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Seeds of Science

Perspective: Focused-Ultrasound Guided Neuropeptide Delivery as a Novel Therapeutic Approach in Psychiatry

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Abstract

Although drugs are a critical component of mental healthcare, most have modest benefits and significant side effects. One way to develop a superior intervention would be to administer drugs with the spatial and temporal precision that better replicates natural diversity within neurotransmitter systems. A technology called focused-ultrasound (FU) may be able to safely and transiently disrupt the blood-brain barrier with spatial precision, permitting the site-specific delivery of molecules that do not conventionally cross the blood-brain barrier. If this method is proven to be safe and effective in larger human trials, it may trigger a paradigm shift in biopsychology research where the level of precision with which neurotransmitter systems can be influenced is massively increased. In this article, we use the example of oxytocin in the treatment of Autism. We propose that intranasal administration is not highly effective because it leads to oxytocin's wide dispersion throughout the brain, failing to specifically stimulate oxytocin's prosocial effects in specific regions. Consequently, we hypothesize that site-specific delivery of oxytocin, particularly in brain regions such as the Nucleus Accumbens and Ventral Tegmental Area, would lead to more consistent benefits.

Introduction

The most convenient method of drug delivery involves compressing drugs into ingestible tablets, topical ointments, penetrative injections, or inhalation devices (Bhagwat & Vaidhya, 2013). Consequently, drugs typically disperse throughout the bloodstream and eventually the whole brain, rather than to specific brain regions. Distributing drugs throughout the brain is not useless, many drugs can be effective for a range of psychiatric conditions. However, across all psychiatric disorders, many people are non-responsive to pharmacological treatment (Leichsenring et al., 2022), and some disorders (e.g. Borderline Personality Disorder) are not widely-accepted to respond to any drug (Tyrer & Silk, 2011). One explanation is that drugs, and the neurotransmitter systems on which they act, have diverse effects on psychology and behavior

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depending on their location in the brain.

Until recently, without invasive surgical procedures, it has not been possible to target drugs to specific brain regions. In this paper, we'll describe a technology called Focused Ultrasound Mediated Drug Delivery (FUDD), which uses low-intensity sonic waves to transiently, safely, and focally disrupt the blood-brain barrier (Tharkar et al., 2019). Most commonly, this method is used to deliver toxic chemotherapeutic drugs to tumors (Beccaria et al., 2020). However, one study has used focused ultrasound to deliver the neurotransmitter GABA in rats (Todd et al., 2019), and the basic principle of focal-drug delivery would likely be valuable for a range of drugs and conditions, including mental disorders.

This paper focuses on the use of oxytocin in the treatment of Autism for three reasons. First, despite early optimism, the largest modern trials show that intranasally administered oxytocin is not beneficial for the social symptoms of Autism (Sikich, 2021). Second, invasive research in animals has shown that oxytocin has contrasting social effects in different parts of the brain (Steinman et al., 2019): this data provides a theoretical rationale for why human treatments are ineffective. Finally, as oxytocin does not readily cross the blood-brain barrier (Yamamoto & Higashida, 2020), it would be a natural candidate for this procedure (more detail in later sections).

However, the utility of FUDD likely extends beyond oxytocin, potentially to any drug or molecule that does not conventionally cross the blood-brain barrier, and has a different effect on behavior depending on its location in the brain. Pending additional safety studies, this technology may usher in a transformative new approach for studying the causal links between neurochemicals and behavior, and could open a new category of treatment targets for many psychiatric conditions.

Oxytocin & Autism

i. Oxytocin Neurobiology

Oxytocin is a neuropeptide and hormone produced primarily in the hypothalamus and is secreted from nerve terminals in the posterior pituitary gland into the bloodstream (Gimpl & Fahrenholz, 2001). In addition to the systemic release, oxytocin neurons project to several brain regions, including the BNST, Nucleus Accumbens, and Ventral Tegmental Area.

ii. Correlations Between Oxytocin And Social Behavior

Several lines of research support a link between oxytocin and social behaviors. For example, genetic deletions of the oxytocin gene leads to changes in animal sociality and sexual behaviors (Winslow & Insel, 2002). In humans, variation in the oxytocin gene is sometimes found in individuals with Autism or other divergent social phenotypes (Cataldo et al., 2018). Outside of genetics, the concentration of oxytocin, measured in the bloodstream, often correlates with social phenotypes. For example, children with autism have significantly lower levels of oxytocin than neurotypical children - but the same was not true for adults (John & Jaeggi, 2021). These findings suggest that oxytocin is a plausible intervention target for people with social disorders like Autism.

iii. Interventional Studies with Oxytocin

Administered intravenously, oxytocin does not readily cross the blood-brain barrier (Mens et al., 1983), but refer to Lee et al. (2018). More commonly, oxytocin is administered intranasally, which may allow it to bypass the Blood Brain Barrier by traveling along olfactory nerves (Quintana et al., 2015). When administered intranasally, oxytocin does not distribute throughout the brain, but it still enters a large set of regions including the orbitofrontal cortex, striatum, brainstem, and thalamus (Lee et al., 2020).

