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Reducing the "Stress": Antioxidative Therapeutic and Material Approaches May Prevent Intracortical Microelectrode Failure

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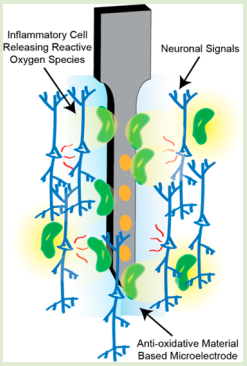
ABSTRACT: Despite the promising potential of intracortical microelectrodes, current designs suffer from short functional lifetimes, due in large part to the neuroinflammatory response to the implanted devices. An increasing body of literature is beginning to link neuroinflammatory-mediated oxidative damage to both the loss of neuronal structures around the implanted microelectrodes, and the degradation/corrosion of electrode materials. The goal of this viewpoint paper was to summarize the current progress toward understanding the role of oxidative damage to neurons and microelectrodes. Further, we seek to highlight the initial antioxidative approaches to mitigate oxidative damage, as well as suggest how current advances in macromolecular science for various applications may play a distinct role in enabling intracortical microelectrodes as reliable choices for long-term neuroprosthetic applications.



Microelectrodes, devices capable of recording or stimulating neural tissue, have been utilized since the early 1900s to aide in the understanding of electrical properties in the peripheral and central nervous system.[1,2] Continued use of microelectrodes in recent years has resulted in novel discoveries in cortical mapping and disease state mechanics.[3] Further, clinical use of microelectrodes implanted into the cortex (termed intracortical microelectrodes) have aided in restoring motor losses in patients with neurological deficits[4,5] with future work investigating feasibility in sensory deficits.[6]

Microelectrodes are able to record and deliver such detailed, high-resolution signals due to the existence of ionic fluxes around neuronal bodies, as shown in Figure 1. Specifically, in both intracellular and extracellular recording, ionic currents from influxes and effluxes of sodium and potassium result in measurable voltage changes in the surrounding area. Changes in ion concentrations can be described by eq 1. Where in eq 1, σ represents the tissue conductivity, I represents the current source, V is the change in voltage from the recording site to the source (neuron) and R denotes the distance of the current source from the recording electrode.

$$\Delta V = \sum \frac{I}{4\pi \cdot \sigma \cdot R} \tag{1}$$

Initial studies with microelectrodes utilized functionalized glass micropipettes. For example, in 1939, Renshaw, Forbes, and Morison, utilized a glass pipet microelectrode and demonstrated the differences between hippocampal and isocortex neuronal activity in anesthetized cats.[2] Their initial results, along with others, began to correlate neuroanatomical drawings from Cajal[7] to neuronal activity patterns. Later, in 1992, Kennedy et al., also showed the utility of glass microelectrodes in long-term neuronal recording in the cortex.[8] In their study, Kennedy and colleagues reported that glass electrodes containing sciatic nerve and neurotrophic medium (termed "cone electrodes") could facilitate neuronal recording up to 15 months after implantation in both rat and monkey models.[8] Kennedy later reported on successful use of cone electrodes in a human model.[9]

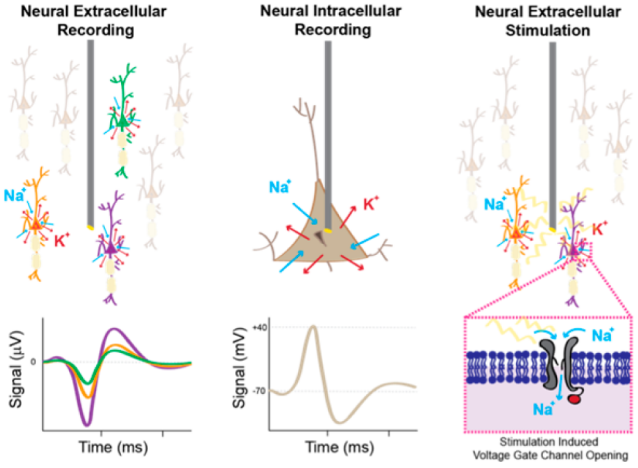


Figure 1. Biological mechanisms for neuronal recording and stimulation with microelectrodes. (Left) For extracellular recording, initial outflow of sodium ions and later influx of potassium ions in the local environment results in an "inverted" action potential on the scale of microvolts. Neurons closest to the electrode exhibit the strongest signals. (Center) Intracellular recording detects changes in initial influx of sodium and the subsequent efflux of potassium at the source of the signal, and therefore, are on the scale of millivolts. (Right) Microelectrode stimulation results in the opening of voltage gated sodium channels in neurons that trigger the onset of an action potential.

