Challenges associated with nerve conduction block using kilohertz electrical stimulation

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Abstract
Neuromodulation therapies, which electrically stimulate parts of the nervous system, have traditionally attempted to activate neurons or axons to restore function or alleviate disease symptoms. In stark contrast to this approach is inhibiting neural activity to relieve disease symptoms and/or restore homeostasis. One potential approach is kilohertz electrical stimulation (KES) of peripheral nerves—which enables a rapid, reversible, and localized block of conduction. This review highlights the existing scientific and clinical utility of KES and discusses the technical and physiological challenges that must be addressed for successful translation of KES nerve conduction block therapies.

Keywords: neural stimulation, nerve conduction block, kilohertz electrical stimulation, kilohertz high frequency alternating current

(Some figures may appear in colour only in the online journal)

What is kilohertz electrical stimulation (KES) nerve block?

A variety of different stimulation therapies and techniques exist within the domain of electrical stimulation. For example, low frequency (<100 Hz, [1]) electrical stimulation is typically used to excite neuronal structures such as cell bodies, axons, or ganglia, resulting in the generation of action potentials. Higher frequency (>100 Hz, but <1 kHz, [2]) electrical stimulation is used to modulate deep brain structures, the spinal cord, and peripheral nerves. Depending on the structure stimulated, high frequency stimulation can lead to generation of action potentials or depletion of neurotransmitters [3]. Less understood and investigated, kilohertz (>1 kHz) electrical stimulation (KES, figure 1, [4]) has increased in usage as a neuromodulation therapy in the last decade. The critical difference between low or high frequency electrical stimulation and KES is that when applied at threshold to peripheral nerves, KES can enable a quick, reversible, and complete inhibition of action potential propagation through the stimulated region of tissue, referred to as nerve conduction block. Block of nerve activity is different than the inhibition achieved at lower frequencies, where the mechanisms may be neurotransmitter depletion, axonal fatigue, collision-block, and/or activity-dependent slowing. KES nerve block has been demonstrated in a variety of animal models and nerve diameters, including...
of clinical products currently utilize KES, it is unknown if these products provide therapeutic benefit by achieving a true conduction block of nerve activity or through other unknown mechanisms of action. Outside of KES, direct currents (DC) have also been shown to enable rapid, reversible, and localized block of nerve conduction [16], however, this method has its own substantial challenges which are not the focus of this discussion.

Why study KES nerve block?

Peripheral nerves are the inter- and intra- neural circuit interface, allowing interaction with different neural circuits, organ systems, and the external world. Blocking undesired hyperactivity through peripheral nerves can be a useful therapeutic approach for alleviating disease symptoms such as pain and hyperactive motor reflexes observed in spinal cord injuries [17], multiple sclerosis [18], and cerebral palsy [19], as well as hyperactivity in autonomic circuits implicated in the development or progression of cardiac, inflammatory, and metabolic diseases [20, 21]. Various methods exist for blocking conduction of neural activity including application of pressure, temperature, and pharmacological agents. However, these methods do not provide temporal or spatial control in terms of time of onset or offset and the tissue region affected. KES provides both temporal and spatial control of the target tissue affected, suggesting its utility in treating a myriad of disorders and thus the need to investigate and understand how it works.

The need to investigate KES nerve block also stems from existing KES clinical products and their effects on disease states. The ability to achieve a true nerve conduction block using KES can vary significantly depending upon the frequency, amplitude, electrode, waveform, duration, and anatomy of the target structure. Under inadequate conditions, KES can lead to significant activation or anatomical modification of the target tissue. Clinically, KES is currently used in Spinal Cord Stimulation (SCS) for treatment of chronic pain without paresthesia [22], abdominal vagus nerve stimulation for modulation of satiety and appetite [23, 24], as well as somatic nerve stimulation therapies for treatment of post-amputee pain [25]. Although not explicitly stated, it is suggested that these therapies provide therapeutic benefit via nerve conduction block, however that remains unknown. How therapeutic benefit is being achieved using KES is critical to mitigating long-term and potentially severe side-effects, as well as maintaining therapeutic benefit for the lifetime of the therapy.

How is KES used experimentally?

