Monitoring of corticostriatal synaptic plasticity with an implantable microbiosensor device to understand cognitive performance in neurodegenerative diseases

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1 INTRODUCTION

The corticostriatal pathway is characterized by a large convergence of cortical neurons into the striatum, and plays a crucial role in motor-skill learning, cognitive performance and reward mechanisms. This pathway is thought to modulate striatal synaptic plasticity, an event that can be defined by long-lasting changes in synaptic efficacy. Aberrant corticostriatal plasticity has been related to levodopa-induced dyskinesia, a common pathology amongst Parkinson patients.

Although the cellular mechanisms underlying corticostriatal synaptic plasticity are not fully understood, evidence suggests that glutamate receptors (mGlu) are involved in these processes. However, the inexistence of suitable methods for simultaneous monitoring synaptic plasticity and glutamate release is hampering a deeper understanding of the role of glutamate in corticostriatal synaptic plasticity.

Therefore, we developed an implantable microbiosensor device (*i*MBD) that included a W-Au needle-type microelectrode based glutamate biosensor for *in vivo* brain biomonitoring based on W-Au needle-type microelectrodes combined with a W based recording electrode (to monitor fEPSPs).

First, we evaluated the performance of the W-Au based glutamate biosensor *in vitro*. After, we assessed the efficacy of the *i*MBD for simultaneous monitoring of changes in fEPSP and glutamate release in the striatum, in response to a cortical stimulation.

2 MATERIALS AND METHODS

In vitro

•The surface of needle-type gold coated tungsten (W-Au) microelectrodes (50 µm Ø x 2 mm) was functionalized in a layer-by-layer manner. First with permselective membrane(s) (Nafion and Nafion-PPD), and after with an hydrogel loaded with an enzyme selective to glutamate(GluOx).

•W-Au based biosensors were characterized *in vitro,* in PBS, at 37 ºC, amperometrically (+700 mV vs Ag/AgCl). We continously monitored changes in the oxidation currents of the biosensors upon exposure to increasing concentrations of glutamate (0 to 100 µM), H_2O_2 and relevant non-specific electroative species (DA, DOPAC, UA and AA).

In vivo

•For *in vivo* glutamate biomonitoring, we developed an implantable microbiosensor (*iMBD*) device based on W-Au glutamate biosensors. The *i*MBD comprised two W-Au biosensors, assembled in a self-referencing manner (with and without enzyme). Additionally, the *i*MBD included a monopolar recording electrode (W, 75 µm Ø), for simultaneous monitoring of field excitatory post synaptic potantials (fEPSP) and glutamate (Fig 1).

•The *i*MBD was implanted in the dorsal striatum of anesthetized Wistar Rats, while an additional bipolar stimulation electrode was placed in the motor cortex (M1), for stimulation of the cortico-striatal pathway. Changes in fEPSPs were induced by the delivery of high frequency stimuli, by the bipolar stimulation electrode. Additionally, *in situ* glutamate (20 mM, ≤ 100 nL) administrations, were performed, using a picospritzer, through a cannula in the *i*MBD.

3 *IN VITRO* EVALUATION

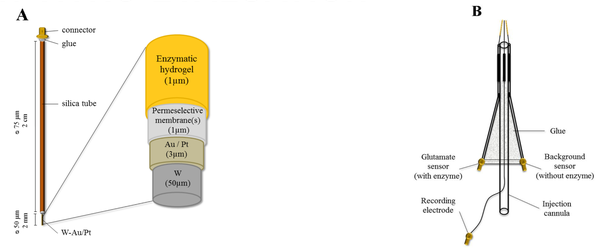

Figure 1 – A - Schematic representation of a W-Au based glutamate biosensor. **B-** Schematic representation of an *i*MBD.

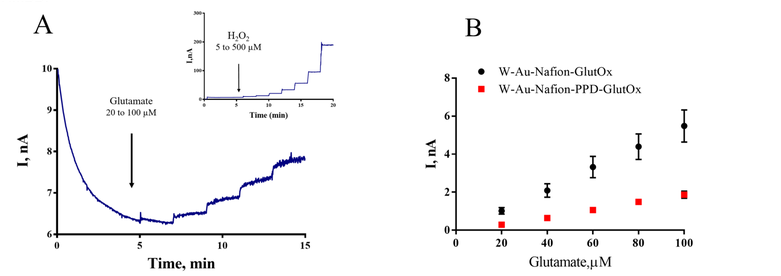

Figure 2 – A- Changes in oxidation currents of a W-Au based Glutamate (W-Au-Nf-GlutOx) biosensor in response to consecutive additions of glutamate. **Inset-** Changes in oxidation current of the W-Au glutamate biosensor in response to increasing H_2O_2 concentrations. **B** – *In vitro* calibration of W-Au glutamate sensors with different permselective membrane configurations.

