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Review

Biomedical

Direct monitoring of ethanol in the brain

G Rocchitta*, PA Serra

Abstract

Introduction

In the past few decades, ethanol has assumed the role of the most widespread psychotropic agent in Western society because of its availability to the youth and adults and also because it is generally considered legal in many societies. It is known that the alcohol can have significant relapses on the central nervous system; hence, there is a need for monitoring the toxicokinetics and the effects of ethanol on the brain with the most appropriate techniques. Among the techniques that aim to measure ethanol concentration in the brain, microdialysis has been the most widely used, but because of its invasiveness, associated with low temporal resolution, and the necessity of using connecting tubes to carry out the experiments, it is not particularly suitable for clinical trials. Recently, electrochemical biosensors, also minimally invasive, have been developed, which offer the possibility of monitoring the real-time variations of ethanol concentrations in the brain of animal models due to the very small dimensions of the transducer electrode. Recently, non-invasive methods have been used for the direct monitoring of alcohol in the brain, which use spectroscopic techniques such as magnetic resonance spectroscopy and magnetic resonance imaging or positron emission tomography, which are principally used to monitor ethanol metabolites. The aim of this review is to discuss all the techniques used to monitor brain ethanol and highlight their strengths and weaknesses.

Conclusion

Microdialysis and biosensors are primarily used in preclinical studies; both are very reliable techniques, but for invasiveness, they can only be used in animal models. Alternatively, spectroscopic techniques are suitable for both preclinical and clinical studies, and are not exclusive for animal models.

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Introduction

In the past few decades, ethanol has assumed the role of the most widespread psychotropic agent in Western society because of its availability to the youth and adults and also because it is generally considered legal in many societies. The main effects of ethanol consumption are visible not only in the gastrointestinal tract or the circulatory system, but also on the central nervous system (CNS) where it causes significant relapses, substantially influencing the balance between excitatory and inhibitory phenomena in the brain, principally enhancing the action of GABA (the major inhibitory neurotransmitter), and consequently generating disinhibition, ataxia and sedation[1].

It has been largely demonstrated that acute and subchronic exposure to ethanol may have important repercussions on the brain, enhancing the dopamine neurotransmission in the mesolimbic system, producing an intensification of the dopaminergic neurons in VTA[2–4] and increasing dopamine levels in the nucleus accumbens[5], thus playing an important role in the 'reward' system in the development of alcohol abuse and addiction[6–8].

Therefore, it becomes significant to monitor the toxicokinetics and the effects of ethanol on the brain with the most appropriate techniques.

In the last decades, several techniques have been used for the preclinical and clinical studies of ethanol dynamics in the CNS. Although many of these point out the neurochemical changes induced by ethanol, some studies are aimed directly at ethanol in order to understand the complex cause-and-effect relationships between alcohol intake and brain levels or addiction.

Among the techniques that aim at measuring ethanol concentration in the brain, microdialysis has been the most widely used. In fact, the technique itself turns out to be useful for giving information about the composition of interstitial fluids after a probe insertion in the brain tissues[9]. Furthermore, this technique has been largely used for preclinical studies on the connection between alcohol consumption and neurochemical variations[10] in different brain regions and also to assess the effects of some therapies against alcoholism. The major limiting factors of the technique are as follows: it is minimally invasive, the temporal resolution is poor and there is a need to have a parallel analytical and usually chromatographic system.

Recently, different designs of an electrochemical biosensor, also minimally invasive, have been developed, which, unlike microdialysis, offer the possibility of monitoring the real-time variations of ethanol concentrations in the brain of animal models. The biosensor exploits the presence of the biological element, alcohol oxidase (AOx), to selectively transform ethanol into an oxidable by-product,

FOR CITATION PURPOSES: *Rocchitta G, Serra PA.* Direct monitoring of ethanol in the brain. OA Alcohol 2013 Sep 01;1(2):15.

Competing interests: none declared. Conflict of interests: none declared.
All authors contributed to conception and design, manuscript preparation, read and approved the final manuscript.
All authors abide by the Association for Medical Ethics (AME) ethical rules of disclosure.

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amperometrically detectable by a transducer[11,12].

