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Stereotactic Radiosurgical Neuromodulation for Chemical Dependency: A Theoretical Approach to Addiction Therapy

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Abstract

Chemical dependency is pervasive and difficult to treat; with current treatment options, studies have shown relapse rates of approximately 77% after completing a private treatment program. Most chemically-dependent individuals are never able to reach long-term sobriety, and many eventually die of their disease. The cost of drug addiction to society, manifested in drug-related illness, crime, lost productivity, and premature death, was estimated at over $140 billion in 1998 in the United States alone. It is imperative that medical professionals gain a better understanding of addiction and its effective treatment. In this paper, we make a two-part proposal: 1) the neural regions that are key participants in drug addiction can be visualized with current imaging technologies, and 2) activity of neurons in that region can be modulated, to therapeutic effect, with stereotactic radiosurgery. We will briefly review imaging findings indicating the effects and correlates of drug dependence, efforts at targeted modulation of brain regions and processes that appear to be importantly involved in drug craving and reward, and propose that stereotactic radiosurgery might be considered as another weapon in the fight against drug dependence.

Categories: Neurology, Psychiatry, Neurosurgery
Keywords: gaba, addiction, neuromodulation, radiomodulation, stereotactic neurosurgery, nucleus accumbens

Introduction And Background

Chemical dependency is pervasive and difficult to treat; with current treatment options, studies have shown relapse rates of approximately 77% after completing a private treatment program [1-3]. Most chemically dependent individuals are never able to reach long-term sobriety, and many eventually die of their disease. The cost of drug addiction to society, manifested in drug-related illness, crime, lost productivity and premature death, was estimated at over $140 billion in 1998 in the United States alone [2]. It is imperative that medical professionals gain a better understanding of addiction and its effective treatment. In this paper, we make a two-part proposal: 1) the neural regions that are key participants in drug addiction can be visualized with current imaging technologies, and 2) activity of neurons in that region can be modulated, to therapeutic effect, with stereotactic radiosurgery. We will briefly review imaging findings indicating the effects and correlates of drug dependence, efforts at targeted modulation of brain regions and processes that appear to be importantly involved in drug craving and reward, and propose that stereotactic radiosurgery might be considered as another weapon in the fight against drug dependence.

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Review

Mechanisms of addiction

Drug addiction results from the interplay of social, behavioral and neurobiological processes. Neural participants in the phenomenon can be appreciated at multiple levels, from sub-cellular to systems-wide, but we may understand a great deal about drug addiction by understanding the brain circuits and neurotransmitters that have been shown to play major roles [4]. Three major neurotransmitters are critically involved in drug addiction. Dopaminergic neurons primarily originate in the ventral tegmentum area (VTA) and synapse on the nucleus accumbens, hippocampus and dorsolateral prefrontal cortex. Stimulation of these neurons results in the net perceptual effect of euphoria and wakefulness. Glutaminergic neurons sprout from the dorsal thalamus, ventral striatum, amygdala, and hypothalamus. They make excitatory synapses with GABAergic neurons in the insula, hippocampus, nucleus accumbens, prefrontal, and motor cortex. This excitatory response may take the form of hyper-vigilance during intoxication or agitation during periods of drug withdrawal. In this regard, a drug has been developed to modulate the glutamate response in alcoholics (acamprosate, Campral). In the case of acamprosate, antagonism of the mGluR5 glutamate receptor decreases craving and attenuates the withdrawal symptoms related to excess synaptic concentrations of glutamic acid [5]. Finally, GABAergic neurons originating in the insula, dorsal thalamus, amygdala, ventral striatum, and hypothalamus synapse on neurons in the pallidum, hypothalamus, midbrain, and other cortical structures. This inhibitory neuromodulatory tone is necessary to balance the excitation caused by many drugs of abuse, and malfunction of GABAergic mechanisms may lead to profound anxiety states.

