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Electrophysiological characteristics of limbic and motor globus pallidus internus (GPI) neurons in two cases of Lesch-Nyhan syndrome

Caractéristiques électrophysiologiques des neurones des régions limbiques et motrices du global pallidus interne (GPI) chez deux patients présentant un syndrome de Lesch-Nyhan

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Abstract

***Objective*. -** Lesch–Nyhan syndrome is a rare and debilitating condition characterized by dystonia and self-mutilating behavior. In order to shed light on the pathophysiology of dystonia, we report the pallidal electrophysiological activity recorded in two patients during deep brain stimulation surgery (DBS).

***Methods*. -** Microrecordings were performed on 162 neurons along four tracks aimed at the right and left anterior (limbic) and posterior (motor) globus pallidus internus (GPI). ***Results*. -** Regardless of the anesthetic agent used (propofol or sevoflurane), both patients showed similar neurons firing rates in the four regions studied, namely the limbic and motor portions of the globus pallidus externus (GPE) or GPI. In both patients, firing rates were similar in the GPE (12.2 ± 1.8 Hz, $N = 38$) and GPI (13.2 ± 1.0 Hz, $N = 83$) portions of the limbic track, while the motor GPE fired at a higher frequency (23.8 ± 2.7 Hz, $N = 18$) than the motor GPI (12.5 ± 1.4 Hz, $N = 23$).

***Conclusions*. -** These results demonstrate that light propofol or sevoflurane anesthesia influences pallidal activity in a similar way. Electrophysiological recordings suggest that Lesch–Nyhan syndrome might be characterized by analogous firing frequencies in the limbic GPE and GPI while motor GPE would tend to fire at higher rate than the motor GPI. It is therefore tempting

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to suggest that the symptoms that are observed in Lesch–Nyhan syndrome might result from motor GPI inhibition.
Significance. - This observation may confirm the Albin and Delong's model of the basal nuclei in hypokinetic and hyperkinetic disorders.

Résumé
Objectifs. - Le syndrome de Lesch-Nyhan est une pathologie rare, caractérisée par une dystonie accompagnée d'actes d'automutilation. Pour mieux comprendre la physiopathologie de cette maladie, nous avons enregistré l'activité électrophysiologique chez deux patients lors de la pose de stimulateurs profonds (DBS) dans le pallidum. ***Méthode***. - Des enregistrements unitaires ont été effectués sur 162 neurones le long de 4 trajectoires en direction du pallidum interne (GPI) antérieur (limbique) et postérieur (moteur).
Résultats. - Quel que soit l'agent anesthésique utilisé (propofol ou sévoflurane), les deux patients montrèrent des fréquences de décharge similaires dans les quatre régions étudiées, soit le pallidum externe (GPE) moteur et limbique et le GPI limbique et moteur. Chez les deux patients, les fréquences de décharges étaient similaires dans le GPE (12.2 ± 1.8 Hz, $n = 38$) et le GPI (13.2 ± 1.0 Hz, $n = 83$) limbique alors que le GPE moteur déchargeait à une fréquence plus élevée (23.8 ± 2.7 Hz, $n = 18$) que le GPI moteur (12.5 ± 1.4 Hz, $n = 23$).
Conclusions. - Ces résultats montrent qu'une légère anesthésie au propofol ou au sévoflurane modifie de manière similaire l'activité dans le pallidum. Les enregistrements électrophysiologiques suggèrent que le syndrome de Lesch-Nyhan pourrait être caractérisé par des fréquences de décharge analogues dans le GPE et le GPI limbique alors que le GPE moteur déchargerait avec une fréquence plus élevée que le GPI moteur. Il est donc tentant de penser que les symptômes observés dans la maladie de Lesch-Nyhan correspondraient à une inhibition du GPI. ***Signifianc***. - Cette observation va dans le sens du modèle de Albin et Delong de fonctionnement des noyaux gris centraux dans les mouvements anormaux.

Introduction

Lesch–Nyhan syndrome (LNS) is an X-linked hereditary disorder of uric acid metabolism caused by a complete deficiency of hypoxanthineguanine phosphoribosyltransferase (HPRT). While a partial HPRT deficit leads to hyperuricemia, nephrolithiasis, renal failure and gout arthritis, a complete enzyme deficit gives rise to additional neuro-behavioral problems such as self-mutilation, developmental delays, and such movement disorders as dystonia and choeroathetosis [15, 18]. Even if the pathophysiology of movement disorders and self-mutilation in LNS is still a matter of debate, abnormal monoaminergic transmission in the basal ganglia is likely to play a key role [25,26,29,33]. However, the cellular activity in the pallidum of LNS patients is still unknown.

According to the Albin and Delong's model, dystonia results from hypoactivity in the globus pallidus internus (GPI) [1,2,6]. One major problem for interpreting pallidal activity in dystonic patients is that they are operated on under generalized anaesthesia, which is sufficient to decrease the firing rate in the pallidum [14], and even induce dyskinesia [17].

Deep brain stimulation of the globus pallidus is a valuable technique to improve generalized or focal dystonia [3–5,9, 19] by mechanisms that are still not fully understood [34]. Four main hypotheses have been put forward to explain DBS beneficial action in movement disorders: depolarization blockade, synaptic inhibition, synaptic depression and modulation of abnormal oscillation in pathological networks [21]. Current views suggest that DBS could induce local inhibition on neurons while increasing the output from the stimulated structures [10].

Recently, the group of Taira [32] reported a striking improvement of movement disorders and self-mutilating behavior following chronic GPI stimulation of a LNS patient. However, no microrecording was performed in their study and the DBS electrodes were positioned in the motor part of the GPI.

Based on anatomical evidence suggesting that the anterior pallidum and posterior pallidum receive limbic and sensorimotor afferents, respectively [16], DBS electrodes were implanted in two LNS patients bilaterally in the anterior (limbic) and posterior (motor) GPI. In this study, we describe the electrophysiological results obtained under two type of generalized anesthesia (propofol and sevoflurane) from microrecordings performed along the four tracks aimed at the GPI.

Methods

Patients

Both patients (12-year old at the time of surgery) were diagnosed before 1 year of age as suffering from Lesch–Nyhan syndrome. From the age of 1 year, both presented severe movement disorders (generalized dystonia associated with axial spasm, ballistic movements and hypotonia) associated with severe self-mutilating behavior (lips, tongue and fingers biting). As they had failed to improve despite multiple medications, a bilateral DBS surgery of GPI was proposed (April 04 for Patient 1 and August 05 for Patient 2). At time of surgery Patient 1 was being treated with a combination of ris-