In recent decades, non-invasive methods have been used for the direct monitoring of alcohol in the brain of primates and humans. These methods use spectroscopic techniques, such as magnetic resonance spectroscopy (MRS) and magnetic resonance imaging (MRI)[13,14] or positron emission tomography (PET), which are principally used to monitor ethanol metabolites[15].

The aim of this review is to show and critically discuss all the techniques used to monitor brain ethanol and highlight their strengths and weaknesses.

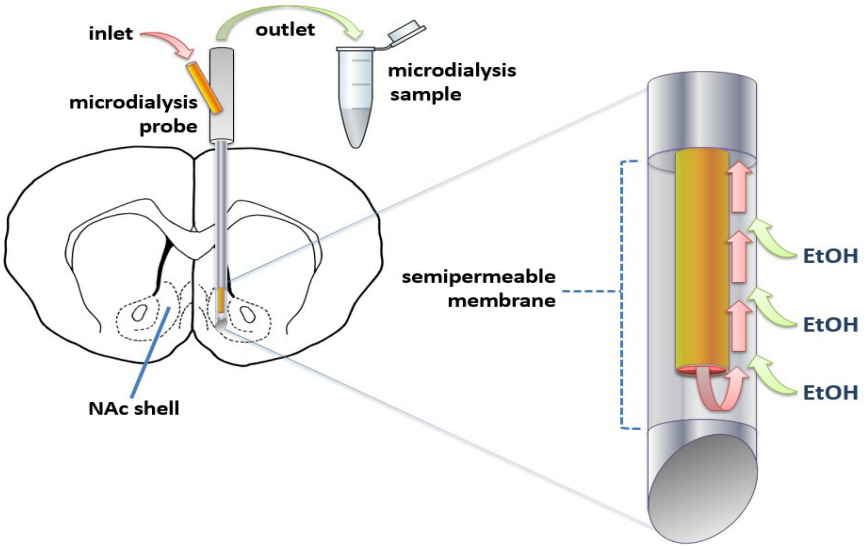

Figure 1: Outline of a microdialysis probe inserted in the nucleus accumbens (shell). The appropriate fluid (pink arrows) is perfused through a capillary into the semipermeable membrane. The passage of substances across membrane pores in both directions – that is, in (green arrows) and out of the probe – is allowed. The collected samples, enriched with the studied substances, are collected at the exit of the probe and then analysed by means of proper analytical method.

Discussion

The authors have referenced some of their own studies in this review. These referenced studies have been conducted in accordance with the Declaration of Helsinki, 1964, and the protocols of these studies have been approved by the relevant ethics committees related to the institution in which they were performed. All human subjects, in these referenced studies, gave informed consent to participate in these studies. Animal care was also in accordance with the institution guidelines.

In vivo microdialysis

Microdialysis is a minimally invasive technique suitable for measuring chemicals in the extracellular compartment of several organs, tissues or specific brain regions[16]. The idea of microdialysis originated in the 1970s with the aim of implanting a thin dialysis fibre into the tissues and simulating the role of a blood capillary so that it is possible to recover molecules from a tissue or eventually supply some molecules to it in order to highlight the changes in metabolism or the topical effects of the molecules[17,18] (Figure 1).

Microdialysis exploits the dialysis principles, based on the insertion of a probe, which loads a semipermeable membrane into a tissue, separating two fluid compartments and exchanging only low molecular weight compounds[16]. The probe is perfused with an appropriate fluid so that neurochemicals are able to diffuse down their concentration gradients in both directions, in and out of the probe. The microdialysis samples are analysed by means of different analytical methods. Invasiveness, poor temporal resolution and sensitivity of the used analytical technique represent the major limitations of this technique.

Despite all its technical implications, microdialysis technique has proved to be particularly suitable for the direct monitoring of ethanol levels in the brain.

Brain ethanol concentrations are a key factor to understanding the physiological repercussions of alcohol intake. Indeed, the time course of brain ethanol concentrations is affected by several aspects, including both the ethanol dose and path of administration[9].