Experimental investigations using KES nerve block typically modulate two key KES parameters to achieve a complete nerve block—frequency and amplitude. Previous studies have demonstrated that sinusoidal or square waveforms of frequencies greater than 5 kHz are required to achieve a true conduction block [9] that is localized to the site of KES delivery, rather than neuromuscular depletion (fatigue) [6] or collision-induced
block. The choice of which waveform (square or sinusoidal) is typically arbitrary and dependent upon the end-application. For integration into implantable pulse generators, square waves are used. Sinusoidal waveforms are preferred in experimental preparations to enable easy filtering of electrical artifacts of a pure harmonic waveform. Frequencies as high as 70kHz are effective experimentally [4], while frequencies up to 100kHz have been evaluated in computational studies [26]. The KES amplitude, typically reported with units of either volts (V) or milliams (mA), further clarified as either peak (i.e. mA_{pk}) or peak-to-peak (i.e. mA_{pp}), depending on the mode of stimulation, is determined by the target nerve’s anatomy, electrical coupling between the interface and target nerve, resolution of the readout used for validation of KES nerve block, and neural interface geometry [27] and configuration [28]. The lowest amplitude (V or mA) at a given KES frequency that provides block of target nerve activity is referred to as the block threshold. Block threshold values depend upon the waveform used, with square waves requiring lower amplitudes due to the increased charge per phase as compared to sinusoidal waveforms. Typically, investigators plot the block threshold as a function of the KES frequency to produce a block threshold curve (figure 2), which depicts the relationship between frequency and amplitude for achieving a true nerve conduction block in the specific nerve tested. The block threshold curve has been shown to increase linearly as a function of frequency for fast fibers (e.g. myelinated, large diameter) and non-monotonically for slow fibers (e.g. unmyelinated, small diameter) [4, 5, 7, 29] (figures 2(B) and (C)). As with electrical stimulation for activation, the block threshold is a function of the charge density within the tissue. The linear increase in block thresholds for both large and small diameter fibers is partly explained by the logarithmic relationship between charge per phase and KES frequency. However, this rationale does not completely explain why non-monotonic block thresholds are observed for small diameter unmyelinated fibers.

History

Tanner [30] first demonstrated the use of KES to block nerve conduction in the frog sciatic nerve. Using compound action potentials as the readout, it was demonstrated that selective block of nerve fibers with varying diameters could be obtained by modulating the amplitude of a 20kHz sinusoidal waveform. Woo and Campbell [31] extended Tanner’s findings in the frog sciatic nerve and demonstrated the same phenomena in the cat tibial nerve. Woo and Campbell used compound action potentials and single fiber recordings as their readout to assess the effects of a 20kHz sinusoidal current-controlled waveform. Their single fiber tests demonstrated that nerve responses to KES varied as a function of stimulation amplitude. As the stimulus amplitude was increased, the axons exhibited an increase in firing frequency with a maximum of 400–700 Hz. Continued increases in stimulus amplitude resulted in asynchronous firing and then termination of all activity. Similarly, Bowman and McNeal [3] evaluated the response of single alpha motoneuron fibers in the cat and demonstrated reversible block of evoked action potentials for up to 20min with 2–10kHz square voltage-controlled waveforms.

A handful of studies have followed up on Tanner’s initial findings that high frequency stimulation could block nerve conduction. However many of the reports lack the necessary experimental detail to clarify if what was investigated was KES nerve block or simply high frequency stimulation of peripheral nerves. Since their initial work, Bhadra and Kilgore [6] have published a number of studies that have established the definition of KES nerve block (referred to kilohertz high frequency alternating current (KHFAC) by them). In their initial studies, Bhadra and Kilgore demonstrated the potential of various voltage-controlled and current-controlled KES waveforms to block nerve conduction in the sciatic nerve of adult bullfrogs. Their experiments were able to show conduction block in 24 sciatic nerve preparations, with a sinusoidal block stimulus with a frequency between 3–5kHz and 3–4 V_{pp} or 0.3–1.6 mA_{pp}. They also concluded that the effectiveness of block was not significantly altered by either voltage-controlled or current-controlled waveforms. These initial findings and report established KES nerve conduction block as a potential neural stimulation therapy. For a thorough historical perspective, we refer the reader to [32].

Biophysical mechanism(s)

To date, nearly all hypotheses related to mechanism(s) underlying KES are derived from a small number of experimental studies and multiple computational studies which model a
single axon with a point source for the stimulation electrode. Although not a thorough review, the studies discussed here represent the primary hypotheses believed to be a part of KES conduction block.

