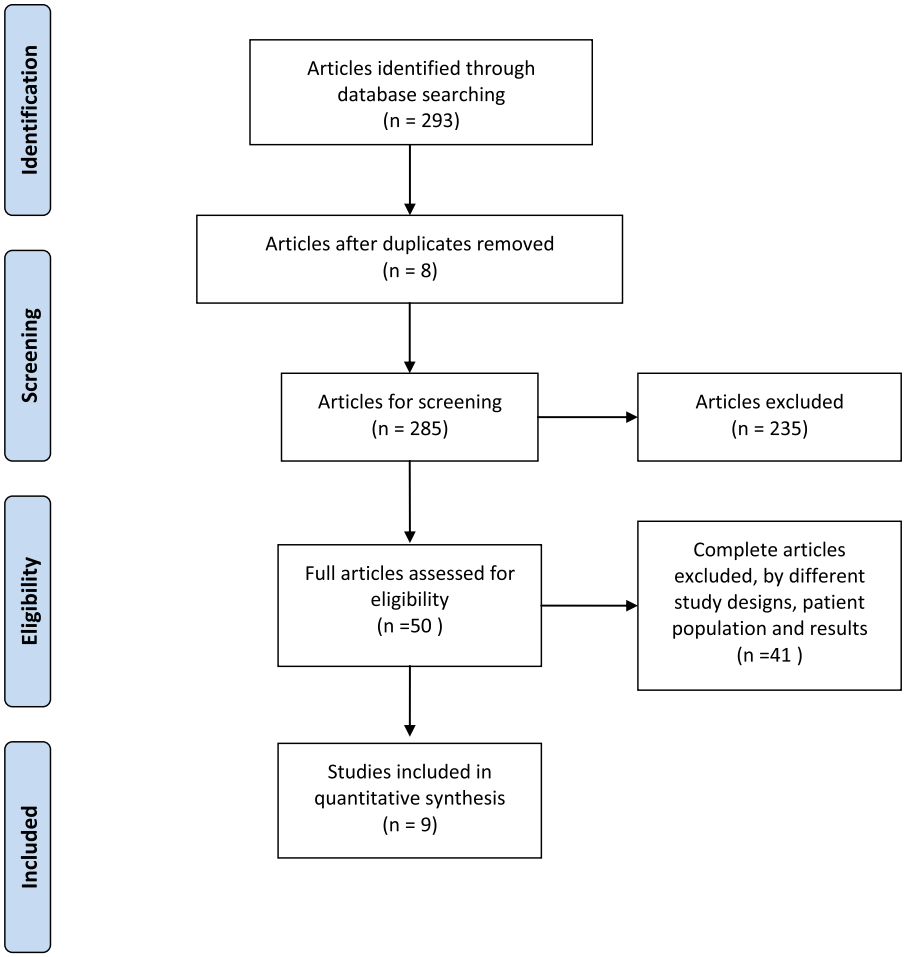

Fig. 1. Flowchart of the search strategy. Preferred reporting items for systematic reviews and meta-analyses (PRISMA).

imaging examinations using scanning and tracking techniques. Positron Emission Tomography (PET) has the ability to detect functional, metabolic, and biochemical changes in organs or tissues through radioactive substances (carbon-11, nitrogen-13, oxygen-15, and fluorine-18) that accompany metabolic processes without interfering with them.

Alcohol abuse is a public health problem; while its precise neurobiology is still unknown, several studies have sought new biomarkers for this disorder. Understanding the levels of dopamine in alcohol abuse is important for prevention strategies. Currently the Best Performance System for evaluation of neurotransmission is the PET Scam.

We developed a systematic review of studies evaluating the dopaminergic system with Proton Emission Tomography (PET) to determine dopamine concentrations in individuals engaging in alcohol abuse.

2. Materials and methods

2.1. Search strategy

A search strategy was developed using the following terms, “dopamine,” “ethanol” or “alcohol,” and “positron-emission tomography,” as text words and Medical Subject Headings (i.e., MeSH and EMTREE) to search MEDLINE, EMBASE, Cochrane Library, Insight, and gray literature (Google Scholar and the British Library) for studies published until March 2018. The search was limited to human studies and had no language restrictions.

2.2. Screening of abstracts for eligibility

Two reviewers independently screened the abstracts with reference to the study inclusion criteria. The screening process was conducted in Covidence (www.covidence.org).

2.3. Study selection

Two reviewers (MCMA and TC) made preliminary relevance assessments with Covidence (www.covidence.org). Potentially relevant studies were examined by two reviewers who obtained full-text copies of the reports. Disagreements between the reviewers were resolved by the involvement of a third reviewer (MIR).