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Repetitive administration of a drug gradually disrupts the interplay in this neural system. For example, acute administration of cocaine decreases synaptic reuptake of dopamine and serotonin, which in turn results in euphoria. The subject experiences increased hedonic tone and pleasure as the nucleus accumbens is stimulated with excessive amounts of dopamine. This subcortical nucleus has been a target for deep brain stimulation. In fact, intraoperative experience shows that stimulation of one nucleus results in contralateral smiling [6]. If cocaine administration becomes chronic, synaptic receptor physiology is changed, and as tolerance to the drug increases, more of the drug is necessary to achieve the desired effect. In addicts, the long-lasting difficulty in remaining abstinent reflects activity in the brain circuits underlying craving and drug seeking. Kalivas and Volkow [4] proposed that cues that promote drug seeking (the drug or similar drugs, mild stressors, or drug-associated stimuli) activate glutamatergic neurons in the prefrontal cortex that project to the nucleus accumbens core, a structure that has become more sensitive to glutamate excitation. Together with the ventral pallidum, these structures constitute a final common pathway for drug seeking [4]. As Kalivas and Volkow point out, targeting such structures pharmacologically or by other neuromodulative means may be a rational approach to effective therapy for treatment-refractory drug addiction.

Functional neurological imaging allows a unique perspective on the anatomical and physiological effects of alcoholism and substance dependence in the brain, including images of brain regions participating in specific states of addiction (craving, withdrawal, intoxication) [7]. For example, during cue-induced opiate craving, the dorsolateral prefrontal cortex is hypermetabolic on positron emission tomography (PET) and functional MRI (fMRI) [8]. Also using fMRI, Wexler, et al. [9] demonstrated activation of the anterior cingulate in cocaine addicts while they watched videos intended to create the craving for cocaine. Activation occurred before reports of craving or even in patients who did not experience craving, and did not occur when addicts watched non-cocaine videos. In a unique study by Kosten, et al. [10], fMRI detected brain activation during exposure to cocaine-related cues in subjects who went on to a 10-week clinical trial. Increased activity in the left precentral, superior temporal, and posterior cingulate cortices and right middle temporal and lingual cortices predicted poorer treatment effectiveness; self-reports of craving during exposure to cocaine cues was not predictive of treatment effectiveness. This is a small sample of the ever-growing literature on brain activity associated with aspects of drug addiction and relapse. They are presented here not to indicate solid targets for neuromodulation but to show that research, technology, and theory have progressed to the point that the identification of clear clinical targets for treatment may require very little additional research.

Deep brain stimulation and psychiatric treatment

Recent and ongoing clinical research utilizing deep brain stimulation (DBS) to treat refractory psychiatric disease may constitute an in-principle demonstration of the concept of neuromodulation for drug addiction. Human clinical research has shown that implantation of deep brain stimulation (DBS) electrodes via open surgery may alter foci of hypermetabolism as in the case of major depression. Mayberg, et al. showed that DBS in Brodmann Area 25 alleviated depression in four of six patients with refractory depression who were hypermetabolic in this area on functional imaging studies [11]. Postoperative scans indicated a normalization of activity in this area, implying that DBS of selected targets effectively down-regulated activity in the regions in which they were placed. A follow-up study of these patients showed a response in 60% of patients and remission in 35% at six months, which was maintained at 12 months. Changes in the metabolic activity in the cortical and limbic circuits involved in depression were noted in PET scans [12]. More recently, an investigation of bilateral DBS to the ventral capsule/ventral striatum (VC/VS) was tested in 15 patients with refractory depression who received open-label DBS at three collaborating clinical sites [13]. At six months, scores on the Hamilton Depression scale showed a clinical response in 40% of patients and remission in 20%; at last follow-up, 40% were in remission.

