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Research Article

Influence of paroxetine (SSRI), cyclooxygenase-2 (COX-2) inhibitor 641784 and their association upon brain haemoglobin (HbO2); an in vivo NIRS analysis

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Abstract

The implication of brain oxygenation within brain functions is well known and oxygen is essential to maintaining normal brain functions. Recent studies showed that anaemia is related to an increased risk of depression either in healthy population and in pathological states. Near infrared spectroscopy (NIRS) supplies a non-invasive, non-ionizing way to measure haemoglobin levels and oxygen saturation in the living tissue and is confirmed as valuable tool to monitor influence(s) of acute drug treatment on metabolic activity of the brain. SSRI/COX-2 inhibitor is a recent dual pharmacology approach to treating major depression. In the present work NIRS has been applied to monitor the influence of COX2 inhibitor 641784 (COX2i) or SSRI paroxetine or this COX2i-SSRI association upon HbO2 levels measured in the brain of anaesthetised rodents.

Keywords: COX-2 inhibition; SSRI; In vivo NIRS; rat brain

Introduction:

The implication of brain oxygenation within brain functions is well known and oxygen is essential to maintaining normal brain functions. In particular, an adequate supply of oxygen must be maintained to meet the high rate of oxygen consumption by the brain [Masamoto et al., 2007]. Additionally, a large body of evidence suggests that the partial pressure of oxygen in brain tissue is physiologically maintained within a narrow range in accordance with region-specific brain activity [Masamoto et al., 2009]. Furthermore, recent studies showed that anaemia is related to an increased risk of depression either in healthy population [Vahdat Shariatpanaahi 2007; Lee & Kim 2020] and in pathological states [Steptoe et al. 2012; Chung & Chang 2023].SSRI/COX-2 inhibitor is a recent dual pharmacology approach to treating major depression and published data on depressed patients suggest that the combination of cyclooxygenase-2 (COX-2) inhibition would improve the clinical outcome of the specific serotonin inhibitor (SSRI) paroxetine by alleviating depression symptoms of patients resistant to classical treatment [Kopschina Feltes et al. 2017; Roman & Irwin 2020]. Near infrared spectroscopy (NIRS) is becoming a widely used research instrument that supply a non-invasive, non-ionizing way to measure haemoglobin levels and oxygen saturation in the living tissue [Crespi 2007; Crespi 2021]. It has been also confirmed as valuable tool to monitor influence(s) of acute drug treatment on metabolic activity of the brain [Crespi et al. 2018a,b].Therefore, in the present experiment NIRS has been applied to monitor the influence of COX2 inhibitor 641784 (COX2i)or SSRI paroxetine or this COX2i-SSRI association upon HbO2 levels measured in the brain of anaesthetised rodents prepared for NIRS analysis as described earlier [Crespi 2007]. The doses of each compound were selected in function of the recent evidence of their efficacy upon neurochemical signals [Crespi 2024a,b].

Material And Methods

Adult male rats (230–250 g) were supplied by Charles-River (Italy) and were kept in temperature- and humidity-controlled rooms (22 oC, 50%, respectively) with lights on from 07.00 h to 19.00 h with water and food available ad labium. All procedures concerning experimentation, transportation and care of the animals were carried out in accordance with the Italian law (Legislative Decree no.116, 27 January 1992), which acknowledges the European Directive 86/609/EEC, and were fully compliant on the care and use of laboratory animal and codes of practice. Furthermore, all efforts were made to minimize the number of animals used and their suffering. The number of animals has been decided based upon the 3Rs, i.e. Reduction in the number of animals required;

Refinement of the methodologies of analysis; Respect of the animals i.e. reducing their suffering as described [Crespi et al. 2019]. The NIRS apparatus used is fully described. Briefly, it integrates six continuous-wave laser diode sources emitting in the near-infrared spectral region and a low-noise detection system based on an avalanche photodiode. The optical probe is based on a compact, reliable, and low-cost fiber based system with four quantitative measuring points.Using this system, the non-invasive in vivo NIRS analysis of HbO2 levels within the whole brain (CNS) was performed in anaesthetized rats: 3% halothane in a 30% -70% O2:N2 gas mixture was used for anaesthesia. Each rat was positioned in a stereotaxic holder (D. Kopf, USA) and the NIRS optic probes were positioned upon the sagittal line as described earlier [Crespi 2007]. NIRS measurements were then performed. At the end of each experiment, the position of the NIRS optical fibers was verified versus bregma.

