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Reversible and irreversible knockout of the ventroposterolateral thalamic nucleus measured by intracerebral SEP recordings in the rat brain—An aid to neuronavigation in small nuclei

James A. Blunk [a,*], Michael Burke [b], Mohammad Maarouf [c], Christian P. Bührle [c]

[a] *Clinic for Anesthesiology, University of Erlangen-Nuremberg, 91054 Erlangen, Germany*

[b] *Faculty of Psychology, Section for Experimental and Biological Psychology, Philipps-Universität Marburg, 35032 Marburg, Germany*

[c] *Department of Stereotactic and Functional Neurosurgery, University of Cologne, Germany*

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Abstract

Centrally active drugs are often hard to administer because of the blood brain barrier, and frequently high systemic doses are required to reach sufficient brain parenchyma concentrations, since these drugs are, additionally, diluted in the total blood volume. Moreover, topical administration via the systemic route is not possible. We here propose a technique for the local, quantitative deposition of active substances at defined intracerebral targets, e.g. the thalamic nuclei. We used a long micropipette and stereotactically advanced it to the desired coordinates under electrophysiological control. The pipette acted as both an electrode for intracerebral recordings and as a transportation means for the drug. The amplitude of intracerebral evoked potentials relayed by the thalamic nucleus to the sensorimotor cortex indicated the distance between the pipette tip and the neurons of the targeted nucleus. Data were obtained from anesthetized rats, where the micropipette was advanced towards the nucleus ventralis posterolateralis (VPL) during contralateral electrical forepaw stimulation and intracerebral recording of somatosensory evoked potentials. Within the VPL we either injected lidocaine or kainic acid, both resulting in an attenuation of the intracerebral as well as the cortical evoked potentials. This proposed tool may be useful for functional investigations of deep brain structures.

Keywords: CPS; Neuronavigation; Rat; Brain; Thalamus; VPL; Kainic acid; Lidocaine; Functional brain structure identification

1. Introduction

Within the thalamus, the nucleus ventralis posterolateralis (VPL) as well as the nucleus ventralis posteromedialis (VPM) relay pain, touch sensations as well as proprioceptive input to the cerebral cortex. The somatosensory representation areas located in the gyrus postcentralis are the areas in the cerebral cortex involved in pain perception as well as sensations mediated by the above-mentioned nuclei. Damage to these nuclei may result in persistent pain.

To further investigate the role of the nucleus ventralis posterior in the processing of sensormotor and pain information we developed an approach for a closely confined, selective administration of neuroactive substances such as hormones, pharmaceutical agents or neurotransmitters in order to study their effects on the brain structure under investigation while avoiding systemic side effects. Furthermore, the direct application of an agent at the stereotactically planned location the target structure minimizes the dosage of the delivered substance needed, and evokes the effect of the agent instantaneously without delay. Such a tool, e.g. a single- or multi-barreled micropipette suitable for extracellular potential recording and ejection of one or more compounds, therefore, allows a more situation dependent control of drug delivery than relying solely on probabilistic stereotactic coordinates derived from an atlas.

What is true for sensormotor signal processing in the VPL/VPM complex, also holds for other nuclei in the brain that are targets of stereotactic intervention, for instance, the subthalamic nucleus (STN), the ventrointermedius nucleus (VIM) and the globus pallidus internus (GPi) for disorders of the extrapyramidal motor system, especially for Parkinson's disease. In other clinical entities such as obsessive-compulsive disorder (OCD),

* Corresponding author at: Klinik für Anaesthesiologie, Universitaet Erlangen-Nuernberg, Krankenhausstrasse 12, D-91054 Erlangen, Germany. Tel.: +49 9131 853 3680.

E-mail address: jamesablunk@web.de (J.A. Blunk).

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anxiety diseases (AD) and major depression (MD), other sometimes quite small and anatomically complex structures such as the accumbens nucleus are the targets of stereotactic intervention such as thermocoagulation or high frequency stimulation (deep brain stimulation, DBS) and therefore have to be identified precisely and unambiguously.

