Cell Transplantation
2019, Vol. 28(9-10) 1127–1131
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/0963689719859299
journals.sagepub.com/home/cll
SAGE

Harnessing Neurogenesis and Neuroplasticity with Stem Cell Treatment for Addictive Disorders

Sheng-Tzung Tsai[1,2,*], Hock-Kean Liew[3,*], Hao-Ming Li[4], Shinn-Zong Lin[1,3], and Shin-Yuan Chen[1,2]

Abstract

Drug and alcohol addiction has become an emerging public health issue and is a great burden to patients, their families, and society. It is characterized by high relapse rates and significant morbidity and mortality, and most available treatments result in only modest improvement. These findings highlight the necessity for new approaches to treat addiction. Scientific reports in the past two decades suggest that addiction involves impaired neural plasticity and decreased hippocampal neurogenesis. Stem cell therapy and its derived neurotrophic factors can potentially target the underlying pathophysiology of addiction. Stem cell applications are showing promise in several preclinical studies and may provide new and noninvasive treatment strategies. Future clinical research is warranted to investigate whether stem cell-based therapy could support the treatment of addiction.

Keywords

stem cell therapy, neurogenesis, neurotrophic factors, neural plasticity, addiction

Introduction

Addiction is a chronically relapsing substance-use disorder and involves a substantial loss of self-control in psychoactive substance consumption. Despite the desire in limiting, this behavior becomes compulsive and is attributed to the activation of the brain's reward system by substances. The term addiction is synonymous with the classification of severe substance-use disorder in the DSM-5. It has been estimated that more than 20 million people, or 8–10% of the population older than 12 years old in the United States, are addicted to alcohol or other substances. Despite efforts to develop behavioral and medical interventions, the available treatments to reduce addiction and relapse rates are limited.

There is increasing evidence from neurophysiological and neuroimaging studies indicating that addiction is a disorder of the brain involving pathology of neural circuitry. Aberrant and impaired neurogenesis has been shown to be one of the main mechanisms in several psychiatric diseases, including addiction, and is implicated as a potential target for new treatments[1]. In this review, we highlight several pivotal preclinical and human studies as well as the potential of cell regenerative mechanisms to treat addiction.

Anatomy and Neural Circuitry of Addiction

The basal ganglia is composed of three parallel circuits, including motor, associative, and limbic circuits. Among them, the limbic circuit plays an important role in emotion, cost-benefit decision making, and addictive behavior. This circuit essentially involves structures from the cingulate cortex, the nucleus accumbens (NAc), the hypothalamus, the amygdala, and the hippocampus. Progressive pathological

[1] Department of Neurosurgery, Buddhist Tzu Chi General Hospital, Tzu Chi University, Hualien
[2] Institute of Medical Sciences, Tzu Chi University, Hualien
[3] Department of Medical Research, Buddhist Tzu Chi General Hospital, Hualien
[4] Department of Psychiatry, Buddhist Tzu Chi General Hospital, Tzu Chi University, Hualien
*Sheng-Tzung Tsai and Hock-Kean Liew contributed equally to this review.
**This article was originally submitted for special collection on Addiction.

Submitted: August 14, 2018. Revised: April 6, 2019. Accepted: April 15, 2019.

Corresponding Author:
Sheng-Tzung Tsai, Department of Neurosurgery, Tzu Chi General Hospital/ Tzu Chi University, 707, Sec 3, Chung-Yang Rd. Hualien.
Email: flydream.tsai@gmail.com

Creative Commons Non Commercial CC BY-NC: This article is distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 License (http://www.creativecommons.org/licenses/by-nc/4.0/) which permits non-commercial use, reproduction and distribution of the work without further permission provided the original work is attributed as specified on the SAGE and Open Access pages (https://us.sagepub.com/en-us/nam/open-access-at-sage).

changes in neurotransmitters and neuronal firing within this circuit also correlate with the recurring three stages of addiction: binge and intoxication, withdrawal and negative affect, and preoccupation and anticipation[2]. The NAc has been pivotal in many drug abuse studies. While the core of the NAc (dorsolateral) projects primarily to the dorsolateral ventral pallidum and the substantia nigra, the shell of the NAc (ventromedial) targets the amygdala, the lateral hypothalamus, and the ventromedial portion of the ventral pallidum[3]. This observation coincides with findings that the NAc shell underlies reward signal processing and is implicated in addictive behaviors[4]. In the amygdala, the basolateral region regulates complex emotional and behavioral responses through its connection with the prefrontal cortex and the NAc. The cingulate cortex is probably the most essential relay nucleus of the limbic circuit involving addictive behavior. With its connection to the NAc, the cingulate cortex not only mediates ongoing decision making and behavioral adaptation, but also modulates response to risk taking, such as drug-seeking behavior in addiction[5].

