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Old and New Hypothesis to The Mechanism Underlying Opioid Addiction and A Novel Treatment – A Review

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Abstract

Previously we presented experimental evidence that the severity of drugs of abuse withdrawal behaviors is correlated with drug-related changes in baseline neuronal firing patterns in 14 regions of the brain that we studied. These 14 areas of the brain participate in reward and pain sensations as well in response to drugs of abuse. Based on these experiments we came to the following hypothesis: Repeated morphine exposure elicits a chain of molecular and cellular events that results in the modulation (disruption) of the baseline (spontaneous) neuronal activities from the initial state to the opioid-induced state which requires continuous morphine use to keep this new baseline (BL). Cessation of morphine consumption disrupts this new morphine modified BL. This BL neuronal activity disruption leads to the expression of the withdrawal. Activation of these brain areas by noninvasive transcranial current stimulation (NTCS) will provide a novel efficacious intervention to diminish the development of opioid tolerance and the severe symptoms of opioid withdrawal. NTCS, when applied to addicted animals when the morphine consumption is discontinued rewires the disrupted neuronal circuits activities and facilitates a return to the initial BL. This will lessen or eliminate the behavioral expression of the withdrawal symptoms. NTCS have the potential to obviate and/or supplement significantly the common treatments of addiction that employ medications with drugs in the opioid family and prolonged behavioral therapies. New approaches to the opioid crisis are badly needed since the current drug treatments require lengthy investments of times.

Key Words: Acute and Chronic Morphine, Tolerance, Withdrawal, Addiction, Non-Invasive Brain Stimulation.

Introduction: The current opioid epidemic is a major public health problem in the U.S. and other countries. One of the major impediments to solving this crisis has been a lack of an understanding of the underlying neurophysiological mechanism of opioid addiction that has prevented development of effective treatments and preventive measures Wilhelm Enb (1883) [1], described a hypothesis and several procedures and therapeutic outcomes following noninvasive transcranial current stimulation (NTCS) treatment for a number of behavioral and physiological illness and the rationale for its effectiveness in his Handbook of Electro-Therapeutics- translated from German to English and published in 1883. His hypothesis was that many behavioral disorders are due to disruption of neuronal circuit activities in the brain and that NTCS stimulates the brain to cause the disrupted neuronal circuits to revert to normal patterns to effectively treat the disorders. He then provided several clinical case reports to support his theory. Our studies on the neurophysiologic properties underlying drugs of abuse have established that repetitive administration of morphine and other drugs of abuse modulate the behavioral and neuronal baseline (BL) activities of several brain areas. These changes correlate closely with the development of tolerance and withdrawal behaviors strongly suggesting a cause-effect relationship. In other words, when this drug is used repeatedly and withdrawn, it produces changes in the BL neuronal firing rates of the above brain regions, and it is these electrophysiologic changes that are causing the subsequent behaviors indicative of withdrawal [2-4]. Moreover, our previous electrophysiologic studies of the above 14 different brain structures exhibit alterations in baseline (BL)

neuronal activity following cession of the drug.

In behavioral studies we show that auricular electrical stimulation (AES) treatment to morphine-dependent animals attenuates significantly the naloxone precipitated withdrawal [5-7]. Based on the above observations (behavioral and electrophysiologic), we developed the following hypothesis "changes in the baseline (spontaneous) neuronal firing patterns of multiple brain structures are the underlying basis for the severity of opioid withdrawal conditions". This led us to consider therapies that could reverse the changes in baseline (BL) neuronal firing patterns as a treatment to attenuate and/or eliminate the withdrawal symptoms that make it so difficult for individuals addicted to opioids to discontinue their drug use. This new model led us to consider non-invasive transcranial current stimulation (NTCS), a procedure developed by Wilhelm Erb over a century ago at as a non-opioid treatment for this devastated epidemic.

