Neuropharmacology 116 (2017) 343–350

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

The effect of NMDA-R antagonism on simultaneously acquired local field potentials and tissue oxygen levels in the brains of freely-moving rats

John Kealy [a, c, *], Sean Commins [b], John P. Lowry [a]

[a] Department of Chemistry, Maynooth University, Maynooth, Co. Kildare, Ireland
[b] Department of Psychology, Maynooth University, Maynooth, Co. Kildare, Ireland
[c] Smurfit Institute of Genetics, Trinity College Dublin, Dublin 2, Ireland

ARTICLE INFO

Article history:
Received 3 August 2016
Received in revised form
7 December 2016
Accepted 9 January 2017
Available online 11 January 2017

Keywords:
Ketamine
MK-801
Phencyclidine
Hippocampus
Striatum
High-frequency oscillations

ABSTRACT

Non-competitive NMDA receptor antagonists are known to induce psychosis-like symptoms in rodents. Administration of such compounds cause behavioural effects such as memory impairment and hyperlocomotion. Additionally, drugs such as phencyclidine (PCP), ketamine and MK-801 all cause distinctive increases in striatal local field potential (LFP) in the high frequency oscillation (HFO) band in the power spectrum (140–180 Hz). Amperometric sensors provide a means to measure tissue oxygen (tO_2; a BOLD-like signal) in the brains of freely-moving rats while simultaneously acquiring LFP using the same electrode. Carbon paste electrodes were implanted into the striatum and hippocampus of male Wistar rats. Rats were administered with saline, ketamine (10 mg/kg), MK-801 (0.1 mg/kg) and PCP (2.5 mg/kg) and recordings were made at 1 kHz using three different potentials (−650 mV to measure tO_2; 0 mV and +700 mV as control conditions). NMDA receptor antagonism caused significant increases in tO_2 in both the striatum and the hippocampus. Power spectrum analysis showed significant increases in HFO power in the striatum but not in the hippocampus. Conversely, there were significant decreases in delta and alpha power along with increases in theta and gamma power in the hippocampus that were absent in the striatum. This supports findings that LFP can be obtained from an amperometric sensor signal; allowing simultaneous acquisition of two translational biomarkers of neuronal activity (LFP and tO_2).
© 2017 Elsevier Ltd. All rights reserved.

1. Introduction

The *N*-methyl-D-aspartate glutamate receptor (NMDA-R) is firmly implicated in normal physiological processes such as synaptic plasticity and learning along with being implicated in diseased and disordered states such as excitotoxicity and schizophrenia. Indeed, non-competitive NMDA-R antagonists are routinely used to model schizophrenia in rodents (Neill et al., 2014; Janhunen et al., 2015). Additionally, given the use of non-competitive NMDA-R antagonists in humans as medical interventions (ketamine) and as drugs of abuse (phencyclidine; PCP), it is important to understand the neurophysiological effects of these drugs to find new clinical uses for existing drugs like ketamine and to design novel antipsychotic and antidepressant compounds with fewer side effects and greater therapeutic value.

In rodents, it has been demonstrated that non-competitive NMDA-R antagonists can induce characteristic changes in electrophysiological measurements in various brain regions. The three classic non-competitive antagonists, ketamine, PCP and MK-801, all alter multiple frequencies of the local field potential (LFP) signal in multiple regions in a dose-dependent manner (for a comprehensive review, see Hunt and Kasicki, 2013). Notably, these drugs are associated with increases in striatal high-frequency oscillations (HFOs; Hunt et al., 2006, 2011) and in hippocampal gamma power (Ma and Leung, 2000; Ehrlichman et al., 2009; Lazarewicz et al., 2010; Hunt et al., 2011; Saunders et al., 2012).

Attempts at using functional magnetic resonance imaging (fMRI) to directly compare changes in brain activity between animals and humans have been made but are limited by the need to anaesthetise or sedate animals, thus introducing a confounding factor when interpreting data (Hodkinson et al., 2012). Even so,

* Corresponding author. Smurfit Institute of Genetics, Trinity College Dublin, Dublin 2, Ireland.
E-mail address: kealyjo@tcd.ie (J. Kealy).

http://dx.doi.org/10.1016/j.neuropharm.2017.01.006
0028-3908/© 2017 Elsevier Ltd. All rights reserved.

Abbreviations

BOLD	Blood-oxygen-level-dependent
CPE	Carbon paste electrode
FFT	Fast Fourier transform
fMRI	Functional magnetic resonance imaging
HFO	High-frequency oscillation
LFP	Local field potential
NMDA-R	*N*-methyl-D-aspartate glutamate receptor
PCP	Phencyclidine
SCE	Saturated calomel electrode
tO2	Tissue oxygen

pharmacological MRI studies in rodents show that non-competitive NMDA-R antagonists are associated with increased regional cerebral blood volume in the striatum (Gozzi et al., 2008a, 2008b; Broberg et al., 2013) and hippocampus (Gozzi et al., 2008a, 2008b) as well as increases in the blood-oxygen-level-dependent (BOLD) signal in the striatum and hippocampus (Littlewood et al., 2006; Chin et al., 2011).