Neurogenesis and Stem Cell Applications in Addiction: Animal and Preclinical Studies

Using transgenic or irradiation approaches to deplete hippocampal neurogenesis in rodents has been used as an animal model for drug addiction. This is based on the finding that depleted hippocampal neurogenesis causes increased motivation to seek cocaine-related cues[1,6]. While a causal relationship between decreased neurogenesis and increased risk for drug-induced addictive behaviors has been established, the mechanism of how diminished endogenous repair leads to addiction remains elusive. One possibility is that the ventral hippocampus projects to the amygdala, the ventral tegmental area, the NAc shell, and the medial prefrontal cortex, which indicates its involvement in emotional processing and cue-related conditioning[7]. Deactivation of the ventral hippocampus significantly correlated with relapse of cocaine-seeking behavior, which further suggests its connection with limbic structures implicated in addictive disorders[8]. Another study showed that adult-born neurons in the hippocampus are required for maintaining the stress response and buffering depressive behavior. The impaired psychiatric response such as anxiety and depressive-like behavior in animals with decreased neurogenesis could be restored after glucocorticoid administration[9]. This further implicates the involvement of the hippocampus in the modulation of the hypothalamic–pituitary–adrenal axis. Therefore, dexamethasome, a commonly used steroid for glucocorticoid supplementation, could potentially be used to mitigate the abnormal reward effects of cocaine[10]. Taken together, these studies imply that strategy to restore the addiction-impaired hippocampal neurogenesis might provide a novel way to treat medically refractory addictive disorders.

Tfilin et al. used intracerebroventricular injection of mesenchymal stem cells to increase hippocampal neurogenesis, leading to an improvement in depressive-like behaviors in rats. This provides the first proof of concept for counteracting impaired endogenous neuroregeneration to treat depressive disorders[11]. This improvement in behavior might result from increased neurotrophic factor secretion within the hippocampus and the restoration of glutamatergic transmission of the neural circuits[12]. Although stem cell transplantation seems quite straightforward and it has received much attention for potential medical treatments, there remain significant obstacles to understanding and controlling stem cells and the ensuing neuroplasticity after transplantation[13,14]. Encapsulated mesenchymal stem cells were shown not only to increase survival of implanted cells and the amount of growth factors in the brain, but also to enhance endogenous neurogenesis and improve treatment-resistant depression in rat models. To our knowledge, there are no available clinical studies using intracerebral or intravenous stem cell treatments for addiction. Using novel therapeutic strategies to increase endogenous neurogenesis in the hippocampus might pave the way for immediate application of stem cells in addiction[15].

Of the currently available treatments for addiction, physical activity has been shown to be effective, and one of its mechanisms is an increase in the expression of brain-derived neurotrophic factor (BDNF) in the brain. In addition, recent studies show that regular exercise not only potentiates neural synaptic plasticity through epigenetic regulation of the BDNF gene, but also increases serum levels of BDNF in humans[16]. These studies suggest that induction of endogenous neurotrophic factors or increased amounts of these factors through exogenous delivery might serve as a novel substitute or adjunct to the current treatment strategies for drug addiction. For example, infusion of BDNF could normalize abnormal plasticity within neural circuits underlying cocaine withdrawal[16]. In addition, stem cell treatment, along with external supplementation from stem cell-derived exosomes, increases synthesis of these neurotrophic factors in the brain[17]. This provides the potential of using these neurotrophins in human clinical studies in the future.