Bhadra and Kilgore [6] hypothesized that delivery of KES resulted in inactivation of sodium channels and tonic depolarization of the axon membrane, resulting in a localized block of nerve conduction. Their hypothesis was derived by studying the response of a myelinated fiber, represented by the McIntyre–Richardson–Grill (MRG) model [33], to a point source extracellular stimulus directly above a Node of Ranvier. Their simulations investigated the behavior of the membrane at frequencies up to 10 kHz and identified conduction block as the lack of action potential propagation to the node opposite to the stimulating end of the axon. These computational results have been observed in experimental studies, where the Node of Ranvier has been observed to be depolarized by a 10kHz KES waveform [34]. Ackermann et al further tested the hypothesis that KES block was achieved via depolarization by using a persistent sodium channel blocker ranolazine and demonstrating that the KES amplitude was higher with ranolazine administration [15]. Tai et al [35] utilized a Hodgkin–Huxley based lumped circuit model of an unmyelinated fiber and demonstrated a correlation between occurrence of a localized nerve conduction block and increased potassium channel activation. Their results showed that axons of various diameters (5–20 μm) could be blocked when the KES frequency is approximately 4 kHz and that large diameter fibers required lower amplitudes to achieve conduction block. Neither of these hypotheses is likely complete. For example, our (unpublished) simulation studies show in some cases KES creates a region of net hyperpolarization of the membrane potential, while in other cases a net depolarization. It is likely that there are multiple mechanisms related to achieving a true nerve conduction block using KES. These mechanisms are likely to be present with different spatial and temporal scales and are thus broken down into mechanisms that (1) achieve the initial nerve conduction block and (2) maintain a nerve block. The latter case—maintenance of a nerve block—can be further broken down into active and passive maintenance. In the active case, KES is continuously delivered to the nerve to maintain the nerve block. In the passive case, KES is no longer delivered to the nerve but nerve conduction is still blocked, commonly referred to as the carry over (discussed later). Existing investigations into mechanism are likely limited to describing the initial occurrence of nerve conduction block and not mechanisms related to maintenance.

**Experimental methods and characteristics of KES nerve block experiments**

Application of KES to nerves consists of additional characteristics that are relevant to application of KES to neural circuits. These characteristics include the onset response, fiber-type and directional selectivity, as well as the carry over effect. These characteristics are significantly impacted by the experimental methods used, specifically the readout for testing for a true KES nerve conduction block. Here we provide a summary of the various experimental methods utilized in the literature and discuss the interplay between the readout of choice for evaluating KES nerve block and common characteristics observed during experimentation.

**Evaluating the effects of KES nerve block**

Assessing the effects of KES nerve block depends upon the target nerve and the complete neural circuit. The readout used to assess the effects of KES is critical for selection of parameters, understanding mechanism(s), and determining causality or correlation in observed physiological changes. Many investigations use measurement of physiological states (e.g. muscle force [36], electromyographic activity [27], cardiorespiratory parameters [20]) to identify the block threshold. Although necessary, measurement of physiological states alone is not sufficient for ensuring that a true nerve conduction block is achieved or is the cause of the desired physiological effect, as this could be achieved through a number of other mechanisms mentioned previously (e.g. collision block, activity dependent slowing, etc). For example, recent reports suggest that the EnteroMedics VBLOC system, which claims to electrically block subdiaphragmatic vagus nerve activity using KES for treatment of obesity, is likely to achieve the physiological effect (i.e. reduction in weight loss) by continuously activating the nerve, as opposed to blocking it [24]. Although therapeutic benefit is achieved, this arbitrarily derived physiological effect could result in yet-to-be observed long-term neural and physiological changes.

Multiple methods have been employed to test for the occurrence of a true conduction block. For example, an electrode placed distal to the block electrode can be used to deliver test pulses which can be used to test for the occurrence of neuromuscular fatigue or depletion (figures 1(B)–3(B)) [9]. A distal electrode can also be used to record electromyogram (ENG) activity (figures 1(B)–3(A), (B)). In cases where distal activation of the neural circuit is not feasible (e.g. short exposable nerve lengths or additional stimulation confounds the physiological state being modulated), measurement of electrical activity directly from the target nerve [4, 21] is preferred for ensuring that the observed physiological effects are a result of a true nerve conduction block. For evaluating mechanisms of action, more invasive measurements (e.g. single fiber) are required.