Only two studies to date have shown a promising effect of DBS neuromodulation for a drug addiction. Witjas, et al. studied two young patients with Parkinson's Disease who had developed severe addiction to dopamine treatment (dopamine dysregulation syndrome, or DDS) [1]. Subthalamic nucleus (STN) DBS for their movement disorder abolished these addictions. Kuhn, et al. reported a case of a 54-year-old patient with remission of alcohol dependency following DBS of the nucleus accumbens [14]. Upon stimulation, the patient reported an acute feeling of pleasant ''inner appeasement'', even though DBS did not alter the severe anxiety that the DBS was originally intended to treat. Importantly, the patient reported alleviation of "the pressing need to consume alcohol."

In addition to DBS experiments, studies of stroke victims have shown promise for the future of stereotactic radiosurgery for chemical dependency. Naqvi, et al. reported that damage to the insula disrupts addiction to cigarette smoking [15]. This group identified 19 cigarette smokers who had acquired lesions in the insular region-six patients with right insula damage, 13 with left. Those who had dysfunction in various regions of the insula completely lost the urge to smoke cigarettes and maintained long-term abstinence. A possible mechanism is that as GABAergic input from the insula to the ventral tegmental area is reduced, there is a relative increase in dopaminergic transmission from the VTA to the nucleus accumbens. Insular stroke, therefore, may act as an indirect "stimulator" on the nucleus accumbens, replacing the former stimulator of nicotine from cigarette smoking.

The nucleus accumbens has been chosen as a target for DBS and radiofrequency/thermocoagulation treatment of addiction, but clinical improvement in these studies has been minimal. These poor results are most likely due to inadequate target selection, because the nucleus accumbens may not be the driver of dysfunctional addiction. Gao, et al. reported a clinical study for alleviating opiate drug psychological dependence using a method of ablating the nucleus accumbens with stereotactic surgery [16]. Twenty-eight opiate-dependent patients underwent bilateral nucleus accumbens lesions via radiofrequency ablation using a 1.8 mm diameter electrode heated to 85 degrees Celsius. Although 65% of the study's participants reported excellent or good therapeutic effect, there was a one-year relapse rate of 57.7%.

Selecting other targets in the complex circuitry related to addiction might prove more beneficial. Could areas of the insula, or even tracts between the ventral tegmental area and the nucleus accumbens, or the amygdala itself represent more effective targets? Despite such potential, a new understanding of functional imaging and a harnessing of neuromodulative capabilities will be necessary for this field to grow.

Neuromodulative approach

It appears that whether a lesion is made or a stimulation probe (DBS) is placed, hypermetabolic regions of the brain are down-regulated. DBS has the theoretical advantage of reversibility, but carries the disadvantage of infection, intracerebral hemorrhage, lead malfunction, limited battery life, and inadvertent tissue damage. Meanwhile, thermocoagulation methods typically create permanent lesions, but also risk infection, hemorrhage, or damage to neighboring structures. It is as yet unclear whether or not frank irreversible lesions are desirable.

The potential for altering brain circuitry with radiosurgical lesioning was first demonstrated when the stereotactic frame-based Gamma Knife, (Elekta, Inc., Stockholm, Sweden) was used to treat refractory obsessive-compulsive disorders and other affective conditions. The non-invasive nature of radiosurgery is an obvious advantage of a radiosurgical approach; while frame placement in the case of the Gamma Knife is unpleasant for the patient and perhaps a nuisance for the neurosurgeon, the overall procedure is relatively non-invasive. Nevertheless, image-guided radiosurgical technology, as embodied in the CyberKnife (Accuray Incorporated, Sunnyvale, CA), now makes it possible to produce comparable radiosurgical outcomes without the use of frames [17-18].