2.4. Criteria for selection of studies

For inclusion, a study must be an observational study of humans in situations of alcohol abuse submitting to a Dopamine Emission Tomography scan for dopamine analysis regardless of dose, age, sex, and ethnicity for comparison to a control group. We excluded studies performed on individuals with pathologies or use of drugs that alter the functioning of the dopaminergic system, as well as preclinical studies.

2.5. Data extraction

Two investigators independently extracted data from the primary studies included in the study. Any disagreements about study inclusion or exclusion were resolved by consensus. The data extraction was performed using a collection form, which included the following information: The country where the study was performed, number of participants in the exposed population and control, sex, time of consumption and abstinence, method used, and results.

2.6. Assessment of quality and risk of bias

To assess bias risk, two MCMA and MIR reviewers independently assessed each study selected using the Newcastle-Ottawa Quality Score Scale (NOS). NOS evaluates observational studies based on eight items categorized into the three following groups: (1) Selection of study participants, (2) population comparability, and (3) verification as to whether exposure or outcome includes any risk of bias, selection bias, or loss bias for follow-up. The NOS is scored from 0 to 9, and studies with scores ≥ 7 are considered high quality. The selection group comprises four questions whose highest value is 1 point and lowest is 0, thus having a maximum score of 4 points. Comparability has two questions with a maximum value of 1 point, and thus can have a maximum score of 2 points. Exposure comprises three questions with a maximum value of 1 point, thus having a maximum score of 3 points.

3. Results

The search of the databases using the specified search strategies yielded a total of 293 studies. After reading titles and abstracts through the Covidence program, 235 were considered irrelevant since they did not meet the inclusion criteria. The full texts of 50 studies were read and analyzed. From these studies, 41 articles were excluded due to the study design, population, and different outcomes. Nine articles involving 125 alcoholics and 131 controls met the criteria for inclusion and were analyzed in the qualitative synthesis of the systematic review (Fig. 1).

The main characteristics of the included studies are shown in Table 1, while Table 2 presents the methods and results of the studies.

Table 3 shows the quality evaluation of the studies included in the systematic review according to the criteria of the Newcastle-Ottawa Quality Assessment Scale (NOS).

(1) Selection questions: All articles presented a good source of selection (the case definition was adequate, as was the representativeness of the cases; the selection of the controls was performed in the community randomly and according to predefined criteria; and the controls had no history of disease).
(2) Comparability issue: All articles used imaging tests (PET) to compare dopamine-related parameters in alcoholics.
(3) Exposure issues: Regarding the determination of exposure, eight of the nine articles carried out a questionnaire/interview not blinded to case-control status, whereas one article (Hietala et al., 1994) did not present a description of how exposure determination was performed. All articles used the same screening method for cases and controls, and all had the same non-response rate for both groups evaluated.

Regarding the score, two studies obtained 7.0 points (Hietala et al., 1994; Erritzoe et al., 2014), four studies had 7.5 points (Volkow et al., 1996, 2007; Spreckelmeyer et al., 2011; Narendran et al., 2014) and three studies (Heinz et al., 2004, 2005; Martinez et al., 2005) reached 8.0 points. According to the NOS score, our systematic review demonstrated high quality (≥ 7).

4. Discussion

The neuroimaging of the dopaminergic system through positron emission tomography (PET) has been fundamental in the characterization of alcohol dependence in humans (Martinez et al., 2007). Molecular neuroimaging techniques are important in the safe and non-invasive investigation of brain proteins, such as neuroreceptors, transporters, and enzymes [17]. In the last two decades the radiotracers [^{11}C] raclopride, [^{11}C] fallypride, [^{123}I] epidepride, and [^{123}I] iolopride (IBZM) have been used to image the D2 receptor family. [^{11}C] raclopride is the most commonly used marker for the evaluation of changes in endogenous striatal dopamine. This radiotracer has an affinity for the D2/D3 receptors and is sensitive to both increases and decreases in dopamine concentration (Thanos et al., 2005). In vivo imaging studies have shown a decrease in the availability of D2 receptors in alcohol-dependent patients compared to controls and cases of alcohol abuse (Hietala et al., 1994; Volkow et al., 1996; Heinz et al., 2004; Martinez et al., 2005).

Many PET tracers are compounds that bind reversibly to a neuronal protein, such as a receptor or a carrier. The most commonly used quantitative relationship is the "binding potential," defined as the ratio B_{max}/K_d, where B_{max} is the concentration of receptors available for binding and K_d is the apparent affinity constant of the radiotracer for its target. The typical interpretation of the binding potential is that it represents the receptor or carrier density or "number of receptors" (Yoder et al., 2011).