**Electrode geometry and configurations**

A critical component of any neural stimulation therapy is an electrode that is electrically and mechanically optimized for the target structure. Optimization of electrode interfaces, most often achieved through computational modeling studies and in vitro or in vivo experiments, has become a critical component of developing any neural stimulation therapy. These methods have been successfully employed extensively to therapies such as deep brain stimulation (DBS) [37], spinal cord stimulation.
To date, most studies have used modified versions of traditional nerve cuff electrodes for KES nerve conduction block. Most published efforts on electrode optimization for KES therapies have been conducted only in vitro or in vivo. Ackermann et al. [28] first demonstrated the effect of the electrode configuration, specifically the inter-electrode distance (IED), on the block threshold in the rat sciatic nerve. The same authors demonstrated the role of the IED in minimizing the onset response [40] measured as the force produced upon initial delivery of KES. Their results suggest that an IED of 1 mm minimized the block threshold and the onset response duration and magnitude. This finding is likely driven and supported by the anatomical organization of the myelinated axons in the rat sciatic nerve, where channels are densely packed into Nodes of Ranvier spaced approximately 1 mm apart. Of importance is that the IED determined by Ackermann et al. may only be applicable to nerves of a diameter and fiber-type composition similar to the rat sciatic nerve. Larger diameter nerves and nerves surrounded by thick layers of connective tissue and fat may require larger IEDs to increase charge penetration into the nerve and minimize shunting of current across the surface of the nerve.

In addition, our previous work has investigated the role of geometric surface area in optimizing block thresholds [27]. These results demonstrated that block thresholds are significantly reduced by achieving circumferential coverage of the rat tibial nerve. In addition to geometry, the role of interface materials has also been evaluated [41]. Evaluation of different materials in the rat tibial nerve preparation suggested that minimal to no benefits are achieved with respect to the block threshold or onset duration (figure 4(D)). The lack of any significant effect of block thresholds is likely driven by the identical (SCS) [38], and various peripheral nerve stimulation therapies [39].

Figure 3. Examples of nerve conduction block. Block of unique compound action potential components corresponding to different fiber-types in the rat (A) sciatic nerve and (B) cervical vagus nerve. Measurements are made using the experimental setup described in figure 1(A). Block of evoked motor contractions in the (C) rat tibial nerve using EMG measurements and the experimental setup described in figure 1(B). (Figure 3(A) and (B) reprinted with permission from [4], copyright (2015) by the American Physical Society. Figure 3(C) reproduced with permission from [27]. © 2017, IEEE.)

Figure 4. Different representations of the onset response have different durations. (A) Onset response measured from the rat sciatic nerve (ENG). Dashed line indicates one continuous delivery of KES to the nerve with the grey box depicting the identified onset duration (B) Characterization of onset durations observed in ENG measurements as a function of KES frequency. (C) Onset response-induced rectified EMG activation in the rat gastrocnemius muscle. Spike at beginning of window depicts evoked muscle contraction, with KES delivery enabled 150 ms after. Grey box indicates the onset response duration. (D) Duration of onset response-induced EMG activation as a function of different electrode materials at two KES frequencies. (Figure 4(C) and (D) reproduced with permission from [27]. © 2017, IEEE.)
electrochemical behavior at KES frequencies. Though there is no direct effect on the efficacy of the conduction block achieved, the use of materials that reduce the interface impedance and are chronically viable may be desired and aide in resolving other issues, such as waveform attenuation and reducing the power (and thus increasing battery life) of the therapy.

Onset response

Upon delivery of KES to a target nerve, a brief period of asynchronous, bi-directional activity is induced in the nerve (figure 4(A)). This discrete event has been labeled the onset response and has previously been measured and quantified directly from nerves in various neural circuits [4, 13]. Depending upon the target nerve and the neural circuit it is part of, the onset response can lead to activation of muscles (figure 4(C)), various reflex loops, or pathway specific efferent or afferent signaling (figure 4(A)) resulting in changes in systemic physiology.

