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Electrical Stimulation Therapies for CNS Disorders and Pain are Mediated by Competition Between Different Neuronal Networks in the Brain

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Summary

CNS neuronal networks are known to control normal physiological functions, including locomotion and respiration. Neuronal networks also mediate the pathophysiology of many CNS disorders. Stimulation therapies, including localized brain and vagus nerve stimulation, electroshock, and acupuncture, are proposed to activate “therapeutic” neuronal networks. These therapeutic networks are dormant prior to stimulatory treatments, but when the dormant networks are activated they compete with pathophysiological neuronal networks, disrupting their function. This competition diminishes the disease symptoms, providing effective therapy for otherwise intractable CNS disorders, including epilepsy, Parkinsons disease, chronic pain, and depression. Competition between stimulation-activated therapeutic networks and pathophysiological networks is a major mechanism mediating the therapeutic effects of stimulation. This network interaction is hypothesized to involve competition for “control” of brain regions that contain high proportions of conditional multireceptive (CMR) neurons. CMR regions, including brainstem reticular formation, amygdala, and cerebral cortex, have extensive connections to numerous brain areas, allowing these regions to participate potentially in many networks. The participation of CMR regions in any network is often variable, depending on the conditions affecting the organism, including vigilance states, drug treatment, and learning. This response variability of CMR neurons is due to the high incidence of excitatory postsynaptic potentials that are below threshold for triggering action potentials. These subthreshold responses can be brought to threshold by blocking inhibition or enhancing excitation via the paradigms used in stimulation therapies. Participation of CMR regions in a network is also strongly affected by pharmacological treatments (convulsant or anesthetic drugs) and stimulus parameters (strength and repetition rate). Many studies indicate that treatment of unanesthetized animals with antagonists (bicuculline and strychnine) of inhibitory neurotransmitter (GABA or glycine) receptors can cause CMR neurons to become consistently responsive to external inputs (e.g. peripheral nerve, sensory, or electrical stimuli in the brain) to which these neurons did not previously respond. Conversely, agents that enhance GABA-mediated inhibition (e.g. barbiturates and benzodiazepines) or antagonize glutamate-mediated excitation (e.g. ketamine) can cause CMR neurons to become unresponsive to inputs to which they responded previously. The responses of CMR neurons exhibit extensive short-term and long-term plasticity, which permits them to participate to a variable degree in many networks. Short-term plasticity subserves termination of disease symptoms, while long-term

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plasticity in CMR regions subserves symptom prevention. This network interaction hypothesis has value for future research in CNS disease mechanisms and also for identifying therapeutic targets in specific brain networks for more selective stimulation and pharmacological therapies.

Keywords

acupressure; acupuncture; amygdala; anesthesia; anxiety; barbiturate; benzodiazepine; brain stimulation; CMR; conditional multireceptive neurons; convulsant drugs; depression; electroshock; epilepsy; hypnosis; ketamine; kindling; learning; memory; neuronal networks; pain; placebo; reticular formation; SUDEP; TENS; vagus nerve stimulation

Stimulation Approaches to Therapy of CNS Disorders

Electrical stimulation in the periphery or within the central nervous system (CNS) has been used to treat a growing number of nervous system conditions, including movement disorders, psychiatric disorders, and seizure disorders as well as chronic pain syndromes. These stimulation approaches include localized electrical stimulation of specific sites within the brain that have resulted in effective treatments for Parkinson's disease and epilepsy (1–4). Acupuncture stimulation in the periphery, which also often employs electrical currents, is a useful treatment for various pain syndromes (5). Stimulation of the vagus nerve via a chronically-implanted stimulator is an effective therapy for epilepsy and may also be useful in treating depression (6,7). There are also several other stimulation approaches that are non-invasive, including transcutaneous electrical nerve stimulation (TENS), transcranial direct current stimulation, and acupressure for reduction of nausea associated with motion sickness (8,9). One of the oldest electrical stimulation therapies in Western medicine is that of electroconvulsive shock, which is a well-established therapy for treatment-resistant depression (10).

