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An evaluation of central penetration from a peripherally administered oxytocin receptor selective antagonist in nonhuman primates

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ABSTRACT

The physiology of the oxytocin receptor has increasingly become a focus of scientific investigation due to its connection with social behavior and psychiatric disorders with impairments in social funciton. Experimental utilization of small molecule and peptide antagonists for the oxytocin receptor has played a role in deciphering these biological and social behavior connections in rodents. Described herein is the evaluation of a potent and selective oxytocin receptor antagonist, ALS-I-41, and details to consider for its use in nonhuman primate behavioral pharmacology experiments utilizing intranasal or intramuscular administration. The central nervous system penetration and rate of metabolism of ALS-I-41 was investigated via mass spectroscopy analysis of cerebrospinal fluid and plasma in the rhesus macaque after intranasal and intramuscular administration. Positron emission tomography was also utilized with [^{18}F] ALS-I-41 in a macaque to verify observed central nervous system (CNS) penetration and to further evaluate the effects of administration rate on CNS penetration of Sprague-Dawley rats in comparison to previous studies.

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1. Introduction

As a hormone, oxytocin (OT) induces uterine myometrial contractions and postpartum mammary gland milk ejection by binding to the oxytocin receptor (OXTR) in these locations [1]. As a neuromodulator, OT modulates maternal nurturing, social recognition, social bonding, and empathy-related behavior by binding to OXTR in specific regions of the brain [2–6]. Our understanding of the neural mechanisms underlying OT's role in social bonding were facilitated by behavioral pharmacology experiments using selective peptide antagonists and by comparing the OXTR densities in brain autoradiograms of a socially monogamous species (*Microtus ochrogaster*) and promiscuous species (*Microtus montanus*) of voles [7]. The socially monogamous species was found to have a very high concentration of OXTR in the nucleus accumbens while the promiscuous species was found to have scarce OXTR density in this same region [8,9]. As the nucleus accumbens is known for its role in cognitive processing of motivation, pleasure, reward, and addiction, the difference of OXTR density in these animal models emphasize its correlation to social bonding behavior [10–15]. Investigations into the localization and function of the OXTR system in human social behavior has since been an ongoing investigation in many facets of science including genetics, brain imaging, immunohistochemistry, in situ hybridization, and behavioral analysis [16–19]. The implications of the OT-OXTR neuromodulation system on human social behavior in clinical and typically developing populations has been a rapidly expanding contemporary focus in research which has resulted in both optimism as well as some criticism [20–22].

The pharmacological viability of potent and selective OXTR antagonists was recognized upon the discovery of OT's physiological role in inducing uterine myometrial contractions; OXTR antagonists have been proven to function as tocolytic agents to prevent preterm labor [23,24]. Further recognition of potential

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pharmacological use for an OXTR antagonist was acknowledged upon the discovery of OXTR in the hippocampus of a rat brain and the later correlations of OXTR to social behavior in various animal models including humans [25–28]. Hence, OXTR antagonists have been administered in pharmacological experiments for deciphering the role of OXTR signaling in behaviors and are potential pharmaceutical targets for treatment of specific disorders [29–32]. To investigate the OXTR neural functionality *in vivo* in a practical manner that does not involve invasive cranial surgery, the OXTR antagonist must be able to cross the blood brain barrier (BBB) when administered peripherally. Without this functionality, the antagonist must be administered directly into the brain, making it impractical for translation to clinical use.

Very few OXTR antagonists have been reported which possess the ability to penetrate the BBB when administered peripherally. Additionally, limited data has been made available regarding their central nervous system (CNS) activity. The only peripherally administered OXTR antagonist which has been utilized for behavior pharmacology studies in the rhesus macaque (*Macaco mulatto*) is the Merck produced L-368,899 [33]. Although there are several extensive reports regarding the peripheral pharmacokinetics of L-368,899 in various animal models due to its use in clinical trials, there are few documentations of pharmacokinetic details regarding its accumulation in the CNS. It was reported by Boccia et al. that a small percentage of a dose of L-368,899 administered intravenously enters the cerebrospinal fluid (CSF) of a rhesus macaque and remains in the CSF for over 250 min post injection. They further evaluated the compound's accumulation in limbic system areas via mass spectrometry of homogenate tissue from specific regions. Our lab has investigated several OXTR antagonists (not all are yet published), some of which incorporated positron emitting isotopes into their structure and utilized positron emission tomography (PET) for brain penetration profiling. We reported a carbon-11 *N*-methylated derivative of L-368,899, but the slight difference in structure prevented the results from being directly comparable to L-368,899 itself [34]. However, it should be taken into consideration that *N*-methylated L-368,899 accumulated in the cynomolgus macaque's choroid plexus, the region of the brain responsible for producing CSF and filtering impurities out of CSF prior to brain entry. This could indicate CSF accumulation of the compound without achieving distribution throughout the entire brain. Although the report from Boccia et al. did evaluate L-368,899 for brain distribution in postmortem tissue samples of the macaque, the analysis was performed via mass spectrometry on tissue homogenate extractions. The data obtained from this methodology had increased experimental variables which could have skewed the data (there were no reported experimental controls with standards concurrently reported and the sample sizes were very small). Brain tissue homogenates also contain capillaries which may give false positive measurements, especially when the amounts are in the picogram range.