Our neurobehavioral and neurophysiological studies of the actions of drugs of abuse that invoked alterations in baseline (BL) neuronal firing patterns following repeated (chronic) consumption of the drug as the underlying mechanistic basis of tolerance and withdrawal, we considered whether NTCS could cause the altered neuronal firing to reverse to its normal patterns and thereby attenuate the withdrawal behaviors. In the remaining sections of this manuscript, we describe the studies and the rational that formed the basis of our model and led us to consider NTCS as a nonopioid therapeutic approach to prevent or attenuate these conditions that underlie the current opioid epidemic and since than the NTCS technology has improved,

Opioids: Morphine is pain medication of the opiate family found naturally in a number of plants and animals [8-10]. Morphine has been widely used since its initial isolation in 1805 by Friedrich Serturner [11]. It was named after Morpheus, the Greek God of Dreams because of the dream-like state it produces. It is the prototype opioid that has been used for many studies of the physiological effects and pharmacological actions of opioids, and it is the drug we and others have used most commonly to study the behavioral and electrophysiological effects of this class of agents. Other widely used opioids include codeine and fentanyl. Additionally, major commercial products with registered tradenames that contain opioids are Vicodin, OxyContin, and Percocet. These naturally occurring compounds, their semi-synthetic derivatives, and synthetic analogs with similar pharmacological activities have been extensively used for therapeutic purposes, primarily for the treatment of pain but also as cough suppressants, anti-diarrheas, and for other purposes. They produce their actions in humans and animals by initially interacting with opioid receptors, membrane-bound proteins that mediate the actions of endogenous molecules (e.g., endorphins and enkephalins).

Morphine is a legally prescribed pain relief medication to treat both acute and chronically severe pain. It is also legally prescribed as an analgesic, as a sedative and for its action in the GI tract to decrease diarrhea. Its repetitive use leads to drug dependence ([10-12]. Opioid dependence is classified as a substance use disorder (SUD), a complex and often chronic health condition with untoward, and often devastating, economic, social, and psychological consequences. Opioids act mainly on the central nervous system (CNS) to produce relief from pain but do not treat the underlying cause of pain. Their repetitive use produces dependence on the drug as well as tolerance. Morphine is a highly addictive substance whose misuse has been noted since 300 BC [13, 14].

Epidemiology of The Opioid Epidemic: Opioids are legitimately used for treating pain [15]. Following their widespread prescription for relief of acute and chronic pain, opioids quickly became the most widely prescribed class of medications in the USA - exceeding the use of even antibiotics and heart medications. Unfortunately, about 20 to 30 percent of patients who are prescribed opioids for chronic pain, become addicted and misuse them to prevent the withdrawal symptoms that occur if they discontinue drug use [16]. Another major public health concern is that a high percent (80%) of heroin users first misuse prescription opioids [17].

The overdose death rate from opioid usage in America since 1980 has increased in an exponential fashion of 76% per year and has now reached 50,000 deaths per year. Allison, Putt, Keother, Humpreyes, and Margaret Brandeau from Stanford University estimate that at the current rate of opioid abuse just over half a million Americans have already died, or will die, of opioid overdose between 2016 and 2025. This epidemic began in the 1990s with the over-prescription of opioids as pain relieving medications in non-cancer patients. In 2014 in the US, about 4.3 million people used opioids for nonmedical purposes including about 435,000 heroin users.

There are now more opioid overdose deaths in the US every year than deaths due to car accidents and gun shots [18]. In the 12-month period ending in Nov. 2017, nearly 70,000 lives were lost nationwide due to opioid overdose making it one of the most serious overdose crises the country has ever had to face [19]. More than 210 million opioid prescriptions were filled in 2010. Close to 12 million people admitted to abusing these drugs by taking them for non-medical reasons, and the misuse of prescription opioids affects millions of Americans each year [20]. For example, in 2015 an estimated 20,100 deaths were due to prescription painkillers, 12,940 deaths due to heroin use, and 591,000 people had some type of substance use disorder. Similarly, in 2016, more than 20,000 deaths in the US were caused by an overdose of prescription opioids and another 13,000 deaths resulted from heroin overdose, while other 2016 studies reported over 64,000 drug overdose deaths due to fentanyl and its analogs [21]. As the opioid crisis continues to devastate the USA and its communities, it is essential to investigate new approaches to combat the crisis which is the objective of a large number of scientists including our own work [22].