The mechanisms of action of these stimulatory treatments are poorly understood. Proposed mechanisms involve a number of different actions on the nervous system, including changes in the levels of inhibitory or excitatory function, which may involve functional alterations of specific neurotransmitters in the brain. A number of these stimulation procedures can produce changes in neuronal networks within the CNS. Some of the stimulation protocols are effective acutely to terminate symptoms that are impending or actively occurring. However, it is often necessary to perform the stimulation procedure, using a repetitive protocol in order to achieve the full therapeutic effect, suggesting that a cumulative effect is producing a persistent CNS change. The effect of the stimulation procedure may initially involve relatively short-term mechanisms, such as ion channel- and neurotransmitter-mediated functional changes, which are likely to mediate short-term plasticity. Repetitive stimulus paradigms may involve more long-lasting processes that contribute to neuronal network activation and control [see Faingold (11) for review]. Mechanisms of activity-driven long-lasting modifications of networks include synaptic plasticity and even neurogenesis, mediated, in part, by activation of neurotrophic factors and other elements in the molecular cascade that underlie long-lasting neuronal changes (11,12–14). Either long-term or short-term network plasticity can be induced in the same exact network pathway, depending on the mechanism of the agent administered within the network (15,16).

The hypothesis proposed here is that the therapeutic action of these stimulatory treatments involves disruption of the function of the neuronal network that mediates the brain disorder. A major mechanism of this disruption involves stimulus-induced activation of a different CNS neuronal network, which was previously dormant. That is, the anatomical connections for the network exist, but the network is normally inactive. This newly-activated network competes

with the disease network for prominence within the CNS, thereby preventing expression of the symptoms of the disorder. This competition between the disease network and the stimulated network involves competition for control of brain regions that contain a high proportion of cells termed conditional multireceptive (CMR) neurons (Fig. 1). The responses of CMR neurons are highly plastic and have the capability of participating in multiple neuronal networks, as discussed below.

Normal brain networks

Extensive research has identified the major elements of CNS neuronal networks that control many normal physiological functions, such as locomotion (17,18) and respiration (19). Some of these networks are normally well-developed at birth, such as the respiratory network, while others require significant development, such as locomotion in altricial species, including man. In the latter type of network significant plasticity is involved in the development of the functional operation of the network, e.g. learning to crawl, walk, and then run. Understanding neuronal network function is quite difficult because of the uncertainties and complexities involved in their operations (20–22). However, elucidating neuronal network function is vital to advancing our knowledge of normal brain function as well as understanding and treating CNS disorders.

Neuronal networks in brain diseases

The advent of brain imaging techniques, such as positron emission tomography (PET), functional MRI (fMRI), single photon emission tomography (SPECT) and others has accelerated the accumulation of knowledge about brain function, particularly in humans. Brain imaging has also shed light on brain malfunctions by identifying specific neuronal network elements that are activated in neurological (e.g., epilepsy) and psychiatric disorders, (e.g., anxiety), as well as acute and chronic pain disorders (23–26). Most CNS disorders are now thought to involve neuronal networks that consist of specific, often widely distributed, brain regions. Comparisons between the results of network studies in human disorders and animal models suggest that there are considerable interspecies network similarities (26,27).

Imaging techniques, such as MRI, can identify brain areas that increase or decrease blood flow. However, imaging data does not yield information about the functional operation of the network, in part, because of relatively poor temporal resolution and difficulties in differentiating inhibition from excitation. The reasons for this include the observation that active inhibition is also associated with increased blood flow, and excitation can also occur without detectable increases in MRI signal (28,29). Thus, after a changing activity pattern in a specific brain area is identified by these imaging techniques, it would be vital to study the change at the neuronal level in the identified area of intact brain to determine the nature of firing change in the millisecond range that can occur during expression of the disorder, especially if the disorder is episodic. This type of research must be carried out in unanesthetized organisms, since anesthetics of various kinds, even in sub-anesthetic doses, significantly alter normal network function in sometimes unpredictable ways, as discussed below (30–34).

Several of the therapeutic stimulation modalities described above have also been investigated using brain imaging techniques in search of brain mechanisms, leading to the identification of the neuronal networks responding to these treatments (9,35–37). Thus, based on an ever-increasing number of investigations, CNS neuronal networks are now strongly implicated in both mediating many brain disorders and also in the therapeutic effects of stimulation of the nervous system.