Deep Brain Stimulation and Endogenous Neurogenesis in Addiction

Given several findings that deep brain stimulation (DBS) for personality or obsessive compulsive disorders also has accompanying benefits in lessening compulsive and addictive behavior for medications or alcohol[18–20], DBS has been investigated as a treatment option for severe addiction[21,22]. DBS involves inserting electrodes into one specific area of the brain to modulate pathological neural circuits in order to attenuate these medically refractory diseases. The most successful example of this treatment is seen in Parkinson's disease using DBS on basal ganglia. High-frequency stimulation, which in effect mimics the lesioning in local nuclei, significantly alleviates the disabling motor symptoms. In recent years, DBS has been found to enhance cognitive function through stimulating endogenous neurogenesis when

targeted to the fimbria-fornix, the region that appears to regulate hippocampal activity[23,24]. Among those potential targets for DBS within the limbic circuit, the NAc seems to receive the most attention based on preliminary results in psychiatric disorders. Three out of ten psychiatric patients at their 30 month follow-up had overcome their habit of heavy smoking after NAc DBS; this was the first implication that DBS could be beneficial for addiction[25]. Subsequently, there have been growing numbers of human and animal studies on NAc DBS for addiction. Although most of them are of small studies without strict blind stimulation tests, there were concomitant neurophysiological changes underscoring the improvement of drug addiction for patients. For example, a patient with severe alcohol addiction was treated with bilateral NAc DBS, and positron emission tomography revealed activation of the paracingulate cortex, the precuneus, and the hippocampus during active DBS[26]. This further highlights the important role of these neural circuits and the hippocampus in addiction and its treatment.

In addition to modulating pathological neural circuits, rodent studies on cognition enhancement demonstrated that DBS induces endogenous neurogenesis in the hippocampus[23,27]. Recruitment of newly formed neurons has been implicated in the cognitive process involving dentate gyrus (DG) or hippocampus, and this finding indicates that it may take a period of time to ensure that newly formed hippocampal neurons integrate into the existing limbic circuit and contribute to long-term plasticity[28]. Chronic DBS over the ventromedial prefrontal cortex, a target in clinical trials for the treatment of mood disorders, also significantly increased hippocampal neurogenesis and ameliorated emotional deficits in rodents[29,30]. These results suggest that triggering endogenous neuroregeneration by stimulating neural circuits involved in addiction provides a potential mechanism that may facilitate stem cell application for the treatment of psychiatric diseases[31]. However, even with limited side effects, DBS is still an invasive surgery involving immediate and long-term postoperative adjustments and related side effects[32–34]. To date, several studies are pursuing noninvasive neuromodulation methods to harness neural circuit plasticity and hippocampal neurogenesis[35,36]. Accordingly, these studies suggest that neuromodulation and neurogenesis could benefit patients with treatment-refractory addiction.

However, there are ethical concerns that need to be addressed. Different neural circuits underlie the three major stages of addiction. Stem cell treatment may provide various degrees of effectiveness depending on the stage when the cells and their associated exosomes are delivered. Another ethical issue involves informed consent; treatment should be initiated only after ensuring patients are free from the interference of drugs on their decision-making capabilities. Therefore, while treating a patient during the withdrawal stage to prevent future relapse seems to be a reasonable approach since abstinence from the drug is certain, reports have shown persistent impaired cognition at this stage, which might undermine the patient's ability to provide informed consent.

Conclusion

Addiction has been an emerging issue in public health and is a great burden to patients, their families, and society. To date, there is no effective treatment that decreases the high relapse rates and significant morbidity and mortality in opioid, alcohol, and cocaine addiction. Given the increasing evidence that impaired hippocampal neurogenesis leads to treatment-resistant addiction, one plausible treatment strategy for addiction may be the correction of pathological neural circuits and potentiation of endogenous neurogenesis. Translational research in regard to stem cell treatment and its derived neurotrophic factors for addiction aims to alleviate impaired hippocampal neurogenesis as a new and noninvasive treatment. Further clinical studies are warranted to investigate the benefit of stem cell treatment for addiction.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Sheng-Tzung Tsai https://orcid.org/0000-0001-6611-9440

References

1. Deroche-Gamonet V, Revest J-M, Fiancette J-F, Balado E, Koehl M, Grosjean N, Abrous DN, Piazza P-V. Depleting adult dentate gyrus neurogenesis increases cocaine-seeking behavior. Mol Psychiatry. 2019;24(2):312–320.
2. Volkow ND, Koob GF, McLellan AT. Neurobiologic advances from the brain disease model of addiction. N Engl J Med. 2016; 374(4):363–371.
3. Kalivas PW, Volkow ND. The neural basis of addiction: a pathology of motivation and choice. Am J Psychiatry. 2005; 162(8):1403–1413.
4. Chen Y-H, Lin B-J, Hsieh T-H, Kuo T-T, Miller J, Chou Y-C, Huang EY-K, Hoffer BJ. Differences in nicotine encoding dopamine release between the striatum and shell portion of the nucleus accumbens. Cell Transplant. 2019;28(3):248–261.
5. Sheth SA, Mian MK, Patel SR, Asaad WF, Williams ZM, Dougherty DD, Bush G, Eskandar EN. Human dorsal anterior cingulate cortex neurons mediate ongoing behavioural adaptation. Nature. 2012;488(7410):218–221.
6. Noonan MA, Bulin SE, Fuller DC, Eisch AJ. Reduction of adult hippocampal neurogenesis confers vulnerability in an animal model of cocaine addiction. J Neurosci. 2010;30(1): 304–315.