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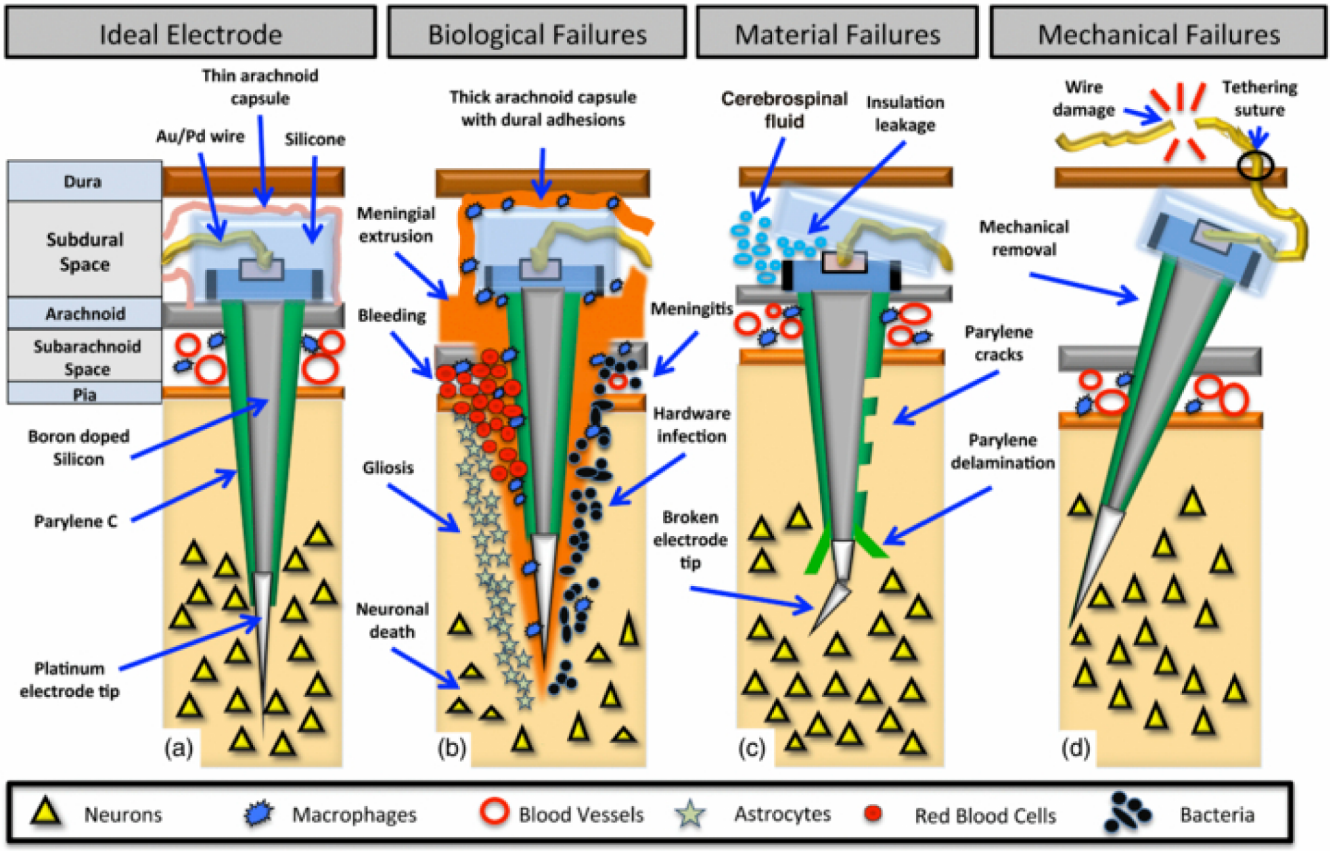

Figure 2. Failure modes after microelectrode implantation. Both abiotic and biotic failure modes, including biological, material, and mechanical, have been hypothesized to occur individually or in combination to result in microelectrode failure after implantation. Oxidative stress has been suggested to facilitate and propagate both biological and material failure modes. Figure reprinted with permission from ref 17 (Barrese et al.). 2013 IOP Publishing.