Network interaction in treating brain disorders

The main hypothesis proposed here is that external stimulation activates a specific neuronal network, and the therapeutic effect of this stimulation procedure is due, in part, to an interaction between the “therapeutic” network and the network that mediates the CNS disorder. This network interaction results in reduction or blockade of the symptoms of the disorder. One major form of interaction is competition between the stimulation-activated network and the disease network. This interaction involves competition for brain sites that contain neurons, which have the capacity to participate in both the network that mediates the disorder as well as the stimulus-activated network. The ability to interact with both networks is conferred on these brain sites, because they contain a high proportion of neurons that have conditional multireceptive (CMR) capabilities. Thus, anatomical connections and the physiological properties of neurons in these CMR brain regions allow them to participate in many different networks, depending on the conditions that the organism is experiencing, as discussed below.

Types of network interactions

In general, the interactions between neuronal networks in the brain can involve 1) competitive effects between networks, 2) cooperative effects between networks, or 3) lack of observable interactive effects. Network interactions can also be acute and/or chronic. Stimulation directly within the disease network, particularly at high frequencies, can also result in disruptive effects on the network (1), and this stimulation may also simultaneously or sequentially activate another network that can compete with the disease network for CMR neuronal involvement. Interactions between neuronal networks may involve sequential and/or simultaneous network activation. An example of sequential network interaction is the interaction of the normal auditory network and the normal locomotion network that occurs in sound-induced (audiogenic) seizures studied in our laboratory (Fig. 2).

Stimulation techniques can be used acutely to abort disease symptoms, which involve short-term plasticity, or chronically to prevent the disease symptoms mediated by long-term plasticity. Thus, many of the successful preventive treatments commonly require repetitive activation of the therapeutic network. Interactions between networks that are proposed to occur also include positive interactions such as those observed in learning paradigms that enhance survival responses (38). Network interactions can also result in negative effects that have been observed in certain types of epileptic seizures (39). A negative sequential effect of competition between networks is postulated to occur in a particularly deleterious aspect of human epilepsy, called sudden unexpected death in epilepsy (SUDEP), which is associated with respiratory difficulties in many human cases. An animal model of SUDEP in DBA/2 mice has been proposed in which a negative sequential interaction occurs. This interaction involves activation of a sound-induced generalized convulsive seizure network that causes disruption of the normal respiratory network, leading directly to respiratory arrest immediately following the seizure, which results in sudden death (40).

Competition between networks can also exert positive effects. The neuronal network subserving acupuncture analgesia is proposed to activate structures of the descending antinociceptive (pain-inhibiting) pathway and deactivate limbic structures within the pain-mediating pathway [see Campbell (41) for review]. This represents an example of both an inhibitory interaction with the pain network, and a positive interaction with the pain control network (42,43). Interestingly, acupuncture-induced imaging changes are quite similar to those seen with placebo-mediated analgesia and in hypnosis (41), which have also been shown to be effective analgesic treatments (44,45), suggesting a generality of the networks subserving these pain-reducing treatments.

Repetitive stimulation of both normal and pathological networks can also cause brain areas that were not participating in the network prior to repetition to become actively involved in the function of the network (31,46–49). Likewise, repetitive exogenous stimulation may act to diminish manifestations of CNS disorders, in part, by enhancing the synaptic strength between neurons and/or by expanding the scope of the dormant network that is activated by the stimulation procedure. A lack of effect of a particular stimulation paradigm on the symptoms of a CNS disorder would suggest that the stimulation is activating a network that does not interact sufficiently with the network that mediates the disorder.

A precursor of this network interaction approach is found in the work of Melzack and Wall (50) in their gate theory of pain in the spinal cord. They proposed that pain could be reduced or blocked by peripheral non-painful stimuli that closed the "gate" in the spinal cord and reduced the transmission of pain impulses to the brain by a competition between the painful and non-painful stimuli for transmission to the nociceptive regions of the brain. Recent modifications of this concept to include brain involvement in a pain "neuromatrix" have been developed (51).