Within healthy populations, intranasal oxytocin may modestly promote the recognition of some facial expressions, and promote in-group trust, but not out-group distrust (IJzendoorn & Bakermans-Kranenburg, 2012; Leppanen et al., 2017). However, these trials have not translated into a clinically useful therapy. The largest existing trials on people with Autism have shown that oxytocin does not benefit social or cognitive functioning (Sikich, 2021). Meta-analyses also support the point that systemically-administered oxytocin does not improve the symptoms of either Autism or Schizophrenia (Martins et al., 2021; Sabe et al., 2021).

These studies provide evidence that oxytocin can influence social behavior, but there is not a clear and consistent effect amongst all participants, particularly considering clinical groups and clinically relevant symptoms.

iv. Diverse Actions of Oxytocin in the Animal Brain

In animal brains, oxytocin has a different relationship with behavior depending on the location of release, see Steinman et. al (2019) for a comprehensive review. Briefly, in the Bed Nucleus of the Stria Terminalis (BNST), a major efferent connection of the amygdala, oxytocin is related to negative social behaviors like avoidance and vigilance (Martinon et al., 2019; Ayers et al., 2011; Nasanbuyan et al., 2018; Duque-Wilckens et

al., 2018; Duque-Wilckens et al., 2020). Contrastingly, in reward-related regions like the VTA and Nucleus Accumbens, oxytocin is related to prosocial behaviors like approaching other animals (Dölen et al., 2013; Dölen & Malenka, 2014). Other brain regions also may have distinct relationships with behavior, for example, in the amygdala, oxytocin can reduce fear responses (Knobloch et al., 2012).

Overall, oxytocin can impact both positive and negative social and emotional behaviors. Hypothetically, in human studies, oxytocin is simultaneously producing several, potentially contrasting, effects from different areas of the brain. Therefore, we suggest that one way to improve human oxytocin therapeutics is to target oxytocin to brain regions such as the Nucleus Accumbens and Ventral Tegmental Area.

Focused Ultrasound

i. Biophysics & Equipment

Focused ultrasound (FU) is a multi-purpose technology based on the spatially-precise direction of short pulses of energy in the form of sound waves (Meng et al., 2021). Some of its applications include thermally ablative surgery (Orsi et al., 2010), stimulation of neuronal activity (Yu et al., 2021), and when used at lower power, transient disruption of the blood-brain barrier (BBB) (Burgess & Hynynen, 2013).

Technically, FU waves start from frequencies of 20 kHz and never exceed 200 MHz (Buch et al., 2018). The precision of focused ultrasounds is achieved with the help of transducers, particularly concave-focused transducers for the purpose of disrupting the blood-brain barrier (Izadifar et al., 2020). Focused ultrasound interventions are often used in tandem with imaging technology, such as MRI or ultrasound sonography, to guide the ultrasound (Izadifar et al., 2020).

ii. Biological Mechanisms Opening the Blood-Brain Barrier

The blood-brain barrier (BBB) refers to a system of endothelial and nervous cells that tightly control what substances can enter the brain (Daneman & Prat, 2015). To a greater extent than other parts of the circulatory system, endothelial cells in the brain are tightly connected with transmembrane proteins called tight junctions. The mechanism through which FU disrupts the BBB relies on the injection of small gas microbubbles into the bloodstream (Hynynen et al., 2003). When exposed to ultrasound, tight junction proteins dissociate from each other (Sheikov et al., 2008). Mechanistically, these bubbles absorb the sound energy and begin to expand, oscillate, and sometimes rupture (Tung et al., 2011), theoretically pressing against and stretching capillary walls, ultimately detaching tight-junctions proteins.

iii. Safety & Characteristics of Human Clinical Trials

At least 9 human clinical studies have used Focused Ultrasound in the brain in an attempt to permeabilize the blood brain barrier (Appendix - Table 1). These studies are typically small, including 3-15 subjects, and have been conducted on people with Alzheimer's Disease, Parkinson's Disease, ALS, and Glioblastoma. The drug delivered varies, some studies introduced toxic chemotherapeutic agents, while others did not use any drug at all.