As a proof of concept we demonstrate a procedure for the intracerebral local application of an agent, where the application instrument is advanced through the brain under the guidance of electrophysiological recordings. Basically, our technique uses a micropipette for the measurement of extracellular potentials to electrophysiologically guide the pipette advancement through the brain, as well as for the micropump-driven injection of substances, in this case: lidocaine and kainate (Benazzouz et al., 2000; Osawa et al., 2004; Ribeiro and Costa, 2003; Jardemark et al., 1998; Shin-Ya, 2005; Schurr et al., 1995; Brann and Mahesh, 1994). To electrophysiologically locate the VPL/VPM complex intracerebral somatosensory evoked potentials (intracerebral event-related potentials, IERP and somatosensory evoked potentials, SEP) during electrical forepaw stimulation (Burke et al., 2000; Grune et al., 1999) were recorded from within the cerebral cortex and in deeper structures. According to the Lambert–Beer–Bougier law the absorption of a wave travelling through an absorbing medium is proportional to the distance covered by the wave. Therefore, the intensity of such a wave depends on the distance to its place of origin and has a maximum

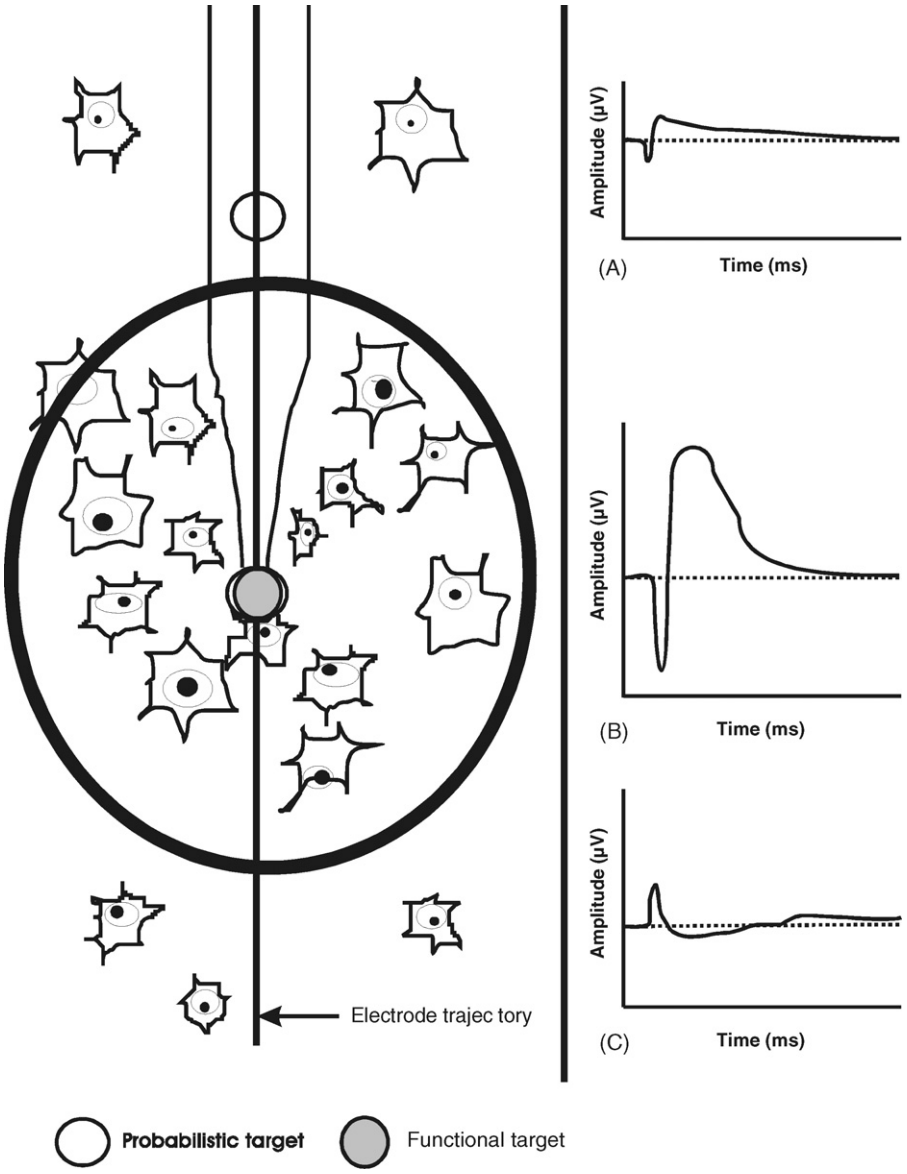

Fig. 1. Schematic representation of electrophysiological target identification. (Left) Dual purpose potential recording and drug delivery pipette in the center of the neuron pool (grey circle). This is the 'true', i.e. functional target, opposed to the probabilistic target derived from atlas coordinates during stereotactic planning (transparent circle). The anatomical boundaries of the nucleus are indicated by the large ellipse. Lidocaine, kainic acid, as well as specific neurotransmitters in vehicle solutions can be administered directly via the recording pipette. (Right) Three phase-locked stimulus responses (IERPs) recorded dorsal to the nucleus (A), within the nucleus (B) and ventral to the nucleus (C). Evidently, the response is largest when the electrode is positioned in the neuron pool of the nucleus, since IERPs predominantly represent postsynaptic activity at the cell soma membrane rather than fiber spikes.