All abuse drugs consumed in excess have in common the direct activation of the brain reward system, which is involved in reinforcing behaviors and memory production. Continuous stimulation of dopamine leads to desensitization of the reward systems (Oliveira and Malbergier, 2014). The mesolimbic and mesocortical systems work in parallel with each other and with the other cerebral structures configuring this system of cerebral reward, and dopamine is the main neurotransmitter present in this system, but not the only one. Neurotransmitters such as serotonin, noradrenaline, glutamate, and gamma-aminobutyric acid (GABA) are responsible for CNS modulation and are also present in the reward system (Nie et al., 2004). The pharmacological mechanisms by which each class of drugs produces rewards are different but generally lead to the activation of this system and produce sensations of pleasure (Kalivas and Volkow, 2005). Alcohol, by potentiating the GABAergic receptors, inhibits the function of this neurotransmitter in the terminals of other neurotransmitters, increasing the activity of the dopaminergic neurons, as well as inhibiting glutamatergic terminals that innervate the nucleus accumbens (Esch and Atefano, 2004). Chronic ethanol action upon GABA receptors triggers progressive desensitization mechanisms that, together with the sensitization of N-methyl-D-aspartate (NMDA) receptors, can play an

Table 1
Characteristics of included studies. Abbreviations: M = Male; F = Female.

Study	Country	Age		Sex		N	
		Control	Alcohol	Control	Alcohol	Control	Alcohol
Martinez et al., 2005	USA	35 ± 6 years	34 ± 6 years	12 M/3F	13 M/2F	15	15
Volkow et al., 1996	USA	47 ± 16 years	44 ± 10 years	15 M/2F	9 M/1F	17	10
Hietala et al., 1994	Finlând	36,3 ± 6,7 years	36,9 ± 6,4 years	8 M	9 M	8	9
Heinz et al., 2005	Germany	43,2 ± 9,5 years	42,5 ± 7,5 years	13 M	12 M	13	12
Heinz et al., 2004	Germany	43,2 ± 9,5 years	44,5 ± 6,5 years	13 M	11 M	13	11
Spreckelmeyer et al., 2011	Germany	45,4 ± 7 years	47,9 ± 7 years	11 M	11 M	11	11
Erritzoe et al., 2014	England	41,5 ± 10,3 years	42,4 ± 9,4 years	13 M	16 M	13	16
Narendran et al., 2014	USA	28 ± 4 years	28 ± 5 years	16 M/5F	16 M/5F	21	21
Volkow et al., 2007	USA	41 ± 6 years	41 ± 6 years	20 M	20 M	20	20

Table 2
Methods and results of included studies. Abbreviations: D2 = dopamine receptors type 2; D = dopamine receptors type 3; DAT = dopamine transporter; DA = dopamine; DMFP = desmethoxyfallypride; [11C] FLB = [11C]Cyclopropyl-FLB 457 is a PET radioligand for low densities of dopamine D2 receptors; GSK598809 = Dopamine receptor antagonista type 3; MOR= γ -Aminobutyric acid; PET = Positron Emission Tomography; PHNO = [(11)C]-(+)-PHNO radioligand with preference for D3 in PET; VT= Total volume of distribution.