Primary sensory and motor networks

Well-defined neuroanatomical pathways carry specific sensations from the periphery via a series of subcortical primary sensory nuclei that project directly to the primary sensory cerebral cortex regions, and the primary motor cortex projects directly to the motor neurons of the spinal cord. Thus, for example, major anatomical and physiological exploration of the auditory pathway has been and continues to be refined. Sensory coding was initially thought to be mediated by a system of dedicated neuronal "cables" that connected the ascending nuclei of the auditory pathway, not unlike the early telephone systems. Early auditory physiology by Von Bekesy (for which he received the Nobel Prize in 1961) seemed to confirm that the neurons in this network merely mimicked the acoustic stimulus very closely. However, the neuronal firing patterns in the more rostral auditory nuclei turned out to be more complex and are still under active investigation (52). Even the earliest investigations of visual stimulus processing indicated its complexity, and the initial elucidation of these processes resulted in a Nobel Prize for Hubel and Weisel in 1981. Research on this topic is continuing (53). The primary corticospinal motor pathway is well studied (54), but the way that coordinated movements, such as locomotion, are mediated involves complex pathways in the brainstem and spinal cord (18). Thus, all of these primary networks are more complex than initially thought, probably due to similar network plasticity mechanisms discussed below, but to a lesser degree than that seen in non-primary networks.

Conditional multireceptive (CMR) brain sites

In contrast to the primary sensory and motor brain pathways, even the earliest research on non-primary brain sites indicated that these brain regions contain a high proportion of cells that can be termed "conditional multireceptive" (CMR) neurons, as mentioned previously. Unlike most primary neurons, CMR neurons show highly inconsistent responses to stimuli. However, the degree of CMR neuronal responsiveness is unpredictable and is capable of exhibiting a major degree of response plasticity, depending on the external and internal milieu that each individual intact organism is experiencing. The plasticity can be of either short-term or long-term duration, as discussed below. The responsiveness of many CMR neurons also varies extensively with pharmacological treatment, particularly with various types of anesthetics and convulsant drugs. Most CMR neurons have minor direct and indirect anatomical connectivity to primary sensory and motor nuclei, and CMR neurons also have connections with many other non-primary brain pathways. CMR regions are those areas that contain a large population and/or high percentage

of CMR neurons, and these brain regions exhibit diverse and extensive connectivity with many other brain regions.

One of these CMR brain regions is the brainstem reticular formation (RF), which has been broadly defined to include a number of brainstem nuclei in the medulla, pons, and midbrain. Other brain areas, including the amygdala, hippocampus, cerebellum, and association areas of the cerebral cortex, also contain significant populations of CMR neurons (30,55–57). The conditional nature of the responsiveness of CMR neurons is a key quality that differentiates these neurons from primary sensory and motor neurons. CMR regions, as defined here, contain a high proportion of CMR neurons.

The physiology of CMR neurons is much more complicated and considerably less consistent than primary sensory neurons. Thus, the same individual CMR neuron can often be responsive to stimuli in multiple modalities, including electrical stimulation in the periphery and in specific sites within the brain as well as sensory stimuli, but it varies considerably depending on the conditions that the whole animal is experiencing. CMR neuronal responsiveness to any given modality can change extensively, depending on stimulus parameter type, strength, and repetition rate, vigilance state, and pharmacological treatment conditions. There is an extreme degree of sensory response plasticity of CMR neurons, such as those in the RF. Many RF and other CMR neurons often appear to be unresponsive to external stimuli, but they can become extensively responsive to these same stimuli after low doses of antagonists of inhibition (e.g., bicuculline) or due to behavioral conditioning (see 30,55,58–61). Thus, the RF neuronal responses to electrical stimulation of peripheral nerves and several brain sites as well as to various sensory stimuli undergo major increases following treatment with agents that block inhibition (Fig. 3).

Many RF neurons that did not respond to electrical stimulation of the sciatic nerve or primary sensory nuclei and multiple sensory stimuli became highly responsive to one or many of these stimuli after low doses of several convulsant drugs administered systemically or directly onto these neurons (Fig. 4) (55,62). This convulsant drug-induced responsiveness to external stimuli is short-term, lasting ~30 min in most cases of systemic administration.

Such convulsant drug-induced increases in neuronal responsiveness also occur in amygdala and pericruciate cortex, although the degree and incidence of firing increases were lower than those in RF neurons. Neurons in several other brain areas, particular primary sensory areas, showed minimal response changes simultaneously under the same exact conditions (30). Although quantification of the percentage of CMR neurons in a given brain region can be problematic, studies have compared the convulsant-induced response enhancement seen in seven different brain regions [see Faingold and Caspary (30) for review]. As seen by the graph in Fig. 5, the region with the greatest percentage of neurons and the greatest degree of convulsant induced firing increase is the brainstem RF, highlighting the intensely CMR nature of this region, while the amygdala exhibits the next greatest CMR percentages. Primary sensory nuclei, including a primary visual nucleus (lateral geniculate) and a primary auditory nucleus (inferior colliculus), show the least capability for change of those examined.