In somatosensory neural circuits, the physiological result of the onset response is a muscle contraction (figure 4(C)) or force production and has been studied extensively by Kilgore and colleagues [32]. Their investigations focused on minimizing the onset response magnitude and duration measured through force production. Their studies elucidated the role of electrode contact spacing (i.e. IED) in reducing the onset response magnitude and duration [40]. In other cases, Kilgore and colleagues completely abolished the onset response by combining both DC and KES waveforms [42]. Application of KES to nerves part of autonomic neural circuits is less studied, but can result in activation of numerous unwanted pathways or circuit functions. For example, application of KES to the thoracic sympathetic chain in anesthetized pigs has demonstrated a substantial elevation of cardiac function that eventually subsides, with the duration of the onset anomalously observed as being related to the electrode configuration and electrode-tissue interface [20].

A key distinction that should be made is that the onset response observed from the perspective of the nerve can be on the order of milliseconds (figure 4(B)), while the physiological response (e.g. muscle contraction, figure 4(D)) resulting from the onset response can last up to tens of milliseconds depending upon the target. Furthermore, nearly all published literature on the onset response are from anesthetized preparations. How and what the onset response presents itself in conscious (unanesthetized) states, where cascades of neural control circuits may prevent the occurrence of detrimental physiological effects, is of great interest and warranted. The lack of clinical reports discussing the onset response in patients currently implanted with KES devices suggests there may be no significant physiological side effect in the conscious state, or no substantial onset response at all, however this remains to be investigated.

Carry over

The onset response is present when KES is initially turned on. In contrast, the effects of KES nerve block are present even after turning of KES. The primary artifact that has received investigation is called the carry over block effect, and is a window of time after KES delivery in which nerve activity is either partially or nearly completely inhibited without delivery of KES. The carry over effect has received little attention, with most investigations in somatosensory circuits such as the sciatic nerve. Bhadra and colleagues demonstrated that the carry over can be observed after as little as 15 min of KES nerve block [43], while Yang and colleagues observed a carry over after as little as 1 min [44]. These studies utilized muscle force production as the readout for nerve conduction block, suggesting that the carry over duration quantified is primarily for large diameter motor fibers, and may not be the same for small diameter myelinated and unmyelinated fibers. An important point to consider when interpreting and extrapolating these results to other nerve targets is the experimental conditions. Both studies used different modalities of stimulation (voltage-controlled [43] and current-controlled [44]), which is unlikely to make a substantial difference from the perspective of achieving KES nerve block. However, neither study incorporated various options [45] for reducing or measuring the DC within their block waveforms and did not measure or report the true waveform delivered to the nerve. As shown in figure 5(B), the true KES waveform delivered to the nerve can vary significantly depending upon the electrophysiological setup, resulting in waveforms that are substantially attenuated or potentially contaminated with substantial amounts of DC.

Both voltage and current controlled sources can produce substantial amounts of output-amplitude dependent DC [45], resulting in continued delivery of DC to the tissue during application of KES and potentially resulting in a carry over that is partially due to a myriad of undesired effects, such as sustained electrode polarization, electrochemical artifacts, or DC induced damage of local axons. Methods for reducing the DC contamination have been reported [45], with the use of an inductor–capacitor circuit being the ideal solution. Other approaches, such as the use of blocking capacitors with voltage-sources, are prone to various sources of errors (e.g. current leak, failure due to over voltage, discharging through the tissue) and are not the optimal method for reducing DC contamination. In addition to experimental setup-induced differences, it is likely that the KES duration after which a carry over is observed and the duration of the carry over duration are functions of the target nerve’s anatomy and physiological functions, as well as yet to be understood molecular mechanisms.

Selectivity and directionality

Until recently, KES-induced conduction block had been reported as being all-or-none, suggesting that all propagating activity in the target nerve was blocked upon delivery of KES. Joseph and Butera were the first to demonstrate that block of different fiber-types could be achieved selectively. They realized this by characterizing the KES block thresholds in unmyelinated Aplysia nerves and finding that the relationship
between frequency and amplitude was non-monotonic for unmyelinated fibers [5]. They used suction electrodes to deliver the KES waveforms and record compound action potentials from the nerve to evaluate the effects of KES on nerve conduction in vitro. To validate these findings in a mixed nerve, they later conducted investigations in the frog sciatic nerve, which is a mixed myelinated and unmyelinated nerve bundle. Using the same electrophysiology approaches as with the Aplysia nerves, Joseph and Butera demonstrated the ability to selectively block myelinated (fast-conducting) and unmyelinated (slow-conducting) axons [7]. They found that the block threshold curve for myelinated fibers was monotonic, as had been shown previously, however the block threshold curve for unmyelinated fibers was non-monotonic, similar to that of their findings in Aplysia. When plotted together, these two curves crossed over (figure 2(A)) and resulted in regions of the block threshold curve where individual fiber-types could be selectively blocked using KES.