For a complete review of safety, see Meng et al. (2019). Briefly, there are two main risks to FUDD. The first safety risk includes the prospects of toxic chemicals or pathogens entering the brain. Even at low energies, FU can trigger the extravasation of red blood cells into the brain and alterations to surroundings cells like pericytes (Wang et al., 2020).

Beyond pathogens and toxins, chemical components found in the bloodstream could more subtly influence neuronal activity and thereby pose an additional psychological risk. For example, most neurotransmitters are present in the bloodstream (Wishart et al., 2022), and therefore, opening the BBB may influence brain function, and consequently behavior, even in the absence of an intentionally-administered drug.

The second risk of FUDD is the potential for a direct interaction between focused ultrasound and brain tissue, independent of effects on the BBB. At least regarding thermal damage, the risk is low, as the energy used for BBB disruption is 1,000 times lower than what is used in surgical ablations (Meng et al., 2019).

Empirically, at least 10 trials have evaluated the safety of FUDD in human clinical populations. Many have reported mild side effects, including: headaches, vagal responses, scalp pain, edema/bruising attributable to placement of the stereotactic frame, musculoskeletal pain, scalp petechial rash, and transient FLAIR hyperintensity in sonicated brain tissue. No existing trials have reported any major side-effects.

One major unresolved question is the effects of long-term frequent FU. This may be an important point when considering psychiatric applications - as many drugs need to be taken on a daily basis, sometimes over months, to achieve their intended effect. The most intensive trial to date has tested 24 separate stimulations (Park et al., 2020), but most other studies used approximately five stimulation sessions.

Potential Limitations of Regionally-Focused Drug-Delivery

FUDD has the potential to overcome a major limitation at the core of modern psychopharmacology - the inability to target drugs to specific brain regions. However, this limitation is not the only reason why drugs are not always effective. In this final section, we offer some reasons why researchers should be cautious in estimating the potential value of this approach for social disorders, and potentially any psychiatric condition.

i. Untested Safety and Uncertain Feasibility of Frequent Application

If the effects of a drug, like oxytocin, are acute, the FUDD procedure may need to take place more frequently. As mentioned, this poses a safety risk - no studies have evaluated the outcomes of long-term, frequent disruption of the blood-brain barrier. Moreover, this would pose a technical implementation challenge. FUDD is currently restricted to clinical settings (Tempany et al., 2011), as it relies on a large, fixed, expensive piece of equipment that requires expertise to operate. If the drug needs to be administered regularly, the FU device may have to become portable and easier to operate.

ii. Limited Biological Precision

There are many remaining technical limitations to FUDD. One limit is temporal resolution: the BBB can remain open for hours after the procedure (Sheikov et al., 2008), and therefore, oxytocin would diffuse for perhaps an unnaturally long amount of time relative to the natural rapid dynamics of oxytocin release. Moreover, although the spatial resolution is precise, it still covers an area of cubic millimeters (Hu et al., 2022). This is small enough to target brain structures like the Nucleus Accumbens or Ventral Tegmental Area mentioned above. However, this area still contains tens of thousands of neurons. The generic release of oxytocin in this area may not adequately simulate the natural complex activity patterns of the neurons within that space. These clear technical limitations could provide an explanation for potential trial failures, and would suggest the need for even further technological development.

Conclusion

Focused ultrasound may represent a novel treatment option in psychiatry as it provides non-invasive targeted drug/neuropeptide delivery by transiently opening the blood-brain barrier. Questions about safety remain, as this approach has not been tested in psychiatric conditions, it has not been tested on large subject populations, and few

studies have tested the effects of frequent administration. Moreover, there is reason to believe that even the spatially-precise administration of drugs may not be adequately detailed to consistently and powerfully manipulate behavior: there will still be diverse neurons upon which the drug acts, even when the drug is restricted to a single brain region. Nonetheless, if safe, this technology could fundamentally change the way that scientists study neurotransmitter systems in the human brain, which would lead to countless new interventional trials for all mental illnesses and social disorders.

Gardener Comments

Roger's Bacon:
This paper is an exploratory survey of a new treatment modality for psychiatric diseases, and in all respects (speculative, rigorous, well-written) is deserving of publication with SoS.