Opioid Addiction and Dependence: Opioids produce their effects via an initial activation of opioid receptors that are G protein-coupled membrane proteins. Opioid binding to these receptors activates a variety of second messenger systems depending upon the specific cell type. These include inhibition of adenylate cyclase activity, activation of potassium channels, activation of phospholipase C, and stimulation of mitogen- activated protein kinases (MAP kinases). These lead to changes in gene expression,

β – arrestins may subsequently down regulate opioid receptors by cellular internalization and inactivation [23]. Opioid receptors are found throughout the central nervous system and in other organs where they are embedded in the outer membrane of neurons. When opioids bind to these receptors, they trigger a series of molecular changes, including transcriptional and epigenetic events and this neuroplasticity leads to relief of pain and produces pleasurable sensations [24-27].

Unfortunately, repeated use of opioids leads to tolerance (See fig 1 compare trace C to trace B) and addiction. Addiction is a term referring to compulsive drug use to prevent the unpleasant withdrawal expression despite harm and is characterized by intensive drug-seeking and use as well changes in brain activities [28]. Opioid dependence is the basis for addiction which is a long-lasting (chronic) disease that typically results in major health, social, and economic problems. It is characterized by a powerful, compulsive urge to use opioid drugs again and again when they are no longer required medically. It is accompanied by well-described physical dependence with a severe withdrawal syndrome and tolerance.

Our studies on the neurophysiological mechanisms underlie drug dependence have established that repetitive administration of morphine and other drugs of abuse modulate the behavioral and the neuronal BL activities. These changes in neuronal BL (spontaneous) activities in a large number of brain regions including the ventral tegmental area, nucleus accumbens, caudate nucleus, several thalamic and hypothalamic nuclei, hippocampus, amygdala, habenula, septum and pre-frontal cortex as well as other CNS sites [29-44]. These changes correlate closely with the development of tolerance and withdrawal strongly suggesting a cause-effect relationship. In other words, when the drug is withdrawn it produces changes in the baseline neuronal firing patterns of involved brain regions, and it is these electrophysiological changes that are involved with causing the subsequent behaviors indicative of withdrawal.

Addiction is a primary, chronic, and brain disease resulting from drug dependence that is characterized by an individual pathologically pursuing reward and/or relief or prevention of the severe withdrawal symptoms cause by discontinuation of opioids or other substances of abuse. This addiction is a chronic medical condition, and it takes much more than will power to break free from the strong urge to continue drug use. One explanation of opioid dependence is that it occurs when an abuser consumes opioids thereby releasing a flood of endorphins, orexin and dopamine in the CNS resulting in reward feelings such as pleasure and satisfaction. The only way a person can experience these sensations again is to repeat the use of the drug, which causes users to crave the drug and drives its repeated use. Opioid addiction is a disease that has destroyed the lives and families of millions of people [45]. Sadly, there is no cure for opiate addiction at this time as the disease has been intractable to date. We feel this is due in large part to a lack of understanding of the basic underlying mechanisms of the disease and we believe that new approaches to the problem will be required for a solution. Thus, we hope that the novel ideas we propose below about the underlying basis for opioid withdrawal and approaches to reduce dependence will ultimately be required to produce solutions to the current opioid epidemic.

Withdrawal: Opioid withdrawal occurs when the drug use is discontinued (i.e., abstinence or spontaneous withdrawal – see figure 1 trace D compare to trace A) or when opioid antagonists such as naloxone are administered to dependent animals (precipitated withdrawal). Opioid withdrawal symptoms can be very severe and last for long periods of time. Human withdrawal is divided into physical and psychological symptoms, and at the height of withdrawal, symptoms typically include intense anxiety, tremors, shakes, muscle cramping, and joint and deep bone pain in addition to piloerection, yawning, diarrhea, sweating, insomnia, restlessness, and more [46]. In experimental studies with rats, withdrawal is expressed by increased locomotor activity which we have studied extensively in our laboratory.