In animal models, ethanol administration is usually performed intraperitoneally[19] or intragastrically[20], sometimes with self-administration[21] and forced drinking in rats[22] ethanol is generally administered in a range between 0.5 g/kg and 2 g/kg.

Some authors claim to measure the concentration of ethanol in the samples by means of gas chromatography technique, generally supplied with a headspace autosampler and flame ionization detector[22,23]. Only Peris et al. provided for the measurement of ethanol in dialysates via an enzymatic assay[24].

Biosensing

In recent decades, the biosensing technique has been emerging because of its versatility, multiple applications, and, most of all, its low temporal and spatial resolutions. In particular, amperometric biosensing has proven to be very sensitive so as to allow the detection of very low concentrations of the studied analytes.

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Competing interests: none declared. Conflict of interests: none declared.
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Recently, an amperometric biosensor for direct ethanol monitoring in the brain has been developed[11,12]. The main feature of the biosensor is to exploit the enzyme AOx for selectively transforming ethanol into a by-product in the form of hydrogen peroxide (H_2O_2), according to the following reactions:

$RCH_2OH + AOx/FAD \rightarrow RCHO + AOx/FADH_2$ (1)

$AOx/FADH_2 + O_2 \rightarrow AOx/FAD + H_2O_2$ (2)

$H_2O_2 \rightarrow O_2 + 2H^+ + 2e^-$ (3)

H_2O_2 can be amperometrically detected on a platinum/iridium surface by applying a high fixed anodic over-potential of +700 mV (reaction 3). The amount of H_2O_2 produced is directly proportional to the ethanol concentration, providing a direct quantification of ethanol present in the vicinity of the biosensor, as represented in Figure 2.

The selected biosensor design has been developed to obtain the best working conditions, especially in terms of working pH, temperature[12], sensitivity and shielding against the main interfering electroactive molecules present in the brain's extracellular spaces as ascorbic acid[11].

Shielding against interfering substances can be achieved by the electrodeposition of particular membranes capable of acting as a molecular sieve, and a good sensitivity is reached by means of enzyme stabilizers, which are capable of enhancing the basic responses of the enzyme.

Because of the very small dimensions of the transducer electrode (active surface of 1 mm and diameter of 125 µm), this device is a very interesting implantable tool for preclinical studies of ethanol toxicokinetics in animal models[11]. Moreover, the possibility of associating the biosensor to a telemetric device can offer a rapid and reliable system for studying ethanol kinetics in the animal brain under totally freely moving conditions[25].

Spectroscopic techniques

Magnetic resonance spectroscopy

MRS is a non-invasive analytical technique that has been used to study metabolic changes in several pathologies, such as brain tumours, strokes and seizure disorders.

MRS, also known as nuclear magnetic resonance (NMR) spectroscopy, is a typical analytical technique used in chemistry applications that permits the identification and quantification of several compounds in samples of different origin. It differs from conventional MRI; in that, spectra are given physiological and chemical information rather than anatomical information.

As a spectroscopy technique, in vivo MRS is able to record peaks of different radio frequencies and intensities from molecules that possess nuclear spins, typical resonance frequencies, spin couplings and unique relaxation properties, which are fundamental molecular properties for the application of the NMR technique[26]. The most commonly investigated nuclei are proton (^{1}H), carbon (^{13}C), phosphorus (^{31}P), lithium (^{7}Li), fluorine (^{19}F) and sodium (^{23}Na). However, hydrogen turns out to be the principally investigated nucleus because of its abundance and also its high sensitivity to the hydrogen (^{1}H) nucleus. Moreover, an analysis could be performed with common clinical MRS equipment associated with the clinical imaging of the brain[27,28].

The proton MR spectra show different peaks along the *x*-axis, labelled in parts per million (ppm), while the amplitude of the resonances is measured on the *y*-axis, generally using an arbitrary scale[29].

MRS has been largely used to measure brain alcohol levels in vivo[30–32], and its added benefit is the ability to monitor alcohol-induced changes in the spectroscopically-visible brain metabolites[13].

Ethanol is detectable by MRS via the methyl protons and can be identified by a distinctive triplet at 1.3 ppm. Conventional one-dimensional (1-D) spectroscopy of the triplet yields the highest temporal resolution when rapid sampling of alcohol kinetics is necessary (Figure 3).