A few thoughts that come to mind:
1) How many drugs (medical or recreational) could have their effects modified (e.g. side effects reduced) through more targeted delivery with FUDD? A next step might be to survey the most common psychiatric drugs and analyze how many of them would have their effects significantly modified if delivery could be targeted to specific brain regions. How useful would FUDD really be if we proved it was safe/effective?

2) Does this have any application to bodily diseases? There may not be a blood-brain barrier (BBB) in the body (obviously) but perhaps this technique could lead to increased absorption in particular organs/diseased tissues?

3) The authors write "Beyond pathogens and toxins, chemical components found in the bloodstream could more subtly influence neuronal activity and thereby pose an additional psychological risk." Is there variation in the tightness of the BBB across different people (presumably variation in relevant proteins)? This could point to some interesting biology - are some people inherently more affected by the ambient neuro-active components of their blood?

Josh Randall:
This paper attempts to apply the concept of focused ultrasound to a new set of clinical questions, specifically the social effects of autism. I am personally very skeptical of research surrounding autism, especially searching for a 'source' or 'cure'. The author makes an effort to showcase the history of this technique in other clinical settings, especially highlighting the safety and related effects of altering the blood-brain-barrier.

Their description of limitations of this work is appreciated, including the need for highly trained operators in clinical settings, the large range that oxytocin would still affect when applied, and the need for regular focused ultrasound administration for possible success. Two criticisms that I still have are: 1) does the BBB being open allow the body to supplement the brain with other secreted proteins/hormones that might reduce the effectiveness of supplying oxytocin and 2) if there is not strong evidence that oxytocin has clinical effects on autistic people, is it ethical to pursue this type of research has a potential 'cure' for autism. My second point more broadly is asking whether autism needs curing and whether this type of work is something that a large number of autistic people would want or need to live fulfilling lives.

Dr. Payal B. Joshi:
The article is written in an extremely scientific manner illustrating oxytocin delivery within the brain using focused ultrasound technique. Authors have critically supported their hypothesis and presented reported clinical trials that depict their robust review. I suggest a minor revision on providing an illustration or a figure in the manuscript where authors have described the biophysics and equipment section.

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Appendix

Table 1

Human Clinical Trials Using Focused Ultrasound to Disrupt the Blood-Brain Barrier

Side effects	Duration and/or frequency of BBB opening	Sample size (n)	Outcome (efficacy)	Drug employed	Condition treated
Clinical Trial #1 - Abrahao et al., 2019					
No major side effects, deaths, or deficits. Mild to moderate effects observed.	1 time, and results analyzed post-operatively at days 1, 7, 30, and 60	6	All subjects displayed gladonium leakage at the site of sonification	Gadolinium (contrast agent used to evaluate entrance into brain)	ALS
Clinical Trial #2 - Lipsman et al., 2020					
No serious adverse events (no deaths, hemorrhage, swelling, or neurological deficits)	2 times, one month apart	5	No measurable change at 3 months	None	Alzheimer's
Clinical Trial #3 - Park et al., 2020					
No adverse effects	1 day per week for 6 4-week cycles (24 weeks)	6	No significant changes	Temozolomide (chemotherapeutic agent)	Glioblastoma
Clinical Trial #4 - Carpentier et al., 2016					
No side effects, safe and tolerated	Monthly for up to 6 months or until no evidence of	15	Effective BBB disruption and carboplatin administration	Carboplatin (chemotherapeutic agent)	Glioblastoma

	tumor progression				
Clinical Trial #5 - Gasca-Salas et al., 2021					
No serious side effects. Brief restlessness in 1 patient	*2* treatments with 2-3 weeks between sessions	5	Improved cognition	Beta-amyloid antibodies	Parkinson's Disease Dementia (PDD)
Clinical Trial #6 - Mehta et al., 2021					
No adverse effects	2-week intervals for 8 months	3	Elicited immune response	None	Alzheimer's
Clinical Trial #7 - D'Haese et al., 2020					
No adverse effects	3 times, 60 day interval	6	Average decrease in β-Amyloid Plaques	None	Alzheimer's
Clinical Trial #8 - Lipsman et al., 2018					
No adverse effects	Twice, 1 month apart	5	No significant changes	None	Alzheimer's
Clinical Trial #9 - Rezai et al., 2020					
No adverse effects	3 sessions, two weeks apart	6	No clinically meaningful changes	None	Alzheimer's