Our mechanistic studies have involved recording of single unit neuronal activity in anesthetized as well as from freely behaving animals before and after acute and repetitive (chronic) morphine administration to develop dependence followed by drug cessation or pharmacological antagonism (e.g., with naloxone) to initiate withdrawal. We have recorded activity from a large number of brain regions including the VTA, LC, DR, NAc, PFC, CN, several thalamic and hypothalamic nuclei, Hipp, Amyg, Hab and Spt and other CNS sites. Our measurements showed significant alterations in baseline neuronal firing to varying degrees in all of these structures, and these changes were accompanied by the development of tolerance and dependence. When the drug is withdrawn or antagonized, severe withdrawal symptoms occur as indicated by behavioral and electrophysiological changes seen in the animals. These observations strongly suggested a relationship between the hyper neuronal excitability in the above brain areas, the development of dependence, and withdrawal symptoms illustrated by the animals' behaviors. Further support for this relationship comes from our previous findings that direct microiontophoretic application of morphine to neurons alters their baseline firing pattern and leads to dependence in experimental animals [47-49].

These findings led to our current mechanistic model as follows. Repeated opioid administration alters the baseline neuronal firing patterns of various brain structures to create a new "opioid induced pattern". The brain has an intrinsic "homeostatic" mechanism to maintain a baseline neuronal firing pattern once it established - this now requires repeated opioid administration to maintain the new opioid induced pattern in dependent animals. If the opioid is discontinued, the new baseline firing pattern is not maintained, and this leads to alteration in neuronal firing rates that result in locomotor and severed behavioral expression i.e., withdrawal symptoms. This mechanism drives the subject to crave repeated drug use in order to maintain the newly established BL pattern.

This model provides a mechanistic basis of why the vast majority of patients addicted to opioids fail currently available treatments for detoxification, and why they relapse and resume opioid use [50, 51]. It also emphasizes the need to facilitate the transition from the opioid induced pattern to the normal firing pattern which could offer a possibility to prevent or attenuate the painful withdrawal symptoms that accompany drug cessation in dependent animals. It would also lessen withdrawal symptoms which make is so difficult for human addicts to discontinue opioid use.

This model prompted us to seek therapeutic interventions that could potentially reverse opioid induce different baseline firing patterns to the pre-drug state and thereby attenuate the withdrawal symptoms that drive recovering addicts to relapse and resume drug use. One approach that we considered was NTCS which is thought to be effective in the treatment of some brain disorders by reversing pathologically induced alterations in neuronal activity patterns.

Current Available Treatment

At present, most treatments for opioid addiction involve long periods of time in treatment with medications such as: Vivitol, Zubsolve, Probuphrine, Lofexidine Hydrochloride, Methadone, Buprenorphine, Sublocade, CAM2038, Naltrexone, Pentazocine, Buprenex, Modafinil, Mirtazapine, Vigabatrin, Baclofen, Topiramate. Moreover, the efficacy and safety of some of these drugs have not been well studied. In addition to the above drugs, counseling and behavioral therapies and/or familial and spiritual support are required for long periods of time [52, 53]. Most of the above-mentioned drugs belong to the opioid family. Some worry that the above treatments are substituting one opioid medication for another opioid [54]. Further, most patients do not comply with these long-term treatments as most of these drugs are mainly for opiate withdrawal management and results show that they lead to stronger cravings and continued use of opioids. Many of these drugs are still in the pipeline and are still under study to be verified as safe and beneficial. Additional novel treatments of non-opioid treatment are needed.

Non- Invasive Transcranial Current Brain Stimulation (NTCS)

As mentioned at the outset, Wilhelm Erb (1883) described several procedures and therapeutic outcomes for non-invasive transcranial electro-stimulation and the rationale for its effectiveness to treat different diseases including behavioral disorders in his Handbook of Electro-Therapeutics published in the 19th century. He hypothesized that NTCS activates the brain in a way that resets the disrupted neuronal circuits that cause behavioral disorders to return to normal. His work provided several clinical cases studies of effective NCTS treatments of several brain disorders.

