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Brain Penetrant Drug Formulations for Central Nervous System Disorders

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Disorders of the central nervous system (CNS) include psychiatric disorders, such as depression, anxiety, substance and alcohol dependence, bipolar disorder, and schizophrenia, as well as neurological disorders, such as Parkinson's disease, Alzheimer's disease, Huntington's disease, epilepsy, and stroke. Although these disorders have been arbitrarily separated into distinct fields of research and clinical treatment, they share in common manifestations that arise from pathology of the CNS. Despite decades of intense research efforts, the worldwide morbidity and mortality attributable to CNS disorders massively overshadows other important clinical disorders, including cancer and heart disease, and the number of patients suffering from brain tumors, depression, schizophrenia, epilepsy, cerebrovascular diseases, Alzheimer's disease, Parkinson's disease, and substance dependence is far higher than those suffering from disorders of peripheral organ systems [1-4]. Moreover, the last several decades have arguably shown much greater strides in the development of therapeutics in cardiology, infectious disease, and other clinical domains that in neurology and psychiatry. This public-health emergency has been recently recognized in presidential and National Institutes of Health initiatives such as the "connectome" and BRAINS projects to support preclinical efforts to elucidate their etiology and to develop better treatments for these devastating CNS disorders.

A fundamental obstacle in neurology and psychiatry medications development efforts is the presence of endogenous and active regulatory processes designed to protect the CNS. A key component of this protection is the Blood-Brain Barrier (BBB), which is only passively permeable to small and lipophilic molecules. This normally limits the invasion of the CNS by bacteria, toxins, viruses, and other untoward organisms and substances, and keeps the cerebral spinal fluid bathing the CNS relatively free of contaminants compared to the blood. However, this also severely limits the number of possible chemical entities that can be used to modulate therapeutic targets for CNS disorders. We now know from preclinical studies that there are many large compounds that could be of tremendous clinical benefit if they could penetrate the CNS. The proof-of-concept that these compounds are effective has largely been established by preclinical animal studies in which they can be injected directly into the brain ventricles (for widespread delivery) or specific brain or spinal regions. These compounds include neurotrophins such as brain derived neurotropic factor (BDNF) [5,6] secretase inhibitors for Alzheimer's disease [7], anti-inflammatory cytokines [8,9], and therapeutic plasmid DNA that may trigger growth factors to stimulate neuronal or myelin recovery and remodeling [10-12]. If a viable approach could be developed to effectively deliver large-molecule therapeutics to the brain following oral or other peripheral administration, it would present a sea change in both the number of targets available and the number of ligands available for any given target in the treatment of CNS disorders. Two such CNS disorders that are primed for particular benefit from brain penetrant large-molecule drug formulations are stimulant abuse and autism spectrum disorder (ASD).

Stimulant abuse is an important public health concern. In 2008, 4.8 million Americans abused cocaine and 1.2 million Americans abused methamphetamine [13]. Acute overdoses are a particularly hazardous aspect of stimulant abuse [14] and it has been estimated that approximately 1 in 3 drug-related emergency room episodes involve cocaine abuse [15,16]. Cocaine abuse is characterized by recreational consumption associated with drug-induced feelings of drug "high" and "euphoria" that are associated with elevated levels of dopamine in key regions of addiction-relevant neural circuitry, such as the nucleus accumbens and striatum. Cocaine addiction is characterized by binge intake patterns, loss of control, and maladaptive decision-making, likely mediated by maladaptive changes in the prefrontal cortex (PFC). Prominent models argue that key transition periods in the cocaine addiction cycle include drug initiation, bingeing, withdrawal, and relapse, which can be modeled in animals using self-administration, appetitive conditioning in the conditioned place preference paradigm, withdrawal/extinction, and reinstatement procedures [17].

Over several decades, significant efforts have been devoted to develop an effective treatment for cocaine addiction. These efforts have focused on the development of small-molecule dopamine agonists and antagonists, GABAergic agonists, kappa opioid agonists, mu opioid partial agonists, and serotonergic agonists and antagonists Despite these efforts, no compound has achieved notable clinical success and there is currently no effective pharmacotherapeutic available for the treatment of cocaine dependence. Eexciting recent studies have shown that brain-derived neurotrophic factor (BDNF) is decreased in the PFC of rats one day after the end of cocaine self-administration, and its protein level is increased in the PFC at longer abstinence durations [18]. Moreover, infusion of BDNF into the PFC immediately after the last of ten cocaine self-administration sessions attenuates context-, cue- and cocaine prime-induced reinstatement of cocaine-seeking, without affecting food-seeking [19]. However, as a large molecule, BDNF has been largely disregarded as a viable early-abstinence treatment for cocaine addiction, and efforts have focused instead on the development of small molecule agonists of the TrkB receptor. A viable approach to the delivery of large molecules to the CNS may allow BDNF and other neurotrophic factors to fulfill their potential to become the first effective treatments for stimulant abuse and dependence.

