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Review article

Intranasal administration: A potential route for targeting CNS

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ABSTRACT

Depression, the common psychological disorder, affects about 121 million people worldwide. It is common psychological disorder, characterized by sadness, loss of interest or pleasure, feelings of guilt or low self-worth, disturbed sleep or appetite, feelings of tiredness and poor concentration. A key obstacle for developing effective drugs and treatment regimens for treating neurological disease is blockage of drug entrance into the Central Nervous System by the Blood Brain Barrier. Depressive symptoms like feelings of hopelessness, suicidal tendencies, irritability, insomnia or hypersomnia etc. may compel the patients not to take medicines orally. So intranasal delivery of antidepressant drug can be a solution, intranasal drug delivery is now recognized to be a potential route for delivery of drugs directly into the CNS. The nasal route provides an attractive needle-free alternative for currently injectable drugs which may improve patient compliance and allow extended use of self-medication for many chronic diseases / acute conditions.

Keywords: Depression, Drug, Central Nervous System, Intranasal. .

INTRODUCTION

Depression is one of the most common psychological condition with a lifetime prevalence of about 15% in the adult population, possibly up to 12% amongst men and 25% amongst women in the Western World, the latter showing a twofold greater prevalence of Major Depressive Disorder than the former. The monoamine theory of depression postulates that depression is due to a deficiency in one or another of three monoamines, namely serotonin, noradrenalin (nor adrenaline) and or/dopamine. In its original form, the hypothesis proposed that depression was caused by a functional deficit of monoamines at key sites in brain, while mania was caused by a functional excess and that antidepressant agents exerted their effect by facilitating monoaminergic neurotransmission by increasing monoamine levels at neuronal synapses. A Post- mortem data from depressed human show that depression is associated with a decrease in amount of brain-derived neurotrophic factor (BDNF) in the hippocampus and an increase in the nucleus accumbens. Functional magnetic resonance imaging (fMRI) or positron-emission tomography (PET) has showed that activity within the amygdala and subgenual cingulate cortex is strongly correlated with dysphoric emotions. According to a study neuronal activity within these regions are increased by transient sadness in healthy volunteers and are chronically increased in depressed individuals, reverting to normal levels with successful treatment. Commonly Selective Serotonin Reuptake Inhibitors (SSRIs) are the drugs of choice for treating moderate to severe depression without psychosis. Switching to another SSRI, an atypical antidepressant or a tricyclic antidepressant (TCA) is considered if patient is not responding. Electroconvulsive therapy (ECT) is also the most effective therapy for severe treatment-resistant depression. Patients often view depression as a personal weakness, and they can be reluctant to discuss their feelings because of the stigma associated with a mental health problem [1, 2].

Barricades that impedes cns drug delivery

The CNS consists of blood capillaries which are

structurally different from the blood capillaries in other tissues. Capillaries are lined with a layer of special endothelial cells that lack fenestrations and are sealed with tight junctions. This permeability barrier, comprising, the brain capillary endothelium, is known as the Blood Brain Barrier. Another barrier that a systemically administered drug encounters before entering the CNS is known as the Blood- Cerebrospinal Fluid Barrier (BCB). Within the CNS there are a number of efflux mechanisms that will influence drug concentrations in the brain. These are called multi-drug transporters like multi-drug resistance protein (MRP), P glycoprotein (Pgp). The presence of natural barriers and activity of efflux mechanisms influence the concentration in brain extracellular fluid of free drugs that are available to interact with drug receptor sites. While enormous progress has been made regarding understanding of pathogenic mechanism of neurological disease, there are only a small number of effective drugs for treating these illnesses. A key obstacle for developing effective drugs for treating neurological disease is blockage of drug entrance into the CNS by the BBB. Less than 2% of all small- molecule drugs and virtually no large- molecule drugs can cross BBB. Therefore, it is of critical significance to search for drug delivery strategies that can effectively deliver drugs into CNS [3, 4].