Since the development of the glass microelectrode, multiple electrode types have been created and successfully used in a research setting; the most popular of the microelectrode styles being microwire, Michigan-Style, Utah Electrode Array, and Moxon-Style (for detailed review see Jorfi et al.).[10,11] However, despite successes, widespread use of microelectrode array technology has been hindered by multiple device failure modes that can occur after device implantation.

In three separate studies, Tracy Cui, Justin Sanchez, John Donohugue, and colleagues recently reported on the prevalence of common failure modes of intracortical microelectrodes following implantation in mice, rats, and primates, respectively.[12−17] In addition, reports of microelectrode failure modes in human models have begun to be elucidated by Richard Normann and colleagues.[13] Collectively, all leading research groups have suggested that the main failure modes of microelectrodes are likely caused by mechanical, material, electrical, or biological events (Figure 2). Ultimately, however, it was suggested that during the lifetime of the implant, multiple failure modes in combination could result in the final failure of the implanted device.

As the failure modes of intracortical microelectrodes begin to be further elucidated, one mechanism that has been suggested to play a key role in several failure modes is oxidative stress and Fenton chemical reactions at the microelectrode−tissue interface.[15−17] Specifically, the presence of oxidative stress can (1) facilitate corrosion and delamination of the microelectrode surface, (2) perpetuate the foreign body response to the implanted device, and (3) directly facilitate neuronal cell death and losses in neuronal cell viability (Figure 2, middle insets).

The release of reactive species and radicals around implanted intracortical microelectrodes can be facilitated or caused by both abiotic and biotic sources. First, electrochemical reactions on the surface of the electrode, as a result of being in an aqueous environment, can attribute to the conversion of water to hydroxyl radicals (eq 2 and 3).[18] In the case of electrical contacts (e.g., gold), chemical redox reactions at the surface can result in the oxidation of the electrode surface, and as a result, the corrosive breakdown of the material,[18] as has been shown by multiple groups in vivo.[19,20]

$$O_2(g) + 2H_2O(aq) + 4e^- \rightarrow 4OH^-(aq) \quad (2)$$

$$2H_2O(aq) + 2e^- \rightarrow H_2(g) + 2OH^-(aq) \quad (3)$$

Additionally, one prominent mechanism of the formation of reactive oxygen species around the device is directly correlated to the extent of the inflammatory response occurring after implantation.[21] Reactive oxygen species, regulators of electrode contact corrosion, are released from cells due to an imbalance in the redox state of the cell.[22−24] Equation 4 shows a simplified progression of the formation of ROS (superoxide anion, hydrogen peroxide and hydroxyl anion) that occurs between the conversion of oxygen to water. Particularly, heavy metals within the cell, such as iron and copper, and mitochondrial dysfunction, are key contributors in driving the formation of reactive oxygen species.[25] Thus, since all cells possess metal ions and mitochondria, unlike other pro-inflammatory molecules,

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ACS Macro Lett. 2015, 4, 275−279

reactive oxygen species can be released by any cell type, not only inflammatory cells.[25]

$$O_2 \rightarrow O_2^- \rightarrow H_2O_2 \rightarrow OH^- \rightarrow H_2O \quad (4)$$

