A drug-free solution

Researchers show that stimulating the nucleus accumbens, a brain structure involved with reward, may offer a new treatment option for those suffering from severe depression and anxiety.

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Introduction

Depression and anxiety-related mood disorders are often treated using methods such as psychotherapy, counseling, pharmaceuticals, or any combination of these. When defining depression, it can often be described as a chemical imbalance, but while this is true, it is much more complex than that expression.[1] There are multiple brain areas and chemicals associated with depression and anxiety. When treating this with pharmaceuticals such as antidepressants, it is hard to target these specific brain areas as the drug cannot be directed to a specific area of the brain. Studies conducted in recent years offer a new potential treatment for these disorders through the use of deep brain stimulation (DBS). This type of treatment aims to do what antidepressants cannot by stimulating the specific brain areas associated with these chemicals to generate long term potentiation or neuroplasticity.

What is DBS and how does it work?

Deep brain stimulation is a type of treatment that has been used to treat people with movement disorders such as Parkinson's Disease. For this treatment, an electrode along with its wire is surgically implanted into the brain and can either be placed bilaterally or unilaterally on the desired site of stimulation.[2,3,4] The amount, strength and duration of the stimulation can be controlled and set based on the specific needs of the patient. This treatment method works by regulating abnormalities in specific brain areas through electrical stimulation.[2,3,4] In the case of mood related disorders, a specific area is targeted by these stimulations and over time the synapses in that area will strengthen and new pathways will generate. In addition to DBS there are other alternative treatment options for those who suffer from depression and anxiety related disorders. Transcranial magnetic stimulation (TMS) is a non-invasive treatment that targets and stimulates a specific brain area similar to DBS but instead uses magnetic fields rather than electricity. TMS treatment for depression often includes stimulating the dorsal lateral prefrontal cortex of the brain in a specific pattern. The results of this treatment are generally similar to the results from DBS treatment.

Why the nucleus accumbens?

The nucleus accumbens is a structure in the brain that is part of the basal ganglia. This structure is often referred to as the reward circuit and is comprised of two main parts, the shell and the core.[5,8] The shell is involved with pleasure and fear behavior while the core is related to addiction and drug behavior.[6] The primary neurotransmitters associated with the nucleus accumbens are norepinephrine and dopamine. In order to understand why the nucleus accumbens would be a viable brain area to stimulate for the treatment of depression, it is important to understand the relationship between these neurotransmitters with anxiety and depression. When talking about depression and neurotransmitters its often about a lack thereof. However, when you throw anxiety into the mix as well, there are other neurotransmitters involved other than dopamine, such as norepinephrine. That is when noradrenergic neurons

come into play. Neurons that express norepinephrine are involved with functions such as alertness and readiness for action. However, this neurotransmitter can often be in excess in people suffering from anxiety. Similarly, too much dopamine in your system can lead to anxiety. The nucleus accumbens, therefore, is a viable brain area to stimulate for the depression and anxiety treatment via DBS. And more specifically, the shell of the nucleus accumbens, which is the target for a study that was conducted recently involving DBS in a depression animal model involving adult male rats.

What was done

This study was conducted by taking three different groups of fifteen adult male rats and surgically implanting electrodes into the right side of the brain onto the nucleus accumbens. The three different groups received varying amounts of stimulation with the sham group receiving none, the intermittent group receiving stimulation for three hours per day and the continuous group receiving constant stimulation. This was conducted for a total of two weeks. Behavioral tests were conducted both before and after the two-week stimulation period followed by analysis of the brain tissue through high-performance liquid chromatography and Golgi-Cox stainings.

What happened as a result?