Study	Time of consumption	Abstinence time	Average consumption	Method	Findings
Martinez et al., 2005	18 ± 7 years	3 weeks	20 ± 8/day 18 ± 7/year	PET and the radiotracer of the D2 receptor [11C] raclopride at baseline and after amphetamine (0.3 mg /kg intravenously)	Reduction in the availability of the D2 receptor in the putamen, ventral striatum and caudate
Volkow et al., 1996	24 ± 7 years	5 days	–	PET and the radiotracer of the D2 receptor [11C] raclopride	Reduction in D2 receptor availability
Hietala et al., 1994	6 years (Minimum)	1 week of abstinence	pure ethanol 300 g (range 120–480 g) per day	PET and the D2 [11 C] racloprid receptor radiotracer at a dose of 3.0 mCi I.V.	Reduction in density / affinity ratio (availability) of the D2 receptor
Heinz et al., 2005	–	36 days (only 5 remained)	–	PET and docarboxylase substrate 6 [18F] fluoro-L-dopa	Low levels of dopamine synthesis capacity in bilateral putamen with high levels of alcohol craving.
Heinz et al., 2004	–	2–4 weeks of abstinence	–	PET and radioligand of benzamide [18F] DMFP, which binds with high affinity to D2 dopamine receptors.	Redução na disponibilidade do receptor D2 no putamen e estriado ventral
Spreckelmeyer et al., 2011	–	Between 8 and 48 days (mean of 32/36 days)	8.2 ± 2 drinks / day cases; 3.6 ± 3 drinks / day controls	PET and the radiotracer of dopamine receptor [18F] fallyride at baseline and 2 weeks after. Remifentanil (MOR agonist)	Reduction in D2 / D3 receptor availability after ingestion of remifentanil compared to baseline in ventral striatum (9.5%), dorsal putamen (8.3%) and amygdala (12.5%).
Erritzoe et al., 2014	26,4 ± 9,5 years of alcohol abuse	4 weeks of abstinence	348 ± 131 unit / week cases; 9.8 ± 7.6 unit / week control	PET and the D3 agonist radioligand, [11C] PHNO, with a selective D3 antagonist GSK598809 60 mg p.o.	Basal binding of [11C] PHNO was higher in alcohol dependent patients in the hypothalamus
Narendran et al., 2014	11 ± 6 years of alcohol abuse	14 abstinent days	13 ± 5 drinks/day	Amphetamine and [11C] FLB457 PET	Reduced availability of D2 / D3 receptors and decreased dopamine transmission in the cortex in alcoholism.
Volkow et al., 2007	23 ± 8 years of alcohol abuse	79 ± 38 abstinent days	16 beers per day	PET and [11C] raclopride + methylphenidate IV (DAT blocks → increasing DA)	Reduction in D2 / D3 receptor availability in the striatum

essential role in the process of alcohol dependence. Cannabinoid, nicotinic, opioid, and serotonergic receptors may play a key role in modulating dopamine discharges in the nucleus accumbens triggered by alcohol consumption (Brebner et al., 2005).

The present systematic review has shown that four studies resulted in showing a reduction in availability only at the D2 receptor in different brain regions (Hietala et al., 1994; Volkow et al., 1996; Martinez et al., 2005). Four studies reported a decrease in both receptors (Heinz et al., 2005; Volkow et al., 2007; Spreckelmeyer et al., 2011; Narendran et al., 2014), and in relation to the D3 receptor alone only one study reported this finding (Erritzoe et al., 2014).

The study by Martinez et al. (2005) included 15 control subjects with a mean age of 35 ± 6 years and 15 alcohol dependent individuals with a mean age of 34 ± 6 years, who had been consumers on average 18 ± 7 years. The alcoholic patients underwent three weeks of hospitalization, with three to five days of detoxification with chlordiazepoxide. In this study, PET and the radiotracer of the D2 receptor [^{11}C] raclopride were used to assess the availability of the D2 receptor at baseline and then with an intravenous injection of amphetamine (0.3 mg/kg) to induce the displacement of the radiotracer. It has been observed that D2 receptor availability is decreased in the subdivisions of the striatum (putamen, caudate, and ventral striatum) in recently detoxified alcoholics compared to control subjects. These results corroborate previous studies suggesting a reduction of 15– 20% in the availability of the D2 receptor in alcohol dependence and show that reduction involves brain structures such as the striatum and ventral tegmental area (VTA) (Hietala et al., 1994; Volkow et al., 1996). Studies of human autoradiography have shown that alcohol dependence is associated with a reduction in D2 receptor density in the striatum (Tupala et al., 2001, 2003). Decreases in D2 receptor availability have been demonstrated in PET studies of other addictive behaviors such as heroin and cocaine dependence, methamphetamine abuse, and even obesity, suggesting that this finding is not specific for a single substance of abuse. The dopaminergic pathways are also related to reward systems, justifying these mechanisms of dependence (Wang et al., 2001; Baldaçara et al., 2011).

On the other hand, Heinz et al. (2004) reported a decrease in D2 receptor availability in the striatum and putamen, but no difference in the caudate nucleus. This study was performed with 13 controls, aged 43.2 ± 9.5 years, and a group with 11 alcoholic participants, aged 44.5 ± 6.5 years, who abstained from alcohol in a supervised treatment program of hospitalization for 2–4 weeks. The severity of alcohol craving was measured with the Alcohol Craving Questionnaire (ACQ). For radiotracer, [^{18}F] desmethoxifalide ([^{18}F] DMFP), which binds with high affinity to D2 dopamine receptors, was used in PET. The study tested the hypothesis of Robinson and Berridge (1993) that alcoholics exhibit fewer D2 receptors in the ventral striatum and that the craving for alcohol is inversely related to the availability of D2 receptors. The theory that dysfunction of dopamine in the striatum, which includes the nucleus accumbens, the central area of the brain reward system, is suggested to be associated with the craving for alcohol assessed through the ACQ. In alcoholics, the higher severity of alcohol craving was significantly and exclusively associated with a low availability of D2 receptors in the striatum and putamen.