To that end, several groups have confirmed that multiple cell types within the brain are capable of releasing reactive oxygen species and other pro-inflammatory molecules.[26−29] Therefore, an understanding of the series of cellular and molecular events involved in the inflammatory response is key in designing engineering strategies to combat failure modes caused by the formation and the accumulation of reactive oxygen species. Thus, it is not surprising that the time course of the molecular and cellular events in the foreign body response have begun to be extensively evaluated with many types of microelectrodes.[11,30−34] For example, we have shown in the case of the single-shank Michigan-style array, a multiphasic neuroinflammatory and neurodegenerative response exists around the implanted device during the first 16 weeks after device implantation (Figure 3).[32] Similar reports for microwire and Utah array electrodes, in both functional (with neuronal recording data) and nonfunctional microelectrodes, have also been reported.[12,31,35−38]

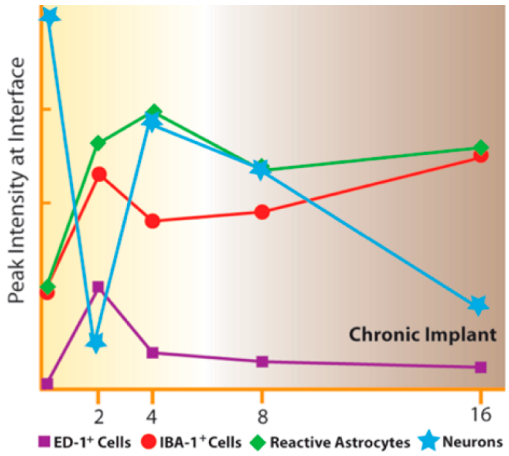

Figure 3. Neuroinflammatory response surrounding planar silicon microelectrode results in a heightened astrocytic (green) and total microglia response (purple/red). A permeable blood−brain barrier (yellow; BBB) is correlated with acute neuronal cell loss (blue) at the tissue-device interface, while chronic neuronal loss is hypothesized to be the result of CNS specific inflammatory events (brown). Oxidative stress has been shown to occur at both early and chronic time points. Figure reprinted from ref 32 (Potter et al.). 2012 IOP Publishing. All rights reserved.

Further, the accumulation of oxidative stress events at the device-tissue interface has been suggested to occur as early as 2 weeks after implantation. McConnell et al. reported in 2009 that implantation of microelectrodes could result in the accumulation of hemosiderin-laden macrophages, cells having the ability to generate high levels of radicals, as early as 2 weeks and up to 16 weeks postmicroelectrode implantation.[33] We have observed similar results in our laboratory, where we found high levels of intracellular reactive oxygen species around implanted microelectrodes at both two and 16 weeks postimplantation (Figure 4). Further, Prasad et al. recently demonstrated the accumulation of ferritin, indicative of perpetuating oxidative stress, around implanted functional microelectrodes 10 weeks after implantation.[14−16] The team suggested the correlation between ferritin

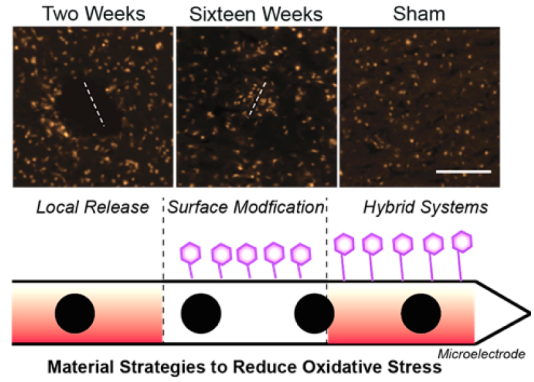

Figure 4. Top: At 2 and 16 weeks postmicroelectrode implantation, high levels of reactive oxygen species are noted around implanted microelectrodes. Dashed lines denoted explanted electrode. Tissue stained with dihydroethidium (DHE); scale bar = 100 μm. Bottom: Summary of our antioxidative material strategies and proposed future directions to reduce oxidative stress.

and corrosion of both insulating and conductive microelectrode material components.