Another important property of CMR neurons is their high sensitivity to various CNS depressants, including, anesthetic, sedative, and anticonvulsant drugs. These depressants will block the sensory responses of CMR neurons in the RF and in the amygdala, but the same drugs do not significantly affect responses in many primary sensory neurons (30,63). In addition, these depressant drugs will reverse convulsant drug-induced enhanced responsiveness to external stimuli in RF neurons (30). Low doses of the dissociative anesthetic, ketamine, selectively suppressed responses of amygdala neurons to sensory but not to electrical stimuli in the brain (Fig. 6) (63–65). These findings indicate that the normal physiology and

pathophysiology of CMR neurons cannot be accurately evaluated in anesthetized animals. In fact, firing suppression of CMR neurons by these anesthetic agents may be a major mechanism for the depressant effects of these agents (66,67).

The extensive response variability of neurons in CMR regions confers the capability for these neurons to exhibit extensively enhanced responses to multiple sources of external input. Thus, CMR regional responses to input from neuronal networks that initiate CNS disorders may result in recruitment of those regions into the disease network (e.g., 63,68). In contrast, the same CMR regions may also become responsive to external stimulation of “therapeutic” sites, becoming a functional part of a previously dormant therapeutic network. This “newly” activated previously dormant network is proposed to compete with the network that mediates the brain disorder for “control” of an overlapping population of CMR neurons, as discussed below.

Short-term plasticity of the responses to external stimulation is a cardinal but often ignored feature of many of these CMR cells although this can occur in certain primary sensory neurons but the incidence and degree is significantly lower (55,69–72). Long-term plasticity is thought to play an important role in shaping existing networks, including network expansion induced by experience and in pathophysiological processes that mediate CNS disorders (38,64,73–75).

Long-term plasticity of responses to external stimuli are common in the amygdala and can be observed during learning paradigms (76) as well with repeated external stimuli in epilepsy models, such as electrical and audiogenic kindling (63,77). Thus, responses to repeated audiogenic seizures (AGS) in rats with inherited susceptibility to AGS result in long-lasting behavior changes (47,49,78,79) accompanied by major increases in amygdala neuronal firing evoked by external stimuli (63). Amygdala neurons respond to auditory stimuli with considerably greater numbers of extracellular action potentials after a repeated AGS protocol (AGS-kindling) than before this stimulation paradigm (Fig. 7). The synapse between the auditory pathway (medial geniculate body) and the amygdala is a major site at which the long-term plasticity occurs (64).

No recovery from the AGS kindling-induced form of long-term amygdala neuronal plasticity is observed, which contrasts with the relatively rapid recovery from the short-term plasticity in amygdala and RF neurons induced by acute convulsant drug administration (80). Thus, either long-term or short-term plasticity can be observed in the same CMR site, depending on the nature of the treatment procedure, and this has been observed prominently in the amygdala (e.g., 15,16).

Subthreshold responsiveness

One important physiological basis for plasticity in CMR neurons is thought to involve the finding that a large percentage of these cells respond to external input with subthreshold excitatory postsynaptic potentials (EPSPs) that do not reliably evoke action potentials. Thus, RF neurons commonly respond to single external stimuli with an EPSP, leading to propagation of an action potential. However, EPSPs evoked by subsequently repeated stimuli decline progressively, and the EPSP amplitude quickly falls below the threshold for evoking an action potential (55,81,82). Subthreshold responsiveness is a key feature of CMR neurons and a cardinal quality that differentiates a “fixed” neuroanatomical pathway from the concept of a neuronal network.

Thus, many CMR neurons within the non-primary components of a network can display a high degree of both short-term and long-term plasticity, which allows the network to undergo major degrees of modification due to experience, disease, drug treatment, or repetitive stimulation.