Volkow et al. (1996) evaluated D2 receptors in 10 alcoholics (44 ± 10 years) with an average history of 24 ± 7 years of alcohol abuse and 17 healthy matched controls (47 ± 16 years) using two different radiotracers, [^{11}C] raclopride to measure D2 and [^{11}C] d-threo methylphenidate receptors to measure dopamine transporters (DATs). All subjects were examined with [^{11}C] raclopride, and in addition 5 of the alcoholics and 16 of the controls underwent a second examination with [^{11}C] d-threo methylphenidate within one week. As measurements of D2 receptors with PET mainly reflect the postsynaptic receptors, [^{11}C] raclopride served as an indicator of the postsynaptic element in the dopaminergic synapse. On the other hand, the evaluation of DATs served as an indicator for the presynaptic element, that is, the

Table 3
Quality evaluation of included studies. Source: From the author, 2018.

Author; year	Selection				Comparability	Exhibition		
	1	2	3	4	1	1	2	3
Erritzoe et al., 2014	A	A	A	A	A (Evaluating brain D3 Dopamine receptors by means of imaging tests)	C	A	A
Volkow et al., 2007	A	A	A	A	A (Check the decrease in Dopamine receptors in alcoholics, but not in Dopamine transporters by imaging)	C	A	A
Spreckelmeyer et al., 2011	A	A	A	A	A (Check the availability of D2 and D3 receptors in alcoholic dependents through imaging tests)	C	A	A
Heinz et al., 2004	A	A	A	A	A (Check the correlation of Dopamine receptors in alcoholics by means of imaging tests)	C	A	A
Heinz et al., 2005	A	A	A	A	A (Compare the ability of Dopamine synthesis in the striatum in alcoholics by means of imaging tests)	C	A	A
Hietala et al., 1994	A	A	A	A	A (Verification of Dopamine binding to D2 dopaminergic receptor in alcoholics by means of imaging tests)	E	A	A
Martinez et al., 2005	A	A	A	A	A (Measure D2 receptors and Dopamine transmission in alcoholics by means of imaging tests)	C	A	A
Volkow et al., 1996	A	A	A	A	A (Check for decrease in Dopamine Receptors, but not in Dopamine transporters in alcoholics by means of imaging tests)	C	A	A
Narendran et al., 2014	A	A	A	A	A (Verify that pre-frontal cortical dopamine transmission is decreased in alcoholics by means of imaging tests)	C	A	A

dopaminergic neuron itself. The availability of dopamine D2 receptors was significantly lower in alcoholics than in controls, and this difference was correlated with age greater than 40 years. Regarding the availability of DATs, there were no significant changes.

Decreases in D2 receptors would in principle result in attenuation of the dopaminergic signal. This could provide an explanation for the higher frequency of dyskinesia in alcoholics than in non-alcoholics, as well as greater sensitivity to dopaminergic antagonists in alcoholics. Decreased dopamine activity may also explain the greater association between alcoholism and parkinsonism. The interpretation of D2 changes differs from that of DATs because the decreases in D2 receptors result mainly from changes occurring in striatal GABAergic neurons, while DATs reflect dopaminergic cells. Therefore, the reduction of D2 receptors implies the involvement of GABAergic cells in dopaminergic abnormalities in alcoholics (Xiao and Ye, 2008; Spreckelmeyer et al., 2011).

The characteristics of the dopamine D2 receptor in the striatum of nine male patients (age 36.9 ± 6.4 years) with alcohol dependence abstinent for 1–68 weeks and eight healthy male volunteers (36.9 ± 6.7 years) were studied in vivo with PET (Hietala et al., 1994). [^{11}C] raclopride was used in an intravenous 3.0 mCi dose to quantify the D2 receptor (K_d) and affinity (Db) density (B_{max}). Abstinent alcoholic individuals had a history of alcohol dependence for at least 6 years (range 6–16 years) with a daily average consumption of pure ethanol of 300 g. A tendency for a decrease in the density and affinity of the D2 receptors in the striatum was observed in patients with alcohol dependence. These isolated parameters did not differ statistically between alcoholics and controls, but the relationship between D2 receptor density and affinity (availability) was significantly lower in alcoholics than in controls. This low ratio of receptor availability is compatible with the reduced accessibility of [^{11}C] raclopride to D2 receptors in alcoholics' striata. Although particularly pronounced in some patients, this reduction was surprisingly stable considering the clinical heterogeneity of abstinent patients. A theoretical explanation for this low relationship in alcoholics is that increased levels of striatal dopamine are competing with the radiotracer [^{11}C] raclopride to bind to D2 receptors (Hietala et al., 1994; Ginovart, 2005; Thanos et al., 2005).