Radiomodulation

Extensive experience with using radiosurgery to treat trigeminal neuralgia and growing experience with epilepsy, demonstrates that lower, sub-necrotic doses, which do not create obvious lesions, may attenuate activity in hypermetabolic foci. The concept of radiosurgical neuromodulation or radiomodulation implies that sublethal focused beam radiation is precisely administered to localized discrete brain targets as in the case of cingulotomy for pain or pallidotomy for dystonia. The critical difference between this approach and previously reported ablation techniques using higher dose radiosurgery (110-160 Gy) is merely the total dose of radiation. Lower, neuromodulative doses should theoretically avoid the radiation injury and perhaps even the permanence that characterizes the more conventional radiosurgical approach to functional brain disorders. Although anecdotal, the author has used CyberKnife radiosurgery to treat a single patient suffering from chronic pain and depression in the setting of end stage head and neck cancer; treatment utilized only 60 Gy (65% isodose) administered to a 0.5 cc target in the anterior cingulum. Significant clinical benefit was observed beginning within hours of the CyberKnife treatment and lasting throughout the final month of the patient's life.

Although the current broad scientific and clinical landscape suggests that radiosurgical neuromodulation for addiction might someday prove feasible, critical treatment details remain unresolved. While some of the relevant anatomy is understood, it is not clear what the optimal target for radio-modulation might be. In this regard, it is unclear if animal studies would necessarily be useful in teasing out the neural circuitry which underlies human addiction. Alternatively, it seems possible that different targets might be selected based on the type of addiction. For example, based on lesion patterns of the aforementioned insular stroke victims and functional image changes, a target could be chosen in the insular region of a cigarette smoker [15]. In such patients, sublethal radiation delivery could potentially alter insular efferent and afferent projections, thus diminishing the urge to smoke. Meanwhile, since the experience of Gao, et al. strongly suggests that modification of the nucleus accumbens and/or its projections can be beneficial for opiate addiction, it would seem logical to also investigate this a target for radiomodulation in opiate-addicted patients [16]. Ultimately, it seems plausible that function brain imaging using fMRI and PET could be helpful in tailoring lesion location for individual addicts.

The optimal dosing needed to achieve a radio-modulatory effect rather than a frank radiosurgical lesion also requires considerable investigation. Complicating matters further is the likely situation that dose will closely interact with target volume, and in turn, the exact location in the brain may be an influence as well. While further study may demonstrate that only frank radiosurgical necrotic lesioning achieves the desired behavioral effect, we believe neuromodulation should be pursued as a possibly more benign (and neurobiologically interesting) first approach. Because sublethal delivery of focused radiation is utilized, serial functional imaging and clinical assessment may leave an opportunity for multi-session retreatment in the case of relapse. In short, radiosurgery, and especially the frameless and non-invasive CyberKnife, represents a compelling possible treatment for addiction. Given the devastating consequences of and the limited treatment options for addiction in the modern world, we believe research in this field is warranted.

Conclusions

Although the argument for using stereotactic radiosurgery for neuromodulation of critical pathological brain pathways in drug addicts is largely conceptual, we believe an intellectual basis exists for using radiosurgery as an addiction therapy. For intractable cases, in which the addiction becomes the primary focus of the patient's existence, such an approach could have the potential to alleviate the self-destructive obsessions and maladaptive behaviors associated with chemical dependency. It might also offer an adjunctive pre-treatment measure to enhance the residential inpatient treatment experience offered to many addicted individuals.

Thoughts of treating chemical dependency with radiosurgery and radiomodulation may now seem little more than science fiction. At the same time, in the eyes of many, talk of such treatment can sound reckless and dangerous. However, greater understanding of addiction neurobiology, combined with functional neurological imaging, radiation physics and radiobiology, should ultimately provide a foundation for more aggressive study and advocacy.

Additional Information

Disclosures

Conflicts of interest: In compliance with the ICMJE uniform disclosure form, all authors declare the following: **Payment/services info:** All authors have declared that no financial support was received from any organization for the submitted work. **Financial relationships:** John R. Adler declare(s) an alternate financial activity from Accuray, Inc. Shareholder. **Other relationships:** All authors have declared that there are no other relationships or activities that could appear to have influenced the submitted work.

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