Therefore, it is desirable to develop techniques that offer greater translational validity to make better-informed interpretations of data generated in animal models. Amperometry is of particular interest as it is possible to measure changes that are comparable to imaging techniques routinely used in humans (BOLD and EEG; see Lowry et al., 2010; Zhang et al., 2009) and can be used in freely-moving animals With electrochemical sensors, it is possible to measure real-time changes in tissue oxygen (tO_2) in the brain with high spatial resolution (Bolger and Lowry, 2005; Bolger et al., 2011a, 2011b) and this tO_2 signal correlates highly with changes in the BOLD signal acquired simultaneously (Lowry et al., 2010). This permits researchers to utilise tO_2 measurements as a surrogate for fMRI in rodents, allowing for pharmacological (Kealy et al., 2013, 2015) and behavioural (McHugh et al., 2011) studies to be performed in awake rodents.

Furthermore, it has been demonstrated by recording LFP while simultaneously measuring changes in choline using an amperometric sensor that the amperometric signal is made up of a low frequency component (<1 Hz) corresponding to neurochemical changes and a higher frequency component (>1 Hz) corresponding to LFP (Zhang et al., 2009). The aim of this study is to confirm that the signal obtained from oxygen sensors can also be broken down into a low frequency component corresponding directly to changes in oxygen and a higher frequency component that corresponds to changes in LFP. In order to test this hypothesis, we use ketamine, PCP, and MK-801 to pharmacologically determine whether the >1 Hz components of the tO_2 signal are in fact changes in LFP. As these drugs all induce known changes in the LFP (Hunt and Kasicki, 2013), we can assume that if the higher frequency components of the tO_2 signal are in fact related to the LFP, they will change in a similar manner. Additionally, baseline activity and the effects of changing oxygen levels *in vivo* along with control experiments *in vitro* will be examined in a similar manner to help determine the relationship between tO_2 and LFP as translational markers of neuronal activity akin to local and scalp electrophysiological recordings made in humans. Taken together, these findings will demonstrate how amperometry can be used to measure changes in tO_2 and LFP simultaneously, allowing for detailed translational assessments of neuropharmacological and behavioural interventions to be performed.

2. Materials and methods

2.1. Subjects

Male Wistar rats (250–300 g; Charles River Laboratories International, Inc.; U.K.) were housed in a temperature-controlled facility with a 12-h light/dark cycle (lights on at 08:00) with access *ad libitum* to food and water. All procedures were performed under license in accordance with the European Commission Directive 2010/63/EU and were approved by the Maynooth University Ethics Committee.

2.2. Data acquisition and statistical analysis

All electrochemical experiments were performed using a low noise potentiostat (Quadstat, eDAQ, Australia). Data acquisition was performed at 1 kHz using an eCorder® interface system and eDAQ Chart software (eDAQ, Australia). Electrophysiological recordings were made using a Micro1401 mk II data acquisition unit (Cambridge Electronic Design, U.K.) and Spike2 software (CED, U.K.). Electrophysiological recordings were made at 10 kHz and the signal was amplified and filtered between 0.1 Hz and 1 kHz using a DAM50 amplifier (WPI, U.S.A.). Data was preliminarily processed in Microsoft® Excel® 2010 before being exported to GraphPad Prism® 5.01 for statistical analysis. Data was either normalised to baseline levels or area under the curve (AUC) analysis was performed to quantify any observed changes in the sensor signals over time for statistical analysis. Fast Fourier transforms (FFTs) were performed on 1-min time bins in eDAQ Chart and resulting power spectra were split into five frequency bands (delta, 1–4 Hz; theta, 5–8 Hz; alpha, 9–12 Hz; gamma, 30–100 Hz; HFO, 140–180 Hz). For multiple comparisons, repeated-measures and mixed-factorial analysis of variance tests (ANOVAs) with Bonferroni *post-hoc* analysis were used as appropriate. $p < 0.05$ was considered to be significant.

2.3. Working electrode preparation and surgery

Carbon paste electrodes (CPEs; O'Neill et al., 1982) were prepared and *in vitro* calibrations were performed using constant potential amperometry in a standard three-electrode glass electrochemical cell containing 20 ml PBS at room temperature using a saturated calomel electrode (SCE) as the reference electrode and a bare platinum wire as the auxiliary electrode (see Lowry et al., 1997; Kealy et al., 2013, 2015). For CPE O_2 calibrations, a three-point calibration protocol was used (0, 240, 1200 μM) using an applied potential of −650 mV versus SCE. The current was recorded throughout the course of each calibration and analysis was performed using quiescent steady-state conditions (Kealy et al., 2013, 2015).

Animals were anaesthetised using isofluorane (4% for induction, 1.5–3.0% for maintenance; IsoFlo®, Abbott, U.K.) and placed in a stereotaxic frame. The skull was exposed and four screws were implanted into the skull with one doubling as the auxiliary electrode. Burr holes were made for the other electrodes. Two CPEs were implanted into each hemisphere, targeting the striatum (+1.7 mm A/P; ±2.5 mm M/L; −5.0 mm D/V) and dorsal hippocampus (−4.0 mm A/P; ±3.0 mm M/L; −2.5 mm D/V). The silver reference electrode was implanted into the left parietal lobe. All electrodes were cemented into place (Dentalon® Plus, Heraeus-Kulzer, Germany) and the gold contacts at the end of each electrode were cemented into a six-pin Teflon® socket (Plastics One, U.S.A.). All animals were given saline (0.9%; 3 ml/kg body weight) and perioperative analgesia was provided (0.3 mg/kg body weight;

Download English Version:

https://daneshyari.com/en/article/5548953

Download Persian Version:

https://daneshyari.com/article/5548953

Daneshyari.com