Alcohol, like other drugs of abuse, stimulates dopamine release and induces down-regulation of dopaminergic D2 receptors in the striatum, and these effects appear more prominent after detoxification and demonstrate a withdrawal recovery during the withdrawal period (Volkow et al., 1996). However, chronic alcohol ingestion reduces the availability of dopaminergic D2/D3 receptors in the striatum, which may represent a compensatory negative regulation that ensures homeostasis of central dopaminergic neurotransmission. In alcoholics, the late recovery of central dopamine D2 receptors predicts an increased risk of relapse and may be associated with persistent pre-synaptic dopaminergic dysfunction during early withdrawal. At present, it is unknown whether the low availability of the D2 receptor observed represents a negative counter-adaptive regulation triggered by chronic alcohol-related dopamine release or whether it is due to alcohol-related neurotoxicity. It is suggested to be a potential mechanism by which persistently low levels of D2 receptors in the ventral striatum can contribute to excessive alcohol use and motivation for relapse (Haber et al., 2000; Fiorillo et al., 2003; Yoder et al., 2011).

To further explore the interaction between the presynaptic production of striatal dopamine and the availability of D2/D3 dopaminergic receptor in detoxified alcoholic patients, Heinz et al. (2005) measured the uptake of dopa substrate 6pa [^{18}F] fluoro-L-dopa ([^{18}F] DOPA), an index of dopamine synthesis capacity, in the same alcoholic patients and control subjects, who also underwent evaluation of D2 dopaminergic receptors with [^{18}F] desmethoxyphalide [13]. The severity of alcohol craving was measured with ACQ in the morning before subjects underwent brain imaging. PET scanning was used to map [^{18}F] DOPA to reveal dopamine synthesis capacity in the brain in vivo by calculating net blood-brain clearance. All subjects received carbidopa (2.5 mg /kg body weight) orally 60 min prior to the search to block extracerebral dopa decarboxylase activity. Five alcoholic patients remained abstinent and seven relapsed during the six-month follow-up period (Heinz et al., 2005).

The magnitude of net brain clearance in the striatum did not differ significantly between the detoxified alcoholic patients and control subjects. However, a correlation analysis of net blood-brain clearance in alcoholic patients related low levels of dopamine synthesis capacity in the putamen with high levels of alcohol craving (Heinz et al., 2005). As previously reported by Heinz et al. (2004), the availability of D2/D3 dopaminergic receptors in the putamen and striatum was significantly lower in alcoholic patients than in healthy individuals. In the alcoholic patients, a negative correlation was observed between the severity of the desire for alcohol and the magnitude of this index along the putamen and the right ventral and caudate striatum.

It is believed that chronic drug use results in adaptive changes in dopamine- modulated regions (circuits) that underlie the neurobiology of dependence (Nestler, 2004). Among these, the prefrontal cortex is increasingly recognized as playing a central role in addiction. Prefrontal cortical dopamine modulates executive functions, such as attention, working memory, and risk/reward decision making—all of which are impaired in alcoholism (Bickel et al., 2012). Volkow et al. (2007) tested the hypothesis that the prefrontal cortex regulates rewards by modulating increases in dopamine in the nucleus accumbens and that this regulation is discontinued in dependent individuals. PET was used to evaluate pre-frontal cortex activity (measuring cerebral glucose metabolism with [^{18}F] fluorodeoxyglucose) and dopamine increases with [^{11}C] raclopride induced before and after intravenous administration of the stimulant drug methylphenidate (0.5 mg/kg) in 20 controls and 20 detoxified alcoholics, both aged 41 ± 6 years.