Possible mechanisms for the inconsistent CMR neuronal responses include low synaptic strength and the presence of extensive tonic inhibition of CMR neurons (30). Tonic inhibition mediated by extrasynaptic GABA_A receptors is proposed to modulate the overall excitability of neuronal networks (83). Drugs that block tonic inhibition, such as GABA_A receptor antagonists (84), have been shown to enhance the responsiveness of CMR neurons in intact animals (30). These antagonists may cause previously subthreshold EPSPs to reach the threshold for eliciting action potentials by allowing the resting membrane potential to rise closer to threshold. This phenomenon would result in consistent responsiveness of these CMR neurons to external stimuli, mediated by short-term plastic changes, as described above (55). Synaptic mechanisms for long-term plastic changes in CMR responsiveness may involve persistent increases in synaptic strength, which may result from enhanced pre-synaptic activity, effectively increasing the stimulation-induced input to these neurons (73).

Network formation and control

An important property shared by many networks in the mammalian brain is the ability to undergo physiological modification. A number of processes that contribute to the formation and control of neuronal networks in the brain have been identified (see 11,49 for review). Included in these important network control mechanisms is external stimulation, which may be a major basis for the ability of stimulation protocols to exert therapeutic effects. Stimulation by electrical or other modes of stimulation activates many neurons in the CNS. If the same stimulation protocol is continuous or repetitive it may result in the persistent activation of a pre-existing but largely dormant neuronal network, which is in accord with the recently postulated “Law of Conservation of Networks” (11). This idea states that there are numerous dormant potential networks that are largely inactive under normal conditions. These dormant networks can be acutely activated and exhibit short-term plasticity, resulting in cessation of ongoing symptoms of the CNS disorder.

Conversely, the previously dormant network can become persistently active due to a repetitive stimulation protocol. This persistent effect may involve long-term plasticity, occurring within or between network sites, which has the potential to prevent symptoms of the disorder. A major mechanism for the long-term activation of this neuronal network may be the ability of the repetitive stimulation protocol to cause subthreshold synaptic interactions to reach threshold more frequently, as discussed above. This newly activated network is hypothesized to contain a significant population of CMR neuronal regions that overlap with the CMR neuronal regions that also participate in the network that mediates a specific brain disorder (Fig. 1).

Thus, repetitive external stimulation can induce persistent activity in these newly-activated networks and lead to competition for the participation of the population of CMR neurons and regions that have the potential to be involved in both networks. Continued and repetitive stimulation can also lead to long-term plastic changes in networks, which include expansion of the seizure network to areas that were not previously involved. This phenomenon is well-known to occur in seizure networks subjected to various forms of repetitive stimulation (“kindling”) approaches, including electrical and acoustically-evoked (audiogenic) kindling (39,49,85). The expanded pathway can become spontaneously active or be readily evoked by previously subthreshold intrinsic or extrinsic inputs in the animal’s milieu.

The capability of neurons to undergo network switching has been widely seen, including in invertebrate networks, such as those in the crustacean stomatogastric ganglia. Certain identified neurons in these ganglia participate actively in a network that mediates a specific physiological function. However, when a network that mediates a different function becomes active this same neuron can change its firing properties to become an integral part of the newly activated network (86,87). Similarly, different modes of locomotion in lampreys can be mediated by

overlapping groups of reticulospinal neurons (88). Likewise, CMR neurons in the brainstem RF can be induced to change the network to which they respond by pharmacological interventions that significantly alter responsiveness to external stimuli. These CMR neurons become reversibly very responsive to external stimuli to which they were previously unresponsive, as described above. This responsiveness change can be induced by administration of several different convulsant drugs most of which block inhibition. These same CMR neurons can also be rendered reversibly unresponsive to external stimuli by certain anesthetics and anticonvulsant agents (55). Even primary auditory neurons in the inferior colliculus, which normally respond robustly to acoustic stimuli, can temporarily cease responding to these stimuli but instead be driven by a generalized seizure network when it becomes active (11,89,90).

This paper postulates that an interaction between neuronal networks in the CNS is likely to occur when external stimulation competes with input from the disease network for “control” of a significant population of CMR neurons. This competition can effectively reduce the scope of the disease network and result in blockade or diminution of the symptoms of the disorder being mediated by this network (Fig. 1). This competition is postulated to be a major mechanism that subserves the ability of various electrical stimulation modalities to exert their therapeutic effects in epilepsy, Parkinsons disease, pain, and depressive illness as well as many other CNS disorders.