The behavioral analysis conducted at the beginning of the experiment showed no difference between the three rat groups whatsoever. However, once the two-week stimulation period was over the behaviors between the three groups differed making it apparent which rats received the stimulation series and which did not. The sham group stood out the most from the intermittent and continuous stimulation groups. The sham group of rats had more recorded anxiety-like behavior than the first behavioral analysis test. This is probably due to the rats being kept separate from each other, which induces stress. However, the two groups that received the stimulation showed a reduction in anxiety-like behaviors and exhibited more exploratory behaviors with a small difference between the intermittent group and the continuous group. The group that received continuous stimulation had the most positive result overall.
With the high-performance liquid chromatography analysis, the levels of dopamine and norepinephrine were measured for the three rat groups. The sham group had increased levels of both neurotransmitters while the other two groups saw a decreased amount of these neurotransmitters. Similarly to before, the group that received the continuous stimulation saw the most decrease in these neurotransmitter levels compared to the other groups. Along with neurotransmitters, the levels of tyrosine hydroxylase were measured. Tyrosine hydroxylase is a precursor to dopamine and the findings were similar to that of the neurotransmitter levels found for each group. The sham group saw increased levels of tyrosine hydroxylase, while the two groups that received stimulation had a decrease with the continuous group seeing the largest decrease overall. The Golgi-Cox staining was done to measure the arbors of the dendrites from each rat brain. Once this was done, it was shown that the rat groups that received stimulation saw an increased length in these arbors indicating that neuroplasticity had taken place during this study. The shame group saw no change in dendritic arborization with the two stimulated groups showing an increase. Comparably to all the data gathered from this experiment listed previously, the group that received continuous stimulation over the two-week period saw the most increase in dendritic arborization.

What does this mean?

Based on the results of this experiment, it can be said that deep brain stimulation of the nucleus accumbens is an alternative treatment method for anxiety and depression-related disorders. This experiment “demonstrates that DBS of the nucleus accumbens not only halted the progression of the disease process but improved it.”[7] Deep brain stimulation is already an available and verified treatment option for various types of disorders. Therefore, it

can be deduced that stimulating a specific brain area would also serve the same purpose when treating anxiety and depression-related disorders. Deep brain stimulation not only strengthens the synapses in the stimulated brain areas, but it also generates neuroplasticity, which is essential in alleviating the symptoms of depression and anxiety long term. Similar to deep brain stimulation, transcranial magnetic stimulation offers the same relief from these symptoms through stimulating areas of the prefrontal cortex. These type of treatment options are perfect for those who do not want the side effects of pharmaceuticals and for those who simply do not want to put foreign chemicals into their bodies.

References

1. Harvard Health Publishing. (2009). What causes depression? Retrieved from https://www.health.harvard.edu/mind-and-mood/what-causes-depression
2. Deep brain stimulation. (2018, December 14). Retrieved from https://www.mayoclinic.org/tests-procedures/deep brain-stimulation/about/pac-20384562
3. Deep Brain Stimulation (DBS). (n.d.). Retrieved from https://my.clevelandclinic.org/health/treatments/21088-deep-brain-stimulation
4. Northwestern Medicine. (n.d.). How Does Deep Brain Stimulation Work? Retrieved from https://www.nm.org/healthbeat/medical-advances/how-does-deep-brain-stimulation-work
5. Neurosci. (2014, June 14). Know your brain: Nucleus accumbens. Retrieved from https://www.neuroscientificallychallenged.com/blog/2014/6/11/know-your-brain- nucleus-accumbens
6. Ambroggi, F., Ghazizadeh, A., Nicola, S. M., & Fields, H. L. (2011, May 4). Roles of nucleus accumbens core and shell in incentive-cue responding and behavioral inhibition. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3145462/
7. Falowski, S. M., Sharan, A., Reyes, B. A. S., Sikkema, C., Szot, P., & Van Bockstaele, E. J. (2011, December). An evaluation of neuroplasticity and behavior after deep brain stimulation of the nucleus accumbens in an animal model of depression. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4707959/
8. Pandya, M., Altinay, M., Malone, D. A., & Anand, A. (2012, December). Where in the brain is depression? Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3619732/
9. Montoya, A., Bruins, R., Katzman, M. A., & Blier, P. (2016, March 1). The noradrenergic paradox: implications in the management of depression and anxiety. Retrieved from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4780187/
10. Zarrindast, M.-R., & Khakpai, F. (2015, September). The Modulatory Role of Dopamine in Anxiety-like Behavior. Retrieved from https://www.ncbi.nlm.nih.gov/pubmed/26317601