At baseline, the availability of the D2/D3 receptor in the ventral striatum was significantly lower in alcoholics. Following the administration of methylphenidate, the availability of these receptors was reduced in the striatum and putamen in alcoholics. In controls the metabolism in the orbitofrontal cortex (region involved with salivation)

was negatively associated with the increase of dopamine induced by methylphenidate in the ventral striatum and putamen. In contrast, in alcoholics, metabolism in the pre-frontal regions was not correlated with changes in dopamine. This suggests that in alcoholics, the regulation of dopaminergic cell activity by prefrontal efferents is discontinued and that their decreased dopaminergic cell activity may represent a loss of pre-frontal regulation of the mesolimbic pathways. One of the major contributions to dopaminergic cells in VTA is the efferent glutamatergic of the prefrontal cortex, and there is increasing evidence that they play an important role in addiction. These results are consistent with the hypothesis that the orbitofrontal cortex modulates the value of the rewards by regulating the magnitude of dopamine increases in the ventral striatum and that disruption of this regulation may lie behind the diminishing sensitivity to rewards in dependent individuals (Kalivas and Volkow, 2005; Homayoun and Moghaddam, 2006; Volkow et al., 2007).

In humans examined using PET, [^{11}C] raclopride following an acute amphetamine test (or methylphenidate) was validated as a noninvasive measure of the change in the induction of extracellular dopamine concentration. Using this approach, two studies reported decreased dopamine neurotransmission in the striata of alcohol-dependent individuals compared to controls (Volkow et al., 1996; Martinez et al., 2005). One limitation of these studies is that the measures of dopamine transmission were restricted to the striatum and its subdivisions. Such studies were limited to the striatum because the [^{11}C] raclopride does not provide a sufficient signal-to-noise/response ratio to quantify the D2/D3 receptors in extrastrial areas, such as the cortex, where the concentration of D2/D3 receptors is less than in striated areas. Thus, no previous study reported the in vivo status of dopamine in the prefrontal cortex in alcoholism.

Based on this, Narendran et al. (2014) used PET and the [^{11}C] high affinity radioligand FLB 457 to measure amphetamine-induced cortical dopamine neurotransmission in a group of 21 recently abstinent alcoholics and 21 healthy paired controls. Subjects were submitted to an initial PET and post-amphetamine [^{11}C] FLB 457 in the same experimental session. At baseline, subjects received an intravenous bolus injection of [^{11}C] FLB 457 restricted to 0.6 μg. A post-amphetamine sweep [^{11}C] FLB 457 was performed 3 h after administration of 0.5 mg/kg-1 of oral amphetamine. A lower displacement of [^{11}C] FLB 457 in the cortex and midbrain after amphetamine was found in recently abstinent alcoholics than in the healthy controls, i.e., decreased availability of D2/D3 receptors in abstinent alcoholics. In an earlier study using PET and microdialysis, the 1% displacement of [^{11}C] FLB 457 in the cortex was shown to correspond to a 57% increase in extracellular dopamine concentration (Koob, 2013; Narendran et al., 2013). This suggests that cortical dopamine in healthy controls and alcohol-dependent individuals increases by 513–798% and 0–228%, respectively, after the same dose of amphetamine. This finding has shown for the first time that there is a decrease in dopamine transmission in the cortex in alcoholism.

The reduction of dopamine transmission in the mesolimbic regions, such as the ventral striatum and the medial temporal lobe, contributes to anhedonia, lack of motivation, and decreased sensitivity to reward in alcohol dependence. The fact that there is also less dopamine in the prefrontal cortex, which governs executive functions, may impair the addict's ability to learn and use behavioral informational/critical strategies to prevent relapse. This is supported by research that links prefrontal cortical dopamine to functions that are compromised in additive disorders (Floresco and Magyar, 2006; Bickel et al., 2012).

Evidence suggests that the reinforcing effects of alcohol are mediated by the interaction between the opioid and dopaminergic systems of the brain. Specifically, the release of β-endorphins induced by alcohol stimulates μ-opioid receptors (MORs), which are believed to cause dopamine release in the brain reward system (Hagelberg et al., 2002; Daglish et al., 2008). Spreckelmeyer et al. (2011) performed a study administering a single dose of remifentanil (0.3 g/kg), which is a MOR agonist, in 11 alcohol-dependent patients (47.9 ± 7 years) detoxified for eight weeks on average and in 11 healthy controls (45.4 ± 7 years) to mimic the endorphin release properties of ethanol and to evaluate the effects of direct stimulation of MOR on dopamine release in the mesolimbic reward system. The availability of D2/D3 receptors was assessed at the baseline and two weeks after administration of a single dose of remifentanil in the two groups via positron emission tomography with the [^{18}F] fallypride radiotracer. The severity of alcohol dependence was assessed with the Alcohol Use Disorders Identification Test (AUDIT). A reduction in the availability of D2/D3 dopaminergic receptors after administration of remifentanil in comparison to baseline values was achieved in (9.5%), the putamen (8.3%), and the amygdala (12.5%), consistent with an increase in dopamine levels. However, group comparison did not find a significant difference between alcoholics and controls. However, in the alcoholic group, the relative decrease in D2/D3 receptor availability was associated with the severity of consumption.