ASD is a developmental disorder that affects 1 out of every 68 children in the U.S., and is characterized by social dysfunction, impaired communication, and hyperactive or repetitive behaviors. Drug treatments are limited to selective serotonin reuptake inhibitors, such

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as fluoxetine, for repetitive or compulsive behaviors and stimulants, such as methylphenidate, for attention deficit issues. These compounds have side effects that include headaches, aggression, increased thoughts of suicide, and abuse liabilities, and they do not treat the social deficits that are the primary symptoms of ASD. There are currently no available pharmacotherapeutics that directly address these social deficits. One such large molecule that has shown recent promise for the treatment of social deficit disorders is oxytocin. Oxytocin is a nine-amino acid neuropeptide that is synthesized by neurons in the paraventricular nucleus and supraoptic nucleus of the hypothalamus. It is released into peripheral circulation by the posterior pituitary gland but also functions as a neurotransmitter throughout much of the mammalian brain [20]. Although oxytocin has been traditionally recognized to be involved in the stimulation of the uterus during parturition, recent studies have convincingly demonstrated roles for the brain neurotransmitter oxytocin system in social behavior, pair bonding, and perhaps some forms of enhanced cognition [21,22]. This has led to considerable interest in the development of oxytocin as a treatment for ASD and other social-deficit disorders.

A critical primary barrier to the use of oxytocin as a treatment for ASD is that, due to its size and hydrophicity, it does not cross the BBB and penetrate the CNS. Previous studies have attempted to overcome this barrier through intranasal delivery of oxytocin, based on the idea that the olfactory epithelial cells project directly into the olfactory bulb of the brain and can therefore bypass the BBB through direct drug transport into the brain. While this is a tremendous advance for ASD research and treatment, intranasal drug delivery is well known be only suitable for potent drugs as a limited drug volume can be sprayed into the nasal cavity, can damage the nasal epithelium following frequent or continuous use, can be contraindicated during upper airway infections, and engenders highly variable drug absorption. The development of a drug delivery system to actively transport oxytocin into the brain would have a substantial impact on ASD research and treatment because 1) it would open up other routes of administration (e.g., oral) that have clinical benefits, 2) it could be used to support intranasal delivery such that lower doses of oxytocin can be used and a better ratio of brain to peripheral drug delivery may be achieved, 3) it could support sustained-release formulations of oxytocin that would make it possible to conduct less frequent dosing and better control drug absorption, and 4) it would allow for preclinical studies of oxytocin that do not require intranasal administration. The fields of substance abuse and ASD research and treatment would therefore be substantially impacted by the development of new technology for the active transport of large molecules into the CNS.

The BBB is a dynamic interface that restricts the movement of most drugs and blood borne molecules into the brain. It is composed of tight junctions of endothelial cells within the continuous capillaries that supply the CNS. The BBB represents one of the most difficult biological barriers to cross to deliver therapeutic agents/ drugs/ peptides and it is exceedingly difficult to design new chemical entities that can passively cross this barrier [23-25]. However, the BBB endothelium is equipped with a variety of molecular transport systems that transport nutrients from blood to the CNS to support the needs of CNS cells. Receptor-mediated transcytosis is one class of these molecular transport systems that transport macromolecules between blood and brain. In the Mercer University College of Pharmacy Center for Drug-Delivery Research, we have begun studies to develop technology that takes advantage of these molecular transport systems to actively transport large-molecule therapeutics into the CNS. We have focused our efforts on substance abuse and ASD for the reasons outlined above, and we have developed a biodegradable and biocompatible drug-delivery system for oxytocin. We are highly encouraged by our preliminary data demonstrating that our formulation has good properties for brain delivery, dramatically enhances the brain penetrance of a large molecule infrared dye, and does not induce any signs of toxicity. We are further encouraged by our finding that brain penetrant oxytocin engenders dramatic behavioral effects indicative of central pharmacological efficacy, including dramatic increases in social interactions and prosocial behavior in mice, which persist for at least one week after oxytocin administration. We have begun studies to determine the potency, maximum efficacy, and time-course of the prosocial effects of brain-penetrant oxytocin formulations and to determine whether central oxytocin and serotonin systems interact synergistically to produce prosocial effects. We look forward to the release and publication of these findings, and we expect that work in this area by ourselves and others will lead to significant advances in the understanding and treatment of CNS disorders.

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