Noninvasive brain stimulation as a potential treatment for drug addiction must be reexplored. The rationale behind this approach is that this stimulation restores normal brain function and dampen addiction behavior. There are two main procedures for brain stimulation: 1. Noninvasive Transcranial Current Stimulation (NTCS) and 2. Transcranial Magnetic Stimulation (TMS) [55-58]. NTCS is delivered via two electrodes placed over the left and right dorsal lateral prefrontal cortex (dlPFC) with low current intensity for 10 to 30 min. This stimulation reduced drug craving and consumption. During stimulation the electrical current flows between the electrodes passing through the brain. The initial hypothesis underlying NTCS is that many behavioral disorders, including drug addiction, result from disruption of the neuronal activity regulating these behaviors. The NTCS rewires the disrupted neuronal circuit that regulates the behavioral disorders [59-65]. The current hypothesis is that the NTCS modulates cortical function by eliciting neuroplasticity, modulating membrane potentials, glutaminergic and dopaminergic signaling transmission, and eliciting long-term potentiation (LTP) or long-term depression (LTD) like changes in synaptic coupling of neurons [66, 67]. The effects are NMDA and AMPA receptor signaling dependent, modulating the neuronal firing rates and the effects are long lasting. Hypothesize that NTCS leads to increased metabolic activity in the brain and increased glutamate and glutamine levels. Neuroimaging studies indicates that NTCS induces cortical and subcortical neuronal activation [69-73].

More recent evidence indicates that the mesocorticolimbic and nigrostriatal dopamine (DA) systems contributes to enhancing the desire for consuming drugs of abuse as a result of changes in the baseline (BL) neuronal patterns in numerous brain structures including the VTA, LC, DR, NAc, PFC, CN, several thalamic and hypothalamic nuclei, Hipp, Amyg, Hab and Spt and other brain sites. In other studies, we compared the effects of invasive deep brain stimulation and NTCS on the response of different subcortical brain areas to noxious pain-inducing stimulation [74-76]. We observed that NTCS (using an earring in each ear as an electrode for stimulation i.e., auricular electrical stimulation (AES) was significant effective in suppressing the single unit neuronal activity following noxious stimulation recorded from several subcortical brain areas compared to deep invasive electrical stimulation in dorsal raphe and central gray area using the same electrical parameters and duration [77, 78]. Importantly, AES significantly attenuated ($p< 0.001$) the behavioral severity of opioid withdrawal in morphine dependent animals. Our AES experiments using single neuronal activity recordings further revealed that several subcortical structure networks are affected by this stimulation, including the neuronal reward/motive network indicating that AES modulates synaptic activity of different brain circuits. Brunoni (2012), validated these observations using neuroimaging procedures, and showed that NTCS simultaneously modulates the excitability of many cortical and subcortical brain sites including the neuronal network that is most affected by consumption of drugs of abuse. These effects of NTCS and the underlying mechanisms are still under active investigation and therefore more relevant findings are anticipated in the near future [79-81].

The AES stimulation as compared to other studies in our opinion is more effective since the location of the stimulating electrodes determines which part of the brain is activated. The use of the ears as the site of stimulation (AES) used by us, evokes NTCS over the entire brain like as the paired electrodes on the dlPFC; as well as stimulate five different cranial nerves (CN) (trigeminal nerve-CN V; facial nerve-CN VII; vestibulo-cochlear nerve -CN VIII; glossopharyngeal nerve-CN IX and the vagus nerve CN-X) whose nuclei are in the midbrain (82-84). AES stimulate these midbrain nuclei and activates the mesocorticolimbic neuronal circuit and more sites to exert its therapeutic effects as compared to the cortical electrode. Based on our previous studies, we observed that repetitive morphine application modulates the baseline (BL) of neuronal activity on these 14 areas (FIG 1). We hypothesize that AES restore the disrupted neuronal activities that caused by repeated use of morphine, to their pre-morphine BL and will prevent the expression of tolerance and behavioral withdrawal symptoms. An additional advantage of the stimulation site and the AES regimen is that it is an easy and simple method for stimulation and will be consistence from subject to subject.