This finding indicates that the sensitivity of the dopamine and opioid pathway to MOR stimulation is not equally pronounced among alcohol-dependent individuals. On the contrary, there appears to be an association between the MOR- mediated dopamine response and the severity of alcohol abuse. This is based on reports that MOR blocking with the naltrexone antagonist, successfully used as a treatment to reduce rates of craving and relapse in alcohol and opiate dependents, is unequally effective and the severity of its side effects differs in different individuals. In the present study, the availability of MOR was not evaluated directly. However, Heinz et al. (2005) reported a higher availability of MOR in detoxified alcohol-dependent patients than in controls, which is also correlated with craving. It can be speculated, assuming a link between the severity of craving and the severity of consumption, that the association between remifentanil-induced dopamine release and alcohol dependence severity may be attributed to a higher number of MORs (greater sensitivity to MOR stimulation) in severe alcoholism. These data indicate that direct stimulation of MORs increases dopamine release in the brain reward system, providing important evidence for the MOR-mediated control of the mesolimbic dopamine pathway (Hagelberg et al., 2002; Barr et al., 2007).

Animal studies support evidence of the role of the D3 receptor in the enhancement or preference for alcohol, suggesting that selective D3 antagonism reduces ethanol preference and consumption in rats that prefer and do not prefer alcohol (Thanos et al., 2005) and reduces the number of reinforcements and amount of alcohol consumed in rodents (Andreoli et al., 2003). The absolute density of D3 is high in the “limbic” dopaminergic system, and this hypothesis is particularly relevant for the treatment of additive disorders. D3 also plays an important role in mediating the effects of stress, leading to drug-seeking behavior (Heidbreder and Newman, 2010). In humans, a single dose of a selective D3 antagonist has been shown to partially alleviate cigarette craving in abstinent short-term smokers (Mugnaini et al., 2013).

Only one study (Erritzoe et al., 2014) reported D3 receptor involvement alone. The availability of brain D3 was compared between 16 alcohol-dependent (42.4 ± 9.4 years) patients abstinent for four weeks and 13 age-matched controls (41.5 ± 10.3 years) using PET and an agonist radiotracer of D3, [^{11}C] PHNO, before and after the oral application of a DRD3 selective antagonist, GSK598809 (60 mg). The basal binding of [^{11}C] PHNO was higher in alcohol-dependent patients in the hypothalamus (a region in which [^{11}C] PHNO almost entirely reflects the availability of D3), and following GSK598809 dose there was a decrease in receptor binding.

A review of the literature by Martinez et al. (2007) evaluated the D2/D3 [^{11}C] antagonist radiotherapists raclopride, [^{18}F] desmethoxyfaloxide, [^{123}I] IBZM, and [^{123}I] epidepride in alcoholism and reported consistently lower (7–22%) availability of D2/D3 in the striatum of alcohol dependents than of controls. Erritzoe et al. (2014) found no difference between abstinent alcoholics and controls in [^{11}C] PHNO binding in the striatum with or without D3 blockade. The hypothesis of

an overall increase in D3 in abstinent alcohol dependence has not been confirmed, although increased D3 binding has been detected in the hypothalamus, a region involved in the control of opioid neurotransmission, which is a key modulator of the mesolimbic dopaminergic pathway (Rominger et al., 2012).

Alcohol is the most widely used licit substance in the world. Alcohol abuse is one of the most severe disorders, affecting the lives of millions of people around the world and having a great impact on patients' quality of life (American Psychiatric Association, 2013). The discovery of biomarkers could help both in diagnosis and in the development of new treatments for addiction (Malbergier and Oliveira Jr., 2005). Several studies suggest that alterations in dopaminergic receptors play an important role in the pathophysiology of alcoholism (Hietala et al., 1994; Volkow et al., 1996; Heinz et al., 2004, 2005; Martinez et al., 2005; Volkow et al., 2007; Spreckelmeyer et al., 2011; Erritzoe et al., 2014; Narendran et al., 2014).

We note that one of the limitations of this study is the low number of good quality studies. The subject is examined in the literature but in a reduced form and with different approaches.

5. Conclusion

PET studies in alcoholic humans suggest alterations in D2 receptors in several brain regions, thus highlighting the important role of the dopaminergic system against alcohol abuse.

The findings of this study allow us to contribute and extend the evidence of recent research to obtain new perspectives on the role of the dopaminergic system and the importance of new studies in order to better understand the harmful effects of alcohol.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2019.112542.

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