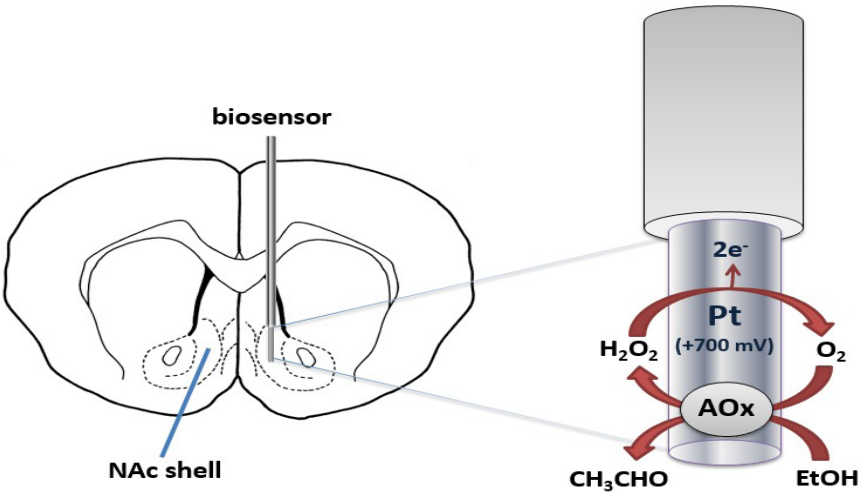

Figure 2: Schematic functioning of an implantable biosensor loading the AOx enzyme. Ethanol is selectively converted into H_2O_2, which is directly oxidized through the application of an anodic potential of +700 mV vs. Ag/AgCl. The biosensor has been tested in vivo after the implantation in the 'nucleus accumbens' (shell).

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Even if ^{1}H MRS signals are significantly affected by the environment, in the human brain, the ethanol signal is well disjointed from the signals of other metabolites and yields the most intense signals in such spectra[33].

Isotopic techniques

This kind of technique is widely used for detecting quite a few chemicals or the metabolism of energy substrates in the brain. Previously, ^{14}C, ^{11}C-labelled ethanol molecules, combined with a radioactivity test and PET, were used to monitor the molecules derived from ethanol metabolism in the body[34–36], but both isotopes have their disadvantages: the harmful radiation effect associated with a large dose of ^{14}C-labelled chemicals and the short half-life ($T_{1/2}$ = 20.38 min) of ^{11}C-labelled ethanol[36].

However, in vivo ^{13}C MRS (Figure 3), combined with the infusion of ^{13}C-labelled ethanol, is commonly used to directly detect not only ethanol but also its metabolites in the brain, in particular ^{13}C-acetate, which is largely used to study cerebral metabolism, neurotransmission and neuronal-glial interactions in both humans and animals[36].

Technique comparison and use

The problem of alcohol addiction has become more widespread in modern society, mainly because of the easy accessibility of alcoholic drinks both to adults and, especially, young people who use them early in life.

To better understand the toxicokinetics and effects of ethanol on the brain, several analytical techniques have been developed in the preclinical and clinical research fields (Table 1).

Microdialysis is a well-known and widely used technique for its widespread applications. The advantages in using this technique include the possibilities of monitoring ethanol kinetics in a specific brain region and of measuring several neurochemicals at the same time, providing a more complete picture of the metabolic changes induced by alcohol intake. Its invasiveness, associated with low temporal resolution, and the necessity of using connecting tubes to carry out the experiments do not make it particularly suitable for clinical trials.

Instead, biosensors are the emerging tool for the preclinical study of neurochemical modifications in the brain. The main characteristics of these devices are represented by very low invasiveness, when compared with microdialysis probes, and, most of all, the capability of monitoring variations of analytes in seconds or fractions. In the case of ethanol monitoring, these tools have proved to be successful, especially when they have been associated with a telemetric system, so that animals are allowed to be totally free to move.

Moreover, in virtue of the electrochemical technique on which the measurement of substances is based, biosensors have proved to be a particularly sensitive tool, capable of detecting concentrations of ethanol in the order of the μM range. Unfortunately, although minimally invasive, biosensors have not proven to be suitable for clinical studies.

