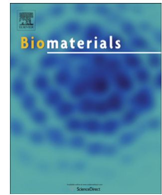
Biomaterials 35 (2014) 9620–9634

Contents lists available at ScienceDirect

Biomaterials

journal homepage: www.elsevier.com/locate/biomaterials



# Effects of caspase-1 knockout on chronic neural recording quality and longevity: Insight into cellular and molecular mechanisms of the reactive tissue response

Takashi D.Y. Kozai [a, b, c, *], Xia Li [a], Lance M. Bodily [d], Ellen M. Caparosa [d], Georgios A. Zenonos [d], Diane L. Carlisle [d], Robert M. Friedlander [d], X. Tracy Cui [a, b, c, **]

[a] Bioengineering, University of Pittsburgh, USA
[b] Center for Neural Basis of Cognition, USA
[c] McGowan Institute for Regenerative Medicine, University of Pittsburgh, USA
[d] Neuroapoptosis Laboratory, Department of Neurological Surgery, University of Pittsburgh, USA

ARTICLE INFO

*Article history:*
Received 26 June 2014
Accepted 1 August 2014
Available online 28 August 2014

*Keywords:*
Foreign Body Response
Mechanical tissue strain
Pericyte
Oligodendrocytes
Blood-brain barrier
Impedance

ABSTRACT

Chronic implantation of microelectrodes into the cortex has been shown to lead to inflammatory gliosis and neuronal loss in the microenvironment immediately surrounding the probe, a hypothesized cause of neural recording failure. Caspase-1 (aka Interleukin 1β converting enzyme) is known to play a key role in both inflammation and programmed cell death, particularly in stroke and neurodegenerative diseases. Caspase-1 knockout (KO) mice are resistant to apoptosis and these mice have preserved neurologic function by reducing ischemia-induced brain injury in stroke models. Local ischemic injury can occur following neural probe insertion and thus in this study we investigated the hypothesis that caspase-1 KO mice would have less ischemic injury surrounding the neural probe. In this study, caspase-1 KO mice were implanted with chronic single shank 3 mm Michigan probes into V1m cortex. Electrophysiology recording showed significantly improved single-unit recording performance (yield and signal to noise ratio) of caspase-1 KO mice compared to wild type C57B6 (WT) mice over the course of up to 6 months for the majority of the depth. The higher yield is supported by the improved neuronal survival in the caspase-1 KO mice. Impedance fluctuates over time but appears to be steadier in the caspase-1 KO especially at longer time points, suggesting milder glia scarring. These findings show that caspase-1 is a promising target for pharmacologic interventions.

© 2014 Elsevier Ltd. All rights reserved.

## 1. Introduction

Penetrating cortical neural microelectrodes are a critical frontend component of brain-computer interfaces [1,2]. The ability to monitor direct neuronal output with high stability and sensitivity would yield powerful neuroscience tools for understanding behavior, memory, plasticity, connectivity, and neural circuitry. While long-term neural implants for spike recordings have demonstrated feasibility [3–5], large variability of implant performance and poor longitudinal reliability has been a major challenge limiting the adoption of this technology [6–8]. This *variability* and *unreliability* is understood to be the result of complex multimodal failure mechanisms [9]. These include, but are not limited to: material failure such as corrosion, insulation failure, material degradation, electrical lead breakage, electrode delamination and biological responses including biofouling, neural degeneration, and inflammatory gliosis [10]. The present study is focused on dissecting the molecular pathways behind the biological responses that are related to chronic neural recording performance.

The *variability* in intracortical hemorrhaging resulting from microelectrode insertion was first demonstrated under *in vivo* two-photon imaging [11]. It was shown that penetrating a single large intracortical blood vessel resulted in significantly larger BBB bleeding areas compared with penetrating through many small

* Corresponding author. Department of Bioengineering, University of Pittsburgh, 5065 Biomedical Science Tower 3, 3501 Fifth Avenue, Pittsburgh, PA 15260, USA
** Corresponding author. Department of Bioengineering, University of Pittsburgh, 5057 Biomedical Science Tower 3, 3501 Fifth Avenue, Pittsburgh, PA 15260, USA. Tel.: +1 412 383 6672; fax: +1 412 648 9076.
*E-mail addresses:* tdk18@pitt.edu, tkozai@umich.edu (T.D.Y. Kozai), xic11@pitt.edu (X.T. Cui).

http://dx.doi.org/10.1016/j.biomaterials.2014.08.006
0142-9612/© 2014 Elsevier Ltd. All rights reserved.

capillaries. This study also revealed the unpredictability of disrupting or avoiding these large intracortical BBB vessels if only the surface vasculatures are avoided during insertion. More recently, it has been shown that implanting ultrasmall electrodes closer to major penetrating blood vessels leads to increased astrocytic GFAP activity [10,12].