Although not thoroughly investigated, Cuellar and colleagues [13] briefly discussed similar findings from in vivo studies in the rat. They delivered KES ranging from 2–100 kHz to the dorsal nerve roots and measured single unit activity from dorsal horn neurons. In their report, they discuss observations of selective block of axons in the target nerve rootlet corresponding to A-fiber and C-fiber latencies. They observed complete block of A-fiber latency responses, without attenuation of C-fiber latency responses between 20–30 kHz KES. In contrast, they observed block of C-fiber latency responses at 50 kHz without attenuation of the A-fiber response.

We further investigated the ability to selectively inhibit myelinated and unmyelinated fibers selectively by conducting in vivo experiments in the rat. Using tripolar cuff electrodes, we characterized the block threshold for both the rat sciatic and vagus nerves increased linearly. Interestingly, the block threshold curves for the slow-conducting fibers demonstrated a non-monotonic amplitude-frequency relationship as observed in Aplysia. The functional role of blocking fast- or slow-conducting fibers was evaluated by using muscle force measurement and evoking compound activity through sensory (thermal) stimulation in the sciatic nerve. These results demonstrated a strong overlap of the block threshold curves derived from block of electrically evoked compound action potentials and sensory evoked compound action potentials.

In line with fiber-type selective inhibition is the idea to modulate peripheral nerves in a direction- and pathway-specific (e.g. afferent, efferent) manner. Most existing neurostimulation therapies do not mitigate the well-known issue of the bidirectional activation that occurs upon electrical stimulation of a peripheral nerve. KES enables a unique approach for achieving direction- and pathway-specific activation of peripheral nerves by blocking all activity in the non-target direction. An example of this is demonstrated in the cervical vagus nerve, in which two electrodes were used to activate and inhibit the nerve simultaneously, with activation and inhibition verified through compound action potential recordings. A caudal electrode was used to maximally activate the nerve while a cranial electrode was used to completely block the nerve. When tested in a standard model of Lipopolysaccharide-induced inflammation, direction-specific activation of the efferents led to more consistent and enhanced anti-inflammatory responses compared to traditional stimulation which evokes bidirectional vagal activity [21].

Selectivity, either in terms of fiber-type or direction, is a key aspect of any neuromodulation therapy. Though KES has been shown to enable block of selective fiber-types, it is important to note that selectivity may not be achievable in all nerves. In order to selectively target fiber-types, the block threshold curves for the various fiber-types need to ‘cross over’, such...
that there area under the threshold curve of the fiber-type of interest does not overlap with the area under the threshold curve for non-target fiber-types (figure 2(A)). Furthermore, for highly heterogeneous nerves, such as the cervical vagus nerve which contains A, B, and C fibers, block of one fiber population might result in activation of another population. Similarly, in large diameter nerves, superficial fibers that are closer to the electrode will experience significantly different charge densities, thus making it difficult to achieve selectivity or even complete block of all fibers within the nerve.

Future perspective

Recent and on-going scientific discoveries have started to unravel the role of neural control in achieving homeostasis, and prompted a variety of investigations as to why neural control fails in chronic disease states. For example, increased chronic sympathetic output to the visceral organs in obese patients contributes to the onset, progression, and development of cardiovascular and metabolic disorders such as diabetes and hypertension. In these disease states, it may be desired to inhibit sympathetic output to either treat symptoms or halt disease onset and progression with quick, localized, and reversible inhibition of nerve activity in relevant neural circuits. KES induces such a block of nerve activity, and holds significant promise as a potential therapeutic intervention as well as tool for scientific investigation.

A significant number of unknowns remain and are necessary to understand for effective translation of KES and achieve therapeutic benefit. These remaining unknowns however, must be approached with a physiology-first mindset, in which the physiological system to be modulated is thoroughly understood in terms of both anatomy and physiology. Only then can engineering and physiological principles be bridged to optimize and effectively translate KES neuromodulation therapies. Here, we outline critical components that should be prioritized to develop a better understanding of KES nerve block as a clinical therapy.

