

Non Invasive in Vivo Technologies for Translational Medicine Applications

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Abstract:

In preclinical studies the feasibility of non-invasive analysis of brain activities is studied in the attempt to overcome the major limitation of actual in vivo methodologies i.e. invasiveness

Keywords: oxygen tension; blood flow

Introduction

Implantation of hip prosthesis can help many people to enhance their function, mobility, and solve different problems such as osteoarthritis. In preclinical studies the feasibility of non-invasive analysis of brain activities is studied in the attempt to overcome the major limitation of actual in vivo methodologies i.e. invasiveness.

Up to now the most commons invasive in vivo techniques i.e. to study brain activities are the electrochemical methodologies of microdialysis or/and voltammetry for the analysis of neurotransmitter functions (for reviews see refs 1,2) as well as concurrent in vivo oxymetry and blood flowmetry performed with a sensor made of optical fibres for the measurement of tissue oxygen tension and blood flow that are markers of brain metabolism [3].

Recently the application of different methodologies have been considered in order to possibly obviate the need of surgery to implant i.e. probes for dialysis or sensors for voltammetry, so that to avoid pain and distress to the animals. Not last to prevent the lesions [macro or micro] that the implant of probes or sensors inevitably causes to the brain tissue. One of such methodologies is Near infrared spectroscopy (NIRS) [4, 5, 6, 7]. NIRS is indeed a non-invasive technique that can be used to monitor changes in oxygenation of hemoglobin (Hb). Importantly, the absorption spectra of near-infrared light differ for the oxygenation–deoxygenation states of Hb (oxygenated form O₂Hb vs. deoxygenated form HHb, respectively) so that the two compounds can be directly monitored. The sum of HHb + O₂Hb is considered = blood volume (V) and initially NIRS studies have been addressed towards physiologic as well as pathologic state(s) of various peripheral tissues such as muscles or breast tumors [8 – 11].

Then, the vulnerability of the preterm cerebral circulation incited researchers to use NIRS to study brain oxygenation–deoxygenation activities in human foetal and neonates in normal or pathological conditions as well as following drug(s) administration [12, 13, 14, 15].

Successively, a number of possible applications of NIRS has been also analyzed in adult brain, i.e. to monitor either oxygen sufficiency and brain functions in physiologic as well as pathological conditions [16, 20].

The evidence of the feasibility of non-invasive analysis of brain activities as demonstrated in human studies as described above, has addressed pre-clinical researchers towards the application of such NIRS methodology within animal experimentation. Indeed, NIRS may allow to overcome the major limitation of invasive in vivo methodologies described above [6]. Initially, peripheral tissues under physiologic as well as

pathological conditions have been monitored with such technique such as mammary tumour or subcutaneous tumour [21, 22]. And then studies on brain oxygenation of animals have been successfully performed. For instance, in piglets Near infrared spectroscopy scans of cerebral tissue *in vivo* were compared to reflectance pulse oximetry of local tissue, then each method was compared to *in vitro* femoral arterial blood [23]. In rats and in gerbils reflection near infrared spectroscopy (reNIRS) was used to evaluate individual variability of total hemoglobin, oxygenated hemoglobin and hemoglobin saturation in the brain, reaching the conclusion that reNIRS renders certain and consistent absolute values of such entities in the brain tissue of small rodents. [24].

In particular, in our experience, optic fibre probes were used as optical head of a novel, highly sensitive near infrared continuous wave spectroscopy (CW-NIR) instrument adapted for *in vivo* NIRS measurements in the brain of rodents. This prototype was designed for non-invasive analysis of the 2 main forms of haemoglobin: oxy-haemoglobin (O_2Hb) and deoxy-haemoglobin (HHb), chromophores present in biological tissues as they are markers of the degree of tissue oxygenation, thus providing an index of blood level and therefore of tissue metabolism [25, 26].

As already stated above, the sum of HHb + O_2Hb is considered = blood volume (V) and a recent work has demonstrated the feasibility of using NIRS to monitor these three parameters in the rat brain. Briefly, the effectiveness of such non-invasive methodology in preclinical studies has been tested via physiologic (i.e. via administration of exogenous oxygen (O_2) or carbon dioxide (CO_2) inflated orally) or pharmacologic (i.e. via administration of drugs of abuse such as cocaine or nicotine) experiments [27, 28].

Furthermore, coupling NIRS with a well established although invasive *in vivo* method such as electrophysiology allowing concomitant analysis of cerebral cell firing in discrete brain areas, was confirming the putative correlation between blood levels, brain metabolism and neuronal activities in rat CNS [29, 30].

Finally, the possibility that changes in brain metabolism as measured by NIRS might be a useful index of brain penetration of chemical entities has been investigated using different compounds from different chemical classes that were selected on the basis of their known brain penetration and overall pharmacokinetic profile [31]. It appeared that *in vivo* non-invasive NIRS might contribute to assess brain penetration of chemicals, i.e. significant changes in NIRS signals could be related to brain exposure, or vice versa the lack of significant changes in relevant NIRS parameters could be indicative of low brain exposure. These data were supported by concomitant standard pharmacokinetic studies of brain penetration [32].

Further improvement of NIRS hardware and software will allow shaping also the distribution of penetrating drugs within discrete brain areas and this could be potentially used to study neurobiological processes and psychiatric diseases in preclinical but also in a translational strategy from preclinical to clinical investigations as proposed [33]. Altogether they indicate that NIRS could be applied to study neurobiological processes and psychiatric diseases in preclinical and also in a translational strategy from preclinical to clinical investigations.

Preliminary outcome of the practicability of such approach can be the recent observation of complementarity of Magnetic Resonance Imaging (MRI) and Near Infrared Spectroscopy (NIRS), the two major *in vivo* non invasive methodologies more and more applied in research, the first more than the second being largely used also in clinical domain. In a recent work we have indeed observed parallel MRI-NIRS data monitored *in vivo* in rat brain subsequent to treatment with cocaine [34]. Furthermore NIRS data detected by means of the identical NIRS apparatus show that administration of alcohol to rodents as well as to man is resulting in superimposable modification of levels of the NIRS parameters and in particular of oxygenated hemoglobin (HbO_2) [35].

These data clearly indicate NIRS as useful methodology as MRI for preclinical and clinical investigations, also taking into account the advantages of NIRS when compared to other non invasive methodologies, i.e. robustness of the instrument, portability, minor cost; lack of acoustic noise; needless of injection or inhalation of radioactivity; movements admitted during measurements; direct measurement of the oxygenation-deoxygenation states of hemoglobin (O_2Hb vs. HHb, respectively) [25, 29].

Finally, the attempt to apply a laser based methodology such as NIRS but using ultraviolet laser sources with wavelength of 402 nm (Near UV) has proposed that also neurotransmitters such as serotonin could be monitored *in vivo* in a non-invasive way [36] and this may open new perspective in the translational studies of physiologic/pathological states in human beings.

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