The disruption of BBB leads to the deposition of plasma proteins foreign to the CNS including albumin, globulins, fibrin/fibrinogen, thrombin, plasmin, complement, red blood cells (hemosiderin), increased acidosis, and reactive oxygen species [13–24], each of which the CNS [25–35]. For example, albumin has been shown to bind to Transforming Growth Factor-β Receptors (TGFβR) in astrocytes [25], leading to upregulation of Myosin Light Chain Kinase (MLCK) immunoreactivity [36]. MLCK phosphorylates myosin light chain (MLC), thereby inducing contractions and weakening endothelial cell–cell adhesion [37,38]. Further, albumin has been shown to activate astrocytes and microglia through the mitogen-activated protein kinase pathway (MAPK) resulting in increased levels of interleukin (IL)-1β and nitric oxide as well as CX3CL1 in astrocytes [39].

Disruption of the BBB and insertion of probes have also been shown to immediately activate nearby microglia [40]. These cells persistently produce high levels of pro-inflammatory cytokines (interleukin-1 and TNFα) and chemokines (such as MCP-1) for the duration of the implantation, which could lead to neuronal degeneration and demyelination [41–48]. In addition, microglia-initiated inflammation cascades result in the progression of the glial sheath that forms an ionic and growth barrier between electrodes and neurons, which may reduce the recording quality [49,50]. Activated microglia also induce dysfunction of the BBB by releasing IL-1β which upregulates MMP-9, a matrix metalloproteinase known to degrade the gap junction of BBB endothelial cells [51]. Persistent BBB breach at the location of indwelling brain implants has been observed, and can have a negative effect on the function of chronic neural implants through recruitment of pro-inflammatory myeloid cells and increased presence of neurotoxic factors. Among these factors, MMP-9 is found to be more highly expressed in the tissue nearby the electrodes compared with non-implant control tissue [52]. One recent study examined the cytokines and soluble factors present around the implanted microelectrode arrays using laser capturing microdissection and gene expression analysis and found elevated levels of several pro-inflammatory and neurotoxic cytokines as well as tumor necrosis factor α (TNF α). Among these, upregulation of IL-1β mRNA is the most significant across all types of electrode designs tested [53].

IL-1β is a key pro-inflammatory cytokine and plays a critical role in inflammation and programmed cell death [54]. The synthesis of IL-1β precursors (pro-IL-1β) is induced by Toll-like receptors or RIG-like receptors, but pro-IL-1β must be cleaved and activated by caspase-1. Caspase-1 in turn, must be activated by inflammasomes, which are mediated by complex cytoplasmic pattern recognition receptors signaling in response to cell injury. Caspase-1 is the only known enzyme that cleaves *in vivo* pro-IL-1β into mature IL-1β. Furthermore, caspase-1 activation is an early event detected in neuronal cell death associated with ischemia as well as in chronic neurodegeneration [55,56]. A previous study has revealed loss of perfusion *in vivo* in multiple adjacent capillaries around an implanted electrode, which creates an ischemic microenvironment around the probe [40]. Using murine models, it has been demonstrated that inhibition of caspase-1 activity, either through knockout of the gene or by overexpression of a dominant negative construct, can slow neurodegeneration caused by a diverse set of circumstances including Huntington's Disease, Amyotrophic Lateral Sclerosis, traumatic brain injury, and ischemic stroke [57–64].

Since caspase-1 plays critical and relevant roles in neuronal cell death and activation of inflammatory pathways, we hypothesize that it mediates these processes after electrode implantation. The ability to prolong neuronal survival in the presence of neuronal stress is a key function of caspase-1 inhibition, and this may be leveraged to decrease the kill zone and inflammation around brain implants, thereby improving neural recording. To understand the effect of caspase-1 inhibition on electrophysiological performance, microelectrode arrays were implanted into primary monocular visual cortex of age-matched caspase-1 KO and WT mice. Neural activity was evoked using visual cortex stimulation paradigms, and recording performance was quantified over months. Here we show that caspase-1 plays an important role in the biological failure mode of chronically implanted electrodes and that the inhibition of caspase-1 improves chronic recording performance.