Spectroscopic techniques have proved to be useful for studying ethanol kinetics in the brain, both in clinical and preclinical studies. Their main advantage is that they offer the possibility of monitoring ethanol concentrations and relative tissue modifications not only in animal models but also in humans because of the absolute non-invasive nature of the procedures. The ethanol monitoring range is in the order of mM.

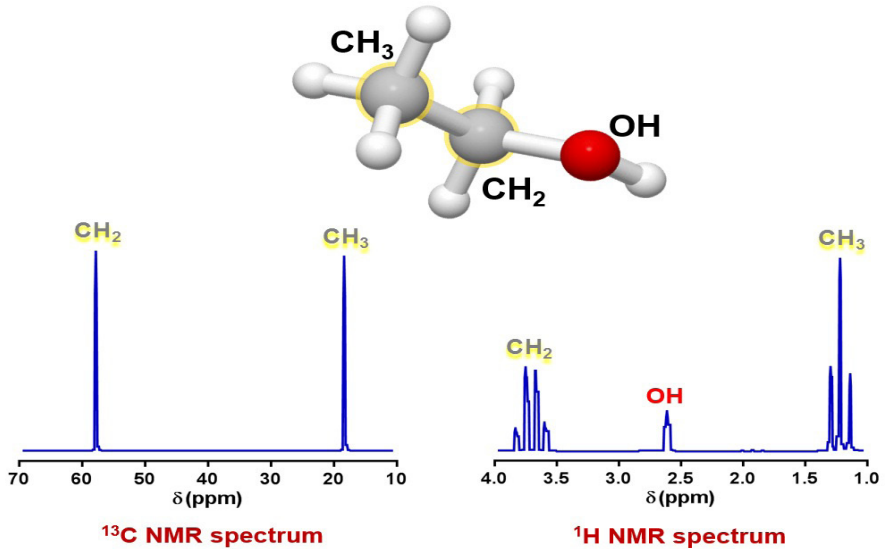

Figure 3: Typical NMR spectra for ethanol molecule. On the left, the ^{13}C NMR spectrum of ethanol (CH_3CH_2OH) is shown. The two carbons in ethanol are in different structural environments, and each produces a typical signal in the NMR spectrum. The carbon that is attached to oxygen, which is more electronegative, shifts its signal towards the left of the spectrum, whereas the carbon that is bonded only to hydrogen appears at the right of the spectrum. On the right, the ^{1}H NMR spectrum is shown. The CH_3 group that is most remote from the oxygen yields a signal towards the right of the spectrum. This signal is detected during an MRS scan.

Conclusion

Even though ethanol equilibrates within brain tissue in minutes, unlike the other techniques, the

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Table 1 Principal characteristics of the main techniques – microdialysis, biosensing and spectroscopic techniques – presented in this review.

Characteristics of the technique	*Technique*		
	Microdialysis	Biosensing	Spectroscopic techniques
Preclinical use	+	+	+
Clinical use	–	–	+
Brain invasiveness	++	+	–
Concentration range	µM/mM	µM/mM	mM
Temporal resolution	minutes	seconds	minutes
Spatial resolution	mm	µm/mm	mm
Monitoring period	hours	hours/days	minutes
Monitoring during self-administration	+	+	–
Movement allowed	+	+	–
Untethered detection	–	+ (telemetry)	+

spectroscopic techniques do not allow for long-term monitoring because sessions may last a few minutes. Moreover, animals as well as humans are not allowed to move during sessions even when no tethering is required.

Microdialysis and biosensors are primarily used in preclinical studies; both are very reliable techniques, but for invasiveness, they can only be used in animal models. Alternatively, spectroscopic techniques are suitable for both preclinical and clinical studies and are not exclusive for animal models.

Abbreviations list

AOx, alcohol oxidase; CNS, central nervous system; MRI, magnetic resonance imaging; MRS, magnetic resonance spectroscopy; NMR, nuclear magnetic resonance; PET, positron emission tomography.

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Competing interests: none declared. Conflict of interests: none declared.
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