7. Voon V, Derbyshire K, Rück C, Irvine MA, Worbe Y, Enander J, Schreiber LRN, Gillan C, Fineberg NA, Sahakian BJ, Robbins TW, et al. Disorders of compulsivity: a common bias towards learning habits. Mol Psychiatry. 2015;20(3): 345–352.
8. Rogers JL, See RE. Selective inactivation of the ventral hippocampus attenuates cue-induced and cocaine-primed reinstatement of drug-seeking in rats. Neurobiol Learn Mem. 2007; 87(4):688–692.
9. Snyder JS, Soumier A, Brewer M, Pickel J, Cameron HA. Adult hippocampal neurogenesis buffers stress responses and depressive behaviour. Nature. 2011;476(7361):458–460.
10. Merkel SF, Andrews AM, Lutton EM, Razmpour R, Cannella LA, Ramirez SH. Dexamethasone attenuates the enhanced rewarding effects of cocaine following experimental traumatic brain injury. Cell Transplant. 2017;26(7):1178–1192.
11. Tfilin M, Sudai E, Merenlender A, Gispan I, Yadid G, Turgeman G. Mesenchymal stem cells increase hippocampal neurogenesis and counteract depressive-like behavior. Mol Psychiatry. 2009;15(12):1164–1175.
12. Shwartz A, Betzer O, Kronfeld N, Kazimirsky G, Cazacu S, Finniss S, Lee HK, Motiei M, Dagan SY, Popovtzer R, Brodie C, et al. Therapeutic effect of astroglia-like mesenchymal stem cells expressing glutamate transporter in a genetic rat model of depression. Theranostics. 2017;7(10):2690–2703.
13. Cramer SC, Sur M, Dobkin BH, O'Brien C, Sanger TD, Trojanowski JQ, Rumsey JM, Hicks R, Cameron J, Chen D, Chen WG, et al. Harnessing neuroplasticity for clinical applications. Brain. 2011;134(6):1591–1609.
14. Hodges H, Pollock K, Stroemer P, Patel S, Stevanato L, Reuter I, Sinden J. Making stem cell lines suitable for transplantation. Cell Transplant. 2007;16(2):101–115.
15. Mandyam CD, Koob GF. The addicted brain craves new neurons: putative role for adult-born progenitors in promoting recovery. Trends Neurosci. 2012;35(4):250–260.
16. Barry SM, McGinty JF. Role of Src family kinases in BDNF-mediated suppression of cocaine-seeking and prevention of cocaine-induced ERK, GluN2A, and GluN2B dephosphorylation in the prelimbic cortex. Neuropsychopharmacology. 2017; 42(10):1972–1980.
17. Shiue S-J, Rau R-H, Shiue H-S, Hung Y-W, Li Z-X, Yang KD, Cheng J-K. Mesenchymal stem cell exosomes as a cell-free therapy for nerve injury-induced pain in rats. Pain. 2019; 160(1):210–223.
18. Kuhn J, Lenartz D, Huff W, Lee S, Koulousakis A, Klosterkoetter J, Sturm V. Remission of alcohol dependency following deep brain stimulation of the nucleus accumbens: valuable therapeutic implications? J Neurol Neurosurg Psychiatry. 2007;78(10):1152–1153.
19. Mantione M, van de Brink W, Schuurman PR, Denys D. Smoking cessation and weight loss after chronic deep brain stimulation of the nucleus accumbens: therapeutic and research implications. Neurosurgery. 2010;66(1):E218–E218.
20. Jahanshahi M, Obeso I, Baunez C, Alegre M, Krack P. Parkinson's disease, the subthalamic nucleus, inhibition, and impulsivity. Mov Disord. 2014;30(2):128–140.
21. Wang TR, Moosa S, Dallapiazza RF, Elias WJ, Lynch WJ. Deep brain stimulation for the treatment of drug addiction. Neurosurg Focus. 2018;45(2):E11.
22. Spagnolo PA, Goldman D. Neuromodulation interventions for addictive disorders: challenges, promise, and roadmap for future research. Brain. 2017;140(5):1183–1203.