Experimentation hardware

A small but important note that also requires attention is the limitations of hardware available for conducting appropriate KES experiments. Traditional electrophysiology experimentation hardware, specifically current sources, were not necessarily designed with applications using continuous kilohertz frequencies, high amplitudes, and feedback-driven control of direct current contamination of the output waveform. When high currents and frequencies are driven into biological tissues, multiple sources—such as high impedance electrodes, slew rate limitations, rise and fall times of the stimulator used, and electrode-tissue properties as a function of frequency (e.g. shunt and coupling capacitances, tissue resistivity and capacitance)—can result in signal attenuation, effectively low-pass filtering the waveform (e.g. loss of higher harmonics, insets of figure 5(A)). This results in skewing of the desired (square or sinusoidal) waveform and thus substantial reductions in the charge delivered to the nerve (figure 5(B)). These challenges result in differences in the reported KES current and waveform (typically what was set on the front panel of the stimulation equipment) and what was actually delivered to the target nerve, introducing potential challenges when attempting to reproduce results. No robust approach exists for completely mitigating the waveform attenuation and skewing, but substantial benefits can be achieved by optimizing electrode geometries and reducing electrode impedances.

Furthermore, as discussed above, the output of many existing current sources are contaminated with significant amounts of DC, which impacts the thresholds, carry over effect, as well as long-term safety of the nerve and electrode. Experimental hardware and configurations used for KES are encouraged to employ DC filter solutions, such as the inductor–capacitor circuit [45]. One approach for understanding the contribution of both issues discussed here to KES nerve block experiments is to measure the voltage waveform in series with the electrode across a low value resistor (e.g. $R = < 1\%$ of electrode impedance) and high impedance amplifier, with careful consideration of the grounding and measurement configurations used. This provides a starting point for understanding the true waveform and currents experienced by the nerve.

Mechanistic studies

Advancing the utility of KES nerve block, specifically in diseases impacting autonomic circuits, requires a true understanding of the mechanism of action of KES nerve block. Many chronic disease conditions are accompanied by systemic changes in neurophysiology, specifically of axons, such as segmental demyelination [46], reduction in internodal lengths and neurons [47], neupathies [48], and changes in innervation [49]. These age- and disease-specific changes in axonal physiology could reduce the therapeutic benefits of KES nerve block in both short- and long-term cases. Understanding the mechanism(s) underlying KES nerve block, and their dependence upon specific axonal physiology states, will be critical for selecting target patient populations, titrating KES over time, and ensuring that a true nerve conduction block is achieved over the course of the long-term therapy. Various hypotheses have been proposed through computational studies, however experimental validation (or invalidation) of the proposed mechanisms remains to be done.

Partial block

A significantly unexplored area of KES nerve block is the parameter space which provides a partial block of the target nerve, and the long-term effects of partial block on nerve and neural circuit function. Partial block is different from selective block in that a non-selective partial block can inhibit activity in a small number of fibers in a target nerve and still provide the desired physiological effect. Due to the complexity of physiological systems, it may be sufficient to inhibit only a few random axons within a target nerve and still obtain varying levels of therapeutic benefit. Joseph and Butera quantified...
the ability of KES to partially block unique components of the compound action potential [7]. Few follow-up investigations have been conducted to understand the characteristics of the partial block parameter space. Similar to all other aspects of KES nerve block, the parameters that partially block a given nerve are likely to differ based upon the target neural circuit of interest.

**Chronic safety and efficacy**

To date, nearly all experimental studies using KES have been conducted in acute, anesthetized animal preparations. Although these are necessary for understanding the direct effects of KES on target neural structures and circuits, it is unclear if these acute effects on physiological function will persist over time in chronic settings. All neural circuits adapt, and it remains to be investigated if adaptation of neural circuits mitigates the effects of KES nerve block. On-going studies aimed at understanding the complex anatomy and physiology of many understudied organs and autonomic circuits will enable thorough investigation of how electrical nerve block using KES (and other modalities) effects long-term function. Furthermore, the safety of KES waveforms, to both the target tissue and the electrode, remains to be investigated. Safety, with respect to neural stimulation therapies, is widely focused on ensuring reversibility of reactions at the electrode-tissue interface to minimize electrolysis of water and electrode damage (e.g. dissolution, pitting, corrosion) [50, 51]. These existing standards likely need to be expanded for characterizing the complete safety of KES nerve block therapies.

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