Intranasal (IN) administration of OT has been utilized quite regularly as a potential means to reach the brain. Indeed, elevated levels of OT have been detected in the CSF after IN administration of OT in humans as well as the rhesus macaque [35]. Various mechanisms by which OT increases in the CSF after IN administration have been hypothesized, yet none of the mechanisms have been proven experimentally [36–38]. Copious investigations of IN administration of OT have reported effects in both normal subjects and subjects having social behavior deficits [22,39–44]. Due to OT being endogenously produced in the hypothalamus and distributed throughout the CNS, it is disputable that measured elevations of central OT concentrations post IN administration derived from the IN dose itself [45]. The mechanisms which induce hypothalamic production and distribution of OT are not completely understood, and it can be hypothesized that an increase of peripheral OT signals hypothalamic release of OT into the CNS [46]. Surprisingly, there has been limited research investigating the effects of IN administration of an OXTR antagonist.

The OXTR is one of a growing list of identified G-protein coupled receptors (GPCR), a list that has now grown to nearly 3000. The probability of a molecule antagonizing only one GPCR without agonizing, antagonizing, or allosterically modulating another GPCR is very low. Therefore, when evaluating the behavior effects of a specific GPCR using a molecule of known affinity and functionality, having or building a knowledge base of a specific compound's potential off-target binding to other GPCRs is essential. In consideration of the high probability of off-target binding, it would be beneficial to investigate behavioral effects using an alternative molecule of entirely different structure to confirm observations. This is especially true when the evaluation involves a high level of experimental variables as is the case with behavioral assessment. Here, we build upon the knowledge base of a previously reported OXTR antagonist (ALS-I-41, Fig. 1) to evaluate its ability to breach the blood brain barrier in macaque models through aerosolized IN, intramuscular (IM), and IV routes of administration [47]. Plasma and CSF samples were collected at specific time points post IN and IM administration and analyzed via liquid chromatography mass spectrometry (LCMS). A PET scan was performed after IV administration of [^{18}F]ALS-I-41. The use of PET with [^{18}F]ALS-I-41 was also performed in Sprague-Dawley rats to further evaluate metabolism and brain penetration differences that may occur with bolus IV, slow infusion IV, and IM routes of administration.

2. Material and methods

2.1. General

The synthesis and radiolabeling synthesis of ALS-I-41 and [^{18}F]ALS-I-41 was performed as previously reported [47]. Propylene glycol, United States pharmacopeia grade, was purchased from Fisher Scientific. The methodology for LCMS analysis of ALS-I-41 in CSF and plasma was first developed on an Advion CMS expression and carried over to an AB Sciex 6500 Triple Quadruple with a Schimadzu Nexera X2 Autosampler and LC tower. Nonhuman primate PET images of the brain region were obtained with a Seimens Focus 220, the PET isotope, and a 10 min transmission scan with a cobalt-57 source for attenuation correction. The Focus 220 has a

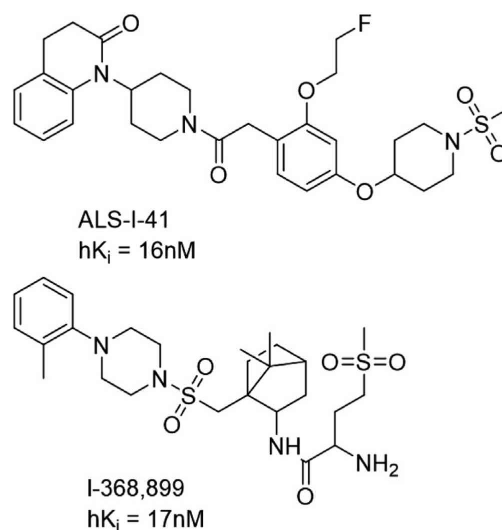

Fig. 1. Structures of ALS-I-41 and l-386,899 and their affinity (K_i) for the human OXTR as determined by the Psychoactive Drug Screening Program at the University of North Carolina, Chapel Hill.

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