In addition to providing a testable potential explanation for how these stimulation protocols are producing therapeutic effects, the network interaction hypothesis may also have heuristic value for the direction of future research. Thus, human imaging studies in humans can identify the brain regions implicated in the neuronal network that mediates a CNS disorder and also identify the brain regions that potentially participate in a stimulation-activated network that is effective in controlling that disorder. This would allow identification of common CMR brain region(s) that may be responsible for the effects of the therapeutic stimulation. Further experiments using neuronal recording from the analogous networks in animals may also suggest more selective pharmacological targets for CNS disease therapy. Thus, if drugs can be identified that act relatively selectively on these specific CMR regions *in vivo* in doses that are therapeutically relevant (e.g., 91), this has the potential to more selectively treat the disorder being mediated by this brain region.

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Fig. 1.

Diagram of Hypothetical Competitive Neuronal Network Interaction between a CNS Disorder Network and a Therapeutic Network. In panel A the neuronal network that mediates the brain disorder is shown as being tonically active. At this time the stimulation procedure has not been presented, so the potential therapeutic neuronal network is dormant. Therefore, the input from the brain disorder network to the conditional multireceptive (CMR) regions(s) of the brain, which may include the brainstem reticular formation and amygdala, are activated by the disorder network and contribute importantly to the expression and severity of the symptoms of the disorder. In panel B the stimulation protocol has been instituted, causing the therapeutic network to become active, which does not produce any noticeable effects of its own. However, the therapeutic network also projects to an overlapping population of neurons in the CMR brain regions, and this input competes for dominance of the CMR regions. This network competition reduces the severity of the symptoms of the disorder and may even prevent these symptoms, allowing the stimulation protocol to be an effective therapy for this disorder.

A. Hearing Network Elements

B. Locomotion Network Elements

Fig. 2.

Diagram of an Example of a Neuronal Network Interaction with Negative Consequences - Audiogenic Seizures (AGS). Elements of the normal network for hearing up to the level of the midbrain are shown in panel A. (Projections to the medial geniculate body and auditory cortex are not shown.) Elements of the normal network for locomotion are shown in panel B. In panel A the inferior colliculus (IC) normally projects to a “minor” degree to the sensorimotor brain regions (elements) of the normal locomotion network, including the deep layers of the superior colliculus (DLSC) and brainstem reticular formation (RF), which project to the substantia nigra reticulata (SNR) and periaqueductal gray (PAG), and PAG, RF and DLSC all project to the spinal cord. A genetically-based or induced defect of γ -aminobutyric acid (GABA) inhibition ($\gamma\downarrow$) in the IC allows high intensity acoustic stimuli to induce excessive firing in of IC neurons that project abnormally intense output to the sensorimotor nuclei, and overdrive their output to the spinal cord, resulting in the sound-induced audiogenic seizure (AGS). The behaviors seen in AGS range in severity from wild running (1), to generalized (four limb) clonus (2), and in the most severe form tonic seizures that may result in tonic hind limb extension (3), which leads to behavioral (post ictal) depression. Other abbreviations: CN = cochlear nucleus, SOC = superior olivary complex, DNLL = dorsal nucleus of the lateral lemniscus, MLR = midbrain locomotion region. [Based in part on (11,18)]

Fig. 3.

Typical example of the major increase in response to an external stimulus of a neuron in a conditional multireceptive (CMR) brain region [brainstem reticular formation (RF)] induced by a convulsant (bicuculline) agent that blocks γ -aminobutyric acid ($GABA_A$) receptor-mediated inhibition. Panel A shows a bar graph of the neuronal firing changes in panel B. Panel B illustrates the effect on single bulbar RF neuron firing in the unanesthetized cat. The three columns in panel B illustrate peristimulus time histograms (PrSTH) in response to visual stimuli (100 μ sec light flash at 0.5 Hz) in control (left column) before drug administration, which has a hint of time-locked firing (peak), suggesting a minor response to the stimulus. After i.v. administration of bicuculline (0.075 mg/kg) (middle column), the same neuron exhibited a considerable increase in firing and a large peak in the PrSTH as well as consistent repetitive firing (inset). The response recovered to the control pattern (right column) 27 min after drug administration ceased. The insets in each PrSTH show oscilloscope trace of the neuron's extracellular action potentials (3 superimposed trials). PrSTH parameters (25 presentations, bin width = 1 msec, scan length 400 msec). N= number of action potentials per PrSTH, Calibration = 1 mv. [Based on data from (92)]. This effect was seen in 88% of over 700 bulbar and midbrain RF neurons in unanesthetized cat and rat by systemic or direct (iontophoretic) application of drug. [see (30)]

Fig. 4.