Treatments

Following a 10 min period of control/control measurements, control rats were treated with vehicle (n=4, 1.4ml saline s.c.). Other rodents received selected doses of COX2 inhibitor 641784 i.e. 10mg/kg s.c. (n=4) or paroxetine 5mg/kg s.c. (n=4). A further group of 4 animals were treated with the combination 641784 10mg/kg s.c. + paroxetine 5mg/kg s.c.

Results

It appeared that the COX2i or SSRI alone were transiently modifying significantly HbO2 parameters when compared to control / control values that were considered as zero µmoles /l. In particular a decrease was noticed 20min after each treatment and it was of approximately -3,5 µmoles/l following COX2i 641784 and more intense i.e. -6 µmoles/l and more persistent following paroxetine injection (Figure 1).

Then again, the association COX2i 641784 + SSRI paroxetine was followed by significant decrease of HbO2 levels down to a minimum of approximately -9.4 µmoles /l after 40min and 60min of treatment with in between a partial recover up to approximately -6 µmoles /l at 50min post treatment (Figure 1).

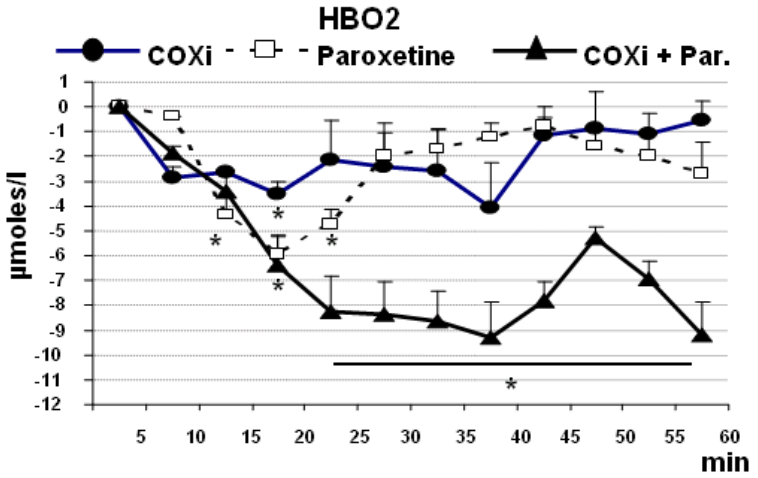

Figure 1: Time 0: treatment with COX2 inhibitor 641784 10mg/kg s.c. (COXi n=4) or paroxetine 5mg/kg s.c. (n=4). A further group of 4 animals were treated with the combination 641784 10mg/kg s.c. + paroxetine (Par.) 5mg/kg s.c.

Treatment data are compared to control/control values (saline treatment, n=4) that were considered as zero µmoles /l.

Statistical analysis details: mean ±S.D. * $p<0.05$; 2ways ANOVA and Dunnett.

Discussion

Treatment with COX2i 641784 or SSRI paroxetine alone where showing a temporary, partial influence upon HbO2 levels in the brain of anaesthetised rats. This effect was more pronounced and lasting longer time with their association. This decrease that could be inducing [mild] acute hypoxia [Subudhi et al. 2007; Liu et al. 2021] may be correlated to the adverse effect reported: i.e. significant increase in the rate of vascular events like stroke with COX-2 inhibitors compared with placebo [Roumie et al. 2008; Auriel et al., 2014]. Concerning SSRIs, their common side effects may include nausea, vomiting, insomnia, drowsiness, headache, decreased sex drive, and agitation while some of the less common adverse effects of SSRIs reported in literature are among others extrapyramidal symptoms (EPS), serotonin syndrome, QT prolongation [for a review Edinoff et al. 2021].On the other hand, this data may also indicate that such association COX2i 641784 + SSRI paroxetine works synergistically upon brain oxygen use; it could be possible that the observed HbO2 reduction is mirroring the rapid implementation and consumption of oxygen in order to increase brain function(s) so that to possibly antagonise states of depression. Further work will be implemented to verify/support such hypothesis that could be of interest as it has been recently reviewed various work proposing beneficial opposed to harmful influence of hypoxia on the aging brain as well as potential therapeutic applications of hypoxia for neurodegenerative diseases [for a review Burtscher et al. 2021].

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