Summary, Conclusions, and A Novel Unifying Hypothesis

Based on our previous neuronal recording studies from 14 different brain sites – ventral tegmental area (VTA), locus coeruleus (LC), dorsal raphe (DR), nucleus accumbens (NAc); prefrontal cortex (PFC), caudate nucleus (CN), lateral hypothalamus (LH), anterior hypothalamus (AH), ventromedial hypothalamus (VMH), medial-thalamus; para fasciculus thalamus (PF-CM), habenula (Hab),hippocampus (Hipp), amygdala (Amyg), and the septum (Spt) before and after repetitive drug of abuse treatments, we developed a model that repeated morphine exposure altered the normal baseline neuronal activity from its initial state to an opioid-induced state [20, 85-89]. An intrinsic homeostatic mechanism seeks to maintain the brain's baseline state, whether naturally occurring or drug-induced, and failure to do so leads to severe withdrawal symptoms if the opioid is discontinued; continued consumption of the opioid maintains the induced state the brain wishes to maintain in order to prevent the development of withdrawal symptoms. This model coupled with previous studies of NTCS have led us to propose the hypothesis that NTCS as well as AES treatment to chronic morphine-treated animals facilitates reversion of the baseline neuronal firing patterns produced by repeated opioid administration to the normal pre-drug pattern and thus attenuate withdrawal symptoms when morphine is discontinued.

We are currently performing further studies to rigorously test this hypothesis and while those studies are in progress we present this new model and potential therapeutic intervention here in hopes it may stimulate creative thinking by others and foster additional development of new therapeutic interventions that are so badly needed to address the severe opioid epidemic now facing the U.S. and other countries.

In closing, it is also noteworthy that NTCS appears safe for use in humans and it is already established that NTCS modulates the altered baseline activity of the neuronal reward network activity previously disrupted by repetitive exposure to drugs of abuse. Thus, the NTCS procedure appears safe, doesn't produce side effects and offers a promising new approach to treat opioid abuse and possibly dependence on other drugs of abuse that leads to addiction [90-112].

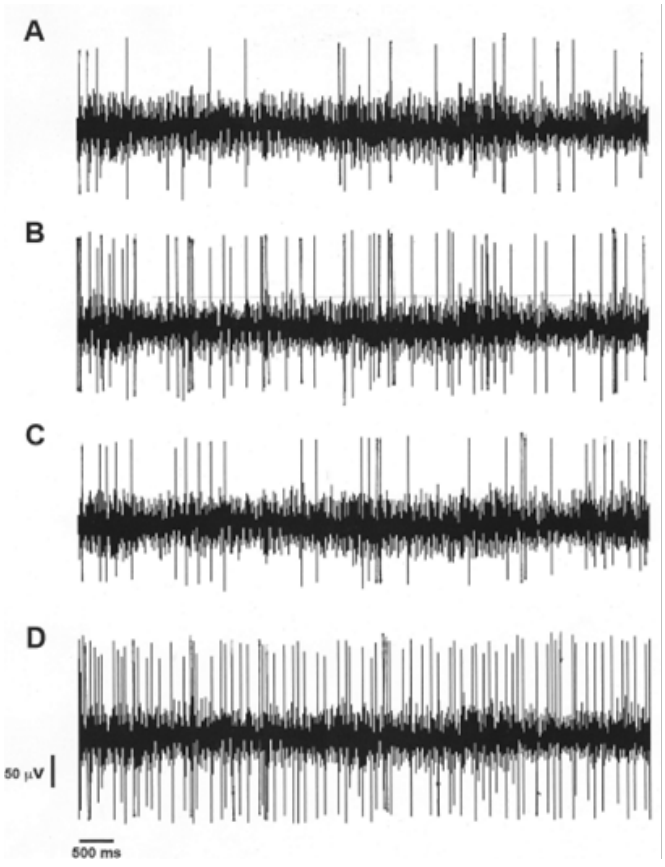

Figure 1: Neuronal recording from the pre-frontal cortex (PFC) in freely behaving animals before and following acute and repetitive (chronic) morphine 5.0mg/kg. In the figurer there are four analog traces take at **A)** after saline (baseline – BL) on experimental day 1 (ED 1BL). **B)** taken after acute 5.0mg/kg morphine on ED 1 (ED 1M) - morphine elicit increase in neuronal activity compare to ED 1BL (trace A). **C)** taken after the six daily morphine 5.0mg/kg at ED 6 (ED 6M) – showing tolerance as compare to trace B (acute morphine effects). In trace **D** is the neuronal activity at ED 7 after abrupt morphine exposure – showing neuronal activity of withdrawal.

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