23. Hao S, Tang B, Wu Z, Ure K, Sun Y, Tao H, Gao Y, Patel AJ, Curry DJ, Samaco RC, Zoghbi HY, et al. Forniceal deep brain stimulation rescues hippocampal memory in Rett syndrome mice. Nature. 2015;526(7573):430–434.
24. Pohodich AE, Yalamanchili H, Raman AT, Wan Y-W, Gundry M, Hao S, Jin H, Tang J, Liu Z, Zoghbi HY. Forniceal deep brain stimulation induces gene expression and splicing changes that promote neurogenesis and plasticity. Elife. 2018; 7:R87.
25. Kuhn J, Bauer R, Pohl S, Lenartz D, Huff W, Kim EH, Klosterkoetter J, Sturm V. Observations on unaided smoking cessation after deep brain stimulation of the nucleus accumbens. Eur Addict Res. 2009;15(4):196–201.
26. Heldmann M, Berding G, Voges J, Bogerts B, Galazky I, Müller U, Baillot G, Heinze H-J, Münte TF. Deep brain stimulation of nucleus accumbens region in alcoholism affects reward processing. PLoS One. 2012;7(5):e36572.
27. Stone SSD, Teixeira CM, DeVito LM, Zaslavsky K, Josselyn SA, Lozano AM, Frankland PW. Stimulation of entorhinal cortex promotes adult neurogenesis and facilitates spatial memory. J Neurosci. 2011;31(38):13469–13484.
28. Hamani C, Stone SS, Garten A, Lozano AM, Winocur G. Memory rescue and enhanced neurogenesis following electrical stimulation of the anterior thalamus in rats treated with corticosterone. Exp Neurol. 2011;232(1): 100–104.
29. Bambico FR, Bregman T, Diwan M, Li J, Darvish-Ghane S, Li Z, Laver B, Amorim BO, Covolan L, Nobrega JN, Hamani C. Neuroplasticity-dependent and -independent mechanisms of chronic deep brain stimulation in stressed rats. Transl Psychiatry. 2015;5(11):e674.
30. Winter C, Bregman T, Voget M, Raymond R, Hadar R, Nobrega JN, Hamani C. Acute high frequency stimulation of the prefrontal cortex or nucleus accumbens does not increase hippocampal neurogenesis in rats. J Psychiatr Res. 2015;68: 27–29.
31. Gonçalves JT, Schafer ST, Gage FH. Adult neurogenesis in the hippocampus: from stem cells to behavior. Cell. 2016;167(4): 897–914.
32. Zrinzo L, Foltynie T, Limousin P, Hariz MI. Reducing hemorrhagic complications in functional neurosurgery: a large case series and systematic literature review. J Neurosurg. 2012; 116(1):84–94.
33. Hu X, Jiang X, Zhou X, Liang J, Wang L, Cao Y, Liu J, Jin A, Yang P. Avoidance and management of surgical and hardware-related complications of deep brain stimulation. Stereotact Funct Neurosurg. 2010;88(5):296–303.
34. Tsai S-T, Lin S-H, Lin S-Z, Chen J-Y, Lee C-W, Chen S-Y. Neuropsychological effects after chronic subthalamic

stimulation and the topography of the nucleus in Parkinson's disease. Neurosurgery. 2007;61(5):E1024–E1029. discussion E1029–30.

35. Zhang Y, Mao R-R, Chen Z-F, Tian M, Tong D-L, Gao Z-R, Huang M, Li X, Xu X, Zhou W-H, Li C-Y, et al. Deep-brain magnetic stimulation promotes adult hippocampal neurogenesis and alleviates stress-related behaviors in mouse models for neuropsychiatric disorders. Mol Brain. 2014;7(1):11.
36. Grossman N, Bono D, Dedic N, Kodandaramaiah SB, Rudenko A, Suk H-J, Cassara AM, Neufeld E, Kuster N, Tsai L-H, Pascual-Leone A, et al. Noninvasive deep brain stimulation via temporally interfering electric fields. Cell. 2017;169(6): 1029–1032.e16.