Having the ability to directly neutralize reactive oxygen species (eq 4) and increase antioxidative enzyme synthesis, antioxidants have emerged as a powerful tool for preventing oxidative stress.[39]

Specifically, since the body naturally generates reactive oxygen species (Figure 4), several utilized antioxidants in biomedical research are derived from those used in the body that naturally prevent the adverse side effects of oxidative stress (e.g., DNA damage, protein oxidation, lipid oxidation; for review, see refs 24 and 40). For example, in diseases such as Alzheimer's and Parkinson's, natural phenols and "food-derived" antioxidants, such as those derived from plants and foods, have shown significant research promise.[41,42] Success of antioxidants utilized in research (e.g., resveratrol, quercetin, curcumin, melatonin, vitamins C and E) is likely due to the ability of these antioxidants to directly neutralize reactive oxygen species (eq 4) but also their ability to freely penetrate cells and work intracellularly.[22]

Given the potential role oxidative stress events play in several failure modes of intracortical microelectrodes, and the potential of antioxidants, our group has been the first to elucidate the role of oxidative stress events occurring around implanted microelectrodes using antioxidative approaches.[43−45] As a proof of principle, our first strategy demonstrated that a two-dose intraperitoneal injection regime of antioxidant (resveratrol) was capable of mitigating oxidative stress events, neuronal degeneration, and neural cell loss up to 4 weeks after implantation.[43] Further, building on our short-term dosing regimen, we have recently shown that similar reduction in ROS accumulation or reductions in neuroinflammation can be achieved by either antioxidative surfaces or local release systems of antioxidants (Figure 4).[44,45]

The study of antioxidative approaches for microelectrodes has begun to be identified as a potentially successful strategy. However, it is critical to remember that antioxidants have been used successfully for years to combat neurodegenerative diseases and inflammatory conditions.[22,39,41,42] In addition, many groups, such as the Anseth and Ameer groups,[46−49] have developed and successfully employed polymeric antioxidative approaches in non-neural applications. Therefore, when beginning to address future questions, we recommend that researchers look to successful work done by the macromolecular science community to aide in a more efficacious approach.

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ACS Macro Lett. 2015, 4, 275−279

In the design of any therapeutic approach to mitigate inflammation, one must realize that complete inhibition could hinder wound healing following device implantation. Therefore, it is important to not only question what and how much intervention is needed, but when it is most effective. For example, given the dynamic time course of microelectrode failure, one pressing question that has yet to be addressed in the field is whether or not it is possible to recover from neuronal losses or oxidative stress events (e.g., electrode insulation degradation) that occur after electrode implantation. In the context of recovery from neuronal loss, we and others have shown that neuronal densities around implanted microelectrodes have a dynamic movement throughout the course of the implant,[31−34,50] though this is not always seen.[51] Therefore, since neurons are also capable of reversing programmed cell death given the right molecular cues,[52] it is possible that delayed therapeutic intervention, such as polymers that have been designed to delay the release of molecules, may be capable of restoring losses in microelectrode signal quality related to oxidative stress failure modes. However, to fully address "rescue" treatment approaches, many types failure modes must be addressed (Figure 2). Specifically, many current antioxidative treatments are not capable of reversing corrosive damage to insulating or conducting components of the electrodes. Therefore, it will also become important for neural engineers to look at self-healing materials, such as those developed by Rowan and Weder,[53−55] but also focusing on insulating properties that may be designed to heal after oxidative damage.

In conclusion, the use of microelectrode technology continues to enhance our understanding of the nervous system and may also provide a way to restore functional deficits to injured individuals. The role of oxidative stress events has been, and will likely continue to be, implicated in multiple failure modes for many commonly employed electrode types. Within the scope of our work and others there has been a growth of literature to support the role of oxidative stress in propagating neurodegeneration, blood-brain barrier instability and mechanical/electrical instability surrounding implanted microelectrodes. We believe that the use of techniques that have the potential to improve the integration between cortical tissue and the implanted microelectrode by mitigating oxidative stress events may be an ideal way to prevent failure modes of microelectrodes. However, future optimization of such antioxidative approaches requires the guidance from successful work highlighted within the macromolecular science community. Therefore, we recommend future work consider designing strategies to mitigate the negative effects of oxidative pathways by pooling from promising strategies demonstrated within the polymer and chemistry community; while we also invite talented materials scientists to consider the significance of applying their innovative materials to neural interfacing applications.

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Notes

The authors declare no competing financial interest.

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