Typical examples of the increases in single neuron responses to an external stimulus of a conditional multireceptive (CMR) brain region in the midbrain reticular formation induced by a convulsant agent (pentylenetetrazol) that reduces the inhibitory effect of γ -aminobutyric acid (GABA). Panel A shows a bar graph of the neuronal firing changes in panel B. Panels B, C, and D illustrate the effect on the firing of three different single midbrain RF neurons in the unanesthetized cat to three types of electrical stimuli. The panels B, C, and D illustrate poststimulus time histograms (PSTH) in response to single electrical stimuli of the sciatic nerve (B), inferior colliculus, or lateral geniculate nucleus (D) of three separate neurons. The control (left column) shows the firing pattern before drug administration, which have no clear indication of time-locked firing (peak) in response to each stimulus. After i.v. administration of a convulsant drug (middle column) [pentylenetetrazol, 15 (B), 10 (C), or 10 (D) mg/kg], the same neuron in each row exhibited a considerable increase in extracellular action potential firing and a large peak in the PSTH. The responses recovered towards the control pattern (right column) 20 (B), 22 (C), and 29 (D) min after drug administration. Stimulus parameters = 100 μ sec single bipolar pulse at 0.5 Hz). PSTH parameters (50 presentations, bin width, 1 msec,

scan length 400 msec). N= number of action potentials per PSTH. [Based on data from (92, 93)].

Fig. 5.

Schematic representation of the different brain regions in which the effects of i.v. administration of convulsant drugs have been examined in the unanesthetized cat. The mean increase of overall firing rate as percentage of control is shown by the scale on the left. The two areas of the brainstem RF exhibited the highest degree of enhancement. AMG = amygdala, HPC = hippocampus, IC = inferior colliculus, LG = lateral geniculate, PC = pericruciate cortex, RF = brainstem reticular formation, SNR = substantia nigra reticulata. [Taken from Faingold and Riaz (55) - Permission to reprint requested from CRC Press.]

Fig. 6.

The ability of an uncompetitive NMDA antagonist (ketamine) that produces dissociative anesthesia to reversibly block the responsiveness of neurons in a conditional multireceptive (CMR) brain region in the lateral amygdala (LAMG). Panel A shows a bar graph of the mean effect in 8 different LAMG neurons in 8 rats. Mean number of action potentials/PSTH in control was 182.1 ± 42.0 (SEM) vs. 9.6 ± 2.0 after ketamine. Panel B shows a typical example of the effect of ketamine (30 mg/kg, i.p.) on the LAMG neuronal firing. The LAMG neuron exhibited an onset response before ketamine treatment (panel B top row). The neuronal firing was significantly ($p < 0.01$, paired t test) and almost completely suppressed 15 min after ketamine treatment (panel B middle panel). Four hr after ketamine treatment, the LAMG neuronal response was comparable to that prior to ketamine treatment (panel B bottom row). The insets (in each row of panel B) show examples of the digital oscilloscope tracings for each PSTH. AP amplitude: $300 \mu\text{V}$. N=number of action potentials in the PSTH. Treatment was given in previously unanesthetized awake behaving rats (Acoustic stimulus parameters: 12 kHz tone burst, 100 ms duration, 5 ms rise-fall, 100 dB SPL, 0.5 Hz rate, 50 presentations). [Based on data from (63)]

Fig. 7.

Mean firing changes and a typical example of the effects of repetitive auditory stimuli [audiogenic seizure (AGS) kindling] on lateral amygdala neurons in an inherited form of AGS (GEPR-9). In panel A the mean firing change is shown with significant firing increases (action potentials/PSTH before kindling 31.4 ± 4.9 (SEM), (36 neurons) vs. 162.1 ± 11.8 (30 neurons) after AGS kindling $p < 0.05$, paired t test. In panel B the firing of typical examples before and after repetitive seizures is shown by PSTHs. The insets (in panel B) show examples of the oscilloscope tracings for each PSTH. AP amplitude: $200 \mu\text{V}$ (left column) and $300 \mu\text{V}$ (right column). N=number of action potentials in the PSTH in unanesthetized behaving rats. [See Fig. 6 for stimulus and PSTH parameters, based on data from (63)]