## 2. Method

This study characterizes and compares the chronic neural recording characteristics of intracortical neural electrodes in C57B6 WT mice and C57B6-caspase-1 KO mice along multiple layers of the cortex and hippocampus. A visually evoked recording model is used (Fig. 1) [65–67], and electrical recording characteristics were evaluated across the metrics of single-unit yield, single-unit SNR, single-unit amplitude, impedance, and noise floor as previously established [68]. The molecular, cellular, and vascular response around the recording sites of implants was examined with postmortem immunohistochemistry at the end of recording periods.

### 2.1. Surgical implantation

Single shank Michigan electrodes (A16-3 mm-100-703-CM15) were implanted unilaterally into the left primary monocular visual cortex, (V1m) of 9 wk old caspase-1 KO ($n = 9$) and WT ($n = 9$) female mice. Each mouse was anesthetized under 1.5% isoflurane and mounted onto a stereotaxic frame (Kopf Instruments, Tujunga, CA). The top surface of the skull was exposed and a drill sized craniotomy was made centered at 1 mm anterior to Lambda and 1.5 mm lateral to midline using a high speed dental drill and a 0.007 drill bit. Saline was applied continuously onto the skull to dissipate heat from the high-speed drill. Extra care was taken to prevent damage to the dura by reducing the drill speed and gently manually feeling the resistance of the skull when the dural blood vessels were visible through the opaque thin skull. A total of three bone screws were installed bilaterally over the primary motor cortex as well as over the contralateral visual cortex. The reference wire was connected to the bone screw over the contralateral visual cortex, while the ground wire was connected to both bone screws over the motor cortex. Arrays were inserted at ~2 mm/s using a stereotaxic manipulator until the top edge of the last recording site was at the edge of the brain surface. Insertion of the array was visualized by a tilted surgical scope. The silicon device and the craniotomy were sealed carefully with silicone (Kwik-sil) and a headcap was created using UV-cured dental cement (Pentron Clinical, Orange CA). Body temperature was maintained throughout the procedure using a warm water pad (HTP 1500, Adroit Medical Systems, Loudon TN). 0.3 mg/kg buprenorphine was administered twice daily for three days as a post-operative analgesic. All animal care and procedures were performed under the approval of the University of Pittsburgh Institutional Animal Care and Use Committee and in accordance with regulations specified by the Division of Laboratory Animal Resources. (For WT: $N = 9$ for 1–8 days, $N = 8$ for 14–35 days, $N = 6$ for 42–133 days, and $N = 4$ for 140–185 days. For caspase-1 KO: $N = 9$ for 14–35 days, $N = 7$ for 42–133 days, $N = 5$ for 140–175 days, and $N = 4$ for 182 days.)

### 2.2. Neurophysiological recording

Neural electrophysiology was recorded as previously described [68] and extensively described in a companion study (Kozai, TDY; Du, Z; Smith, MA; Chase, SM; Bodily, LM; Caparosa, EM; Friedlander, RM; Cui XT). Spontaneous recording was conducted in a dark room. Visual stimuli was presented using the MATLAB-based Psychophysics toolbox [65,67,69] on a 24" LCD (V243H, Acer. Xizhi, New Taipei City, Taiwan) monitor placed 20 cm from the eye contralateral to the implant, spanning a visual field of 60° wide by 60° high. Solid black and white bar gratings were presented drifting in a perpendicular direction and synchronized with the recording system (RX7, Tucker–Davis Technologies, Alachua FL) at 24,414 Hz. Each 1 s grating presentation (rotated in 45° increments) was separated by a 1 s dark screen period and the entire set was repeated 8 times per recording. The raw data stream was filtered from 0.3 to 5 kHz to produce spike data streams. The spike data stream was further pre-processed using published methods [70,71]. Possible spikes were detected using a fixed negative threshold value of 3.5 SD. Offline spike sorting was carried out using a custom MATLAB script modified from previously published methods [68,72]. Average signal-to-noise ratio (averaging the amplitudes of single-units for each channel) and average amplitude of noise (2 SD) were used to quantify electrode recording performance. Only channels exhibiting sortable single-unit

Download English Version:

https://daneshyari.com/en/article/10227172

Download Persian Version:

https://daneshyari.com/article/10227172

Daneshyari.com