Alterntive route for delivery of antidepressnts

Intranasal drug delivery is now recognized to be a potential route for delivery of small, non-polar compounds directly into the CNS (probably by bypassing the BBB). The nasal passages are highly vascular, an important feature mediating the absorption of many drugs into the systemic circulation. The neuroepithelium of olfactory region is the only part of the CNS that is directly exposed to the external environment. Non-invasive, ease of self-administration, large surface area for absorption, rich vascular sub-mucosa and possible direct pathways to CNS bypassing the blood-brain barrier are some of the advantages associated with this delivery option. The precise pathways and mechanisms by which a drug travels from the nasal epithelium to various regions of the CNS have not been fully elucidated. Research into whether the IN route might deliver potentially therapeutic amounts of larger biologics such as proteins to the CNS was first described only a little over a decade ago. Potential pathways for drug delivery across the olfactory epithelium following intranasal administration are reported as follows:

Intracellular pathway that extends from the olfactory epithelium to the olfactory bulb within olfactory sensory neurons following adsorptive, receptor- mediated or non-specific fluid phase endocytosis.

Para-cellular or trans-cellular transport to reach the lamina propria, where a number of different extracellular pathways for distribution are possible.

Absorption into olfactory blood vessels and entry into the general circulation.

Absorption into olfactory lymphatic vessels draining to the deep cervical lymph nodes of the neck.

Extracellular diffusion or convection in compartments associated with olfactory nerve bundles and entry into the cranial compartment.

The nasal respiratory epithelium lines approximately 50% of the nasal cavity in rats and 80–90% in humans. It is a pseudo stratified columnar secretary epithelium which warms and humidifies inspired air in addition to removing particulates, microorganisms, and allergens. The human respiratory epithelium is comprised of goblet cells, ciliated cells, intermediate cells, and basal cells. In addition serous glands, seromucous glands, and intraepithelial glands are also present. The seromucous glands are responsible for producing most nasal secretions while the goblet cells also secrete mucus. The nasal respiratory epithelium is innervated by branches of the trigeminal nerve; fibers from trigeminal ganglion cells ramify extensively within the nasal mucosa, with many extending almost completely through the epithelium so that the free nerve endings lie very near the epithelial surface. Altman et al., 1965 first of all described the route what is known as the Rostral Migratory Stream (RMS). It connects the olfactory bulb (OB) to the periventricular regions and is well described in rodents. The inferiolateral wall of the lateral ventricles in the mammalian brain forms the sub-ventricular zone (SVZ). Luskin et al., 1993 observed neuro progenitor cells arising in the SVZ appearing as interneurons in the glomerular and periglomerular layers of the olfactory bulb (OB) and hypothesized that there exists a route connecting the two areas. Basically it is a path several millimeters in length extending from the SVZ to OB. Literature points to the presence of a human RMS, but the function at various stages of development remains to be clarified. Analysis of human fetal brains has shown a ventral extension of the anterior horn of the lateral ventricles that is analogous to the rodent RMS [5, 6].

Previous Investigations about Targeting Brain through Intranasal Route

Udenafil which is mainly used for erectile dysfunction (ED) was examined by Cho HJ et al., 2012 in form of drug loaded micro- emulsion for intranasal delivery. [7, 8].

Author reported rapid onset of action and improved bioavailability after intranasal administration of an udenafil-loaded micro- emulsion and negligible toxicity to the nasal

epithelium that was observed in the histo- pathological staining. Uchida M et al., 2011 investigated the Intranasal Administration of Milnacipran (a serotonin–noradrenaline reuptake inhibitor, SNRI) in Rats and concluded that i.n. administration of milnacipran was found to produce a higher direct delivery to the CNS as well as to the systemic circulation, suggesting that this is a promising route of administration and an alternative to peroral (p.o.) administration. Intranasal delivery of Zidovudine by PLA (poly-L-lactide) and PLA-PEG [poly (L- lactide)-poly(ethylene glycol)] blend nanoparticles was reported by Mainardes RM et al., 2010. In the same year Sintov AC et al., reported systemic delivery of insulin via nasal route using a microemulsion system in rabbits. Zhang QZ et al., 2004 studied the brain distribution of nimodipine (mainly used for cerebrovascular spasms and senile dementia) following intranasal administration in rats. Along with this patient inability or reluctance to follow a proper regimen due to poor physiological health and the potential benefits offered by intranasal route, research was carried out in this field for finding brain levels after intranasal administration in mice. The intra nasal administration of antidepressant drugs produces a higher direct delivery to brain suggesting that it is a promising route of administration and an alternative to per oral administration. The direct transport to brain, results in higher antidepressant effect compared to that with per oral administration. The above review is based on study that was carried out to assess in vivo availability and distribution of antidepressant drugs in the brain after intra nasal administration in mice, in comparison with oral administration. Our overall data suggest that the nasal route could be exploited to increase the availability of antidepressants inside the brain. This review points towards beginning of the formulative study that will develop a suitable dosage form from which antidepressants uptake into the brain may be further enhanced [9, 10].