4 *IN VIVO* BIOMONITORING

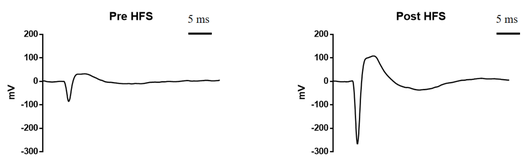

Figure 3 - Typical fEPSP monitored in the striatum, following single cortical stimulation, before and after HFS.

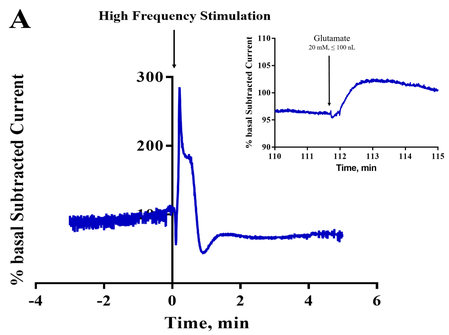

Figure 4 - A- Fast changes in the subtracted current of an *i*MBD implanted in the striatum in response to HFS in the motor cortex. **Inset** - Changes in *i*MBD subtracted current in response to local administration of glutamate (20 mM, ≤ 100 nL)

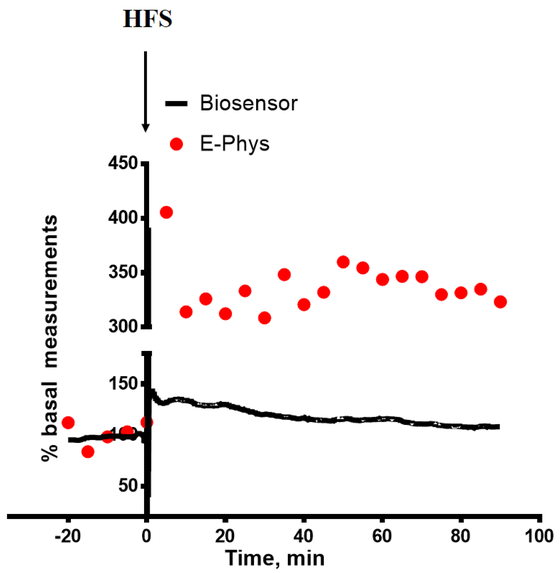

Figure 5 -Typical example of real-time simultaneous monitoring of changes in both fEPSP and glutamate biosensor signal by the *i*MBD.

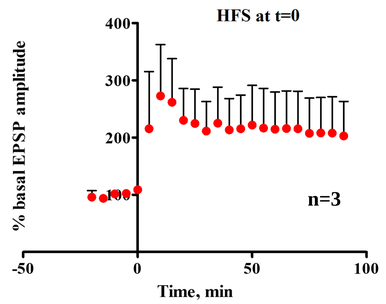

Figure 6 - Changes in striatal fEPSP amplitude in response to cortical HFS.

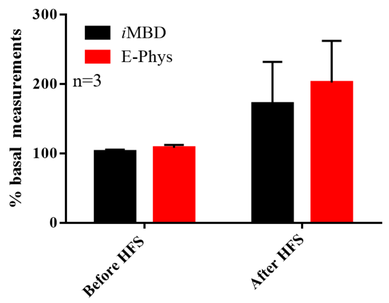

Figure 7 - Long term changes (≥ 90 min post HFS) in the subtracted current and the fEPSP amplitude monitored by the *i*MBD.

5 CONCLUSION

-*In vitro* evaluation showed that W-Au based glutamate biosensors were suitable for in vivo continuous glutamate monitoring.

-Functionalization of the W-Au microelectrode surface resulted in better higher biosensor selectivity, yet lower but suitable sensitivity to glutamate.

-The use of an *i*MBD with W-Au based glutamate biosensors enabled simultaneously and in real-time monitoring of changes in fEPSP and glutamate levels in the striatum.

-Our *i*MBD was able to monitor *in vivo* simultaneously and in "real-time" neurochemical and electrophysiological changes associated with synaptic plasticity