CONCLUSION

A promising way to deliver drugs to the brain is the nasal route. Nasal drug delivery has many advantages from a clinical perspective for its non-invasiveness, accessibility, ease of administration and patient compliance. In addition, the olfactory region is the only site of the body where the CNS is somehow in contact with the external environment, due to the presence of the olfactory receptor neurons, whose axons end in the olfactory bulb. Hence, a drug administered into the nasal cavity and deposited on the olfactory mucosa should have a good chance to reach the cerebrospinal fluid (CSF), upon diffusion across the mucosa itself. Afterwards, the drug could diffuse into the interstitial fluid and reach the olfactory and/or trigeminal nerve pathways, or the vascular, lymphatic or CSF pathways, eventually penetrating the brain parenchyma. The aim of the present study was to assess in vivo availability and distribution of antidepressant drugs in the brain after intra nasal administration in mice, in comparison with oral administration. The present study was carried out to formulate and investigate the most suitable nasal delivery system of antidepressant drugs and evaluate it. The review explained about the potential route of drug administration for treating central nervous system and showed how needle free approaches may have potential to improve patient compliance.

REFERENCES

1. Pagnin D, de Queiroz V, Pini S, Cassano GB. 2004. Efficacy of ECT in depression: a metaanalytic review. J ECT. 20, Pages13-20.
2. Crone, 1986. The blood–brain barrier: a modified tight epithelium, in Suckling AJ: Rumsby MG: Bradbury MWB (eds) 1986 The Blood–Brain Barrier in Health and Disease. Ellis Harwood. Pages 17–40.
3. Glenn GM, Kenney RT, Ellingsworth LR, 2003. Transcutaneous immunization and immunostimulant strategies: capitalizing on the immunocompetence of the skin. Expert Rev Vaccines. 2, Pages 253–267. Doi: 10.1586/14760584.2.2.253.
4. Frey WH 2nd, Liu J, Chen X, et al. 1997 Delivery of 125 I-NGF to the brain via the olfactory route. Drug Deliver 4, Pages 87-92.
5. Lochhead JJ, Thorne RG. 2012 Intranasal delivery of biologics to the central nervous system. Adv Drug Deliv Rev. 15; 64 (7), Pages 614-28.
6. Schaefer ML, Bottger B, Silver WL, Finger TE. 2002 Trigeminal collaterals in the nasal epithelium and olfactory bulb: a potential route for direct modulation of olfactory information by trigeminal stimuli. J Comp Neurol. 12; 444 (3), Pages 221-226.
7. Altman J, Das GD, 1965. Autoradiographic and histological evidence of postnatal hippocampal neurogenesis in rats. J Comp Neurol124. Pages 319–335.
8. Baker JT, Borris RP, Carte B, 1995. Natural products drug discovery and development: new perspectives on international collaboration. Journal of Natural Products. 58, Pages 1325-1357.
9. Robert A. Freitas, 2005. Current Status of Nanomedicine and Medical Nanorobotics. Journal of Computational and Theoretical Nanoscience. 2, Pages 1–25. Doi: 10.1142/9789812835581_0001.
10. Charlton S, Jones NS, Davis SS, 2007 Distribution and clearance of bioadhesive formulations from the olfactory region in man: Effect of polymer type and nasal delivery device. Eur J Pharm Sci. 30, Pages 295-302.