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ROLE OF NEUROHYPOPHYSIS IN VARIOUS PATHOLOGICAL CONDITIONS

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ABSTRACT

The neurohypophyseal peptide oxytocin may function in the brain to mediate a number of affiliative behaviours, according to a number of recent experiments **[1]**. Both animals and humans also exhibit altered behaviour after receiving the neurohypophyseal chemicals vasopressin and oxytocin. Several studies made an effort to describe these modifications as improvement in memory or attention processing for vasopressin and amnesic properties for oxytocin **[2]**.

Keywords: Neurohypophyseal, Oxytocin, Vasopressin, Affiliative, Amnesic

INTRODUCTION

Definition: The neurohypophysis is a neurovascular interface that the brain uses to regulate surrounding organs in order to maintain the body in a homeostasis condition **[3]**. The neurohypophysis consists of three poorly defined regions: **[1]** the neural lobe, **[2]** the infundibular stem and **[3]** the median eminence **[4]**. The neurohypophysis (NH) comprises the neuropeptides oxytocin (OXT) and arginine vasopressin (AVP), which control lactation

and bodily fluid homeostasis, respectively **[5]**.

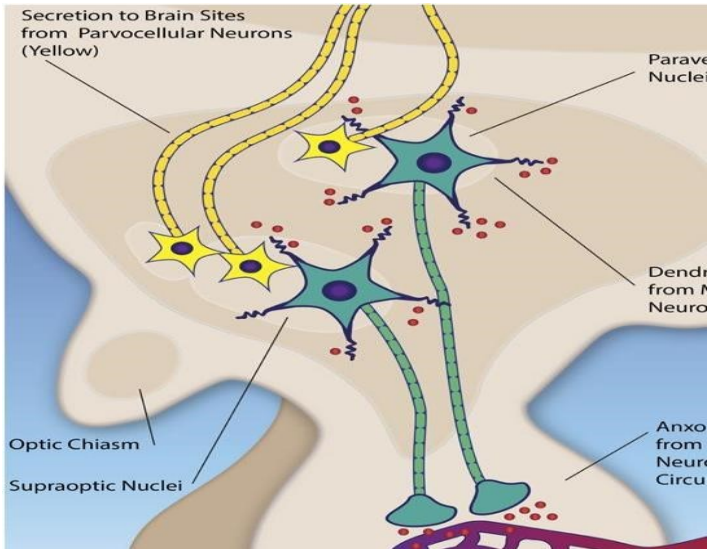
By releasing the neurohormones oxytocin (OXT) and arginine-vasopressin (AVP) from the brain into the peripheral blood circulation, the neurohypophysis (NH), located at the posterior lobe of the pituitary, regulates osmotic balance, blood pressure, reproduction, and lactation. The main biological elements of the NH are the pituicytes, which are resident astroglia, fenestrated endothelial, and hypothalamic axonaltermini **[6]**.

Mechanism of Action

Pituitary nonapeptide oxytocin and vasopressin contain nine amino acids in common and have a cyclic structure. There are only two amino acids at locations 3 and 8 that differentiate these molecules (isoleucine and leucine in oxytocin are replaced by phenylalanine and arginine in vasopressin, respectively). All vertebrate species contain related peptides, which are considered to have originated from substances with a similar structure. On chromosome 20, oxytocin and vasopressin are both expressed in a precursor form **[7]**.

Both substances are produced in regions of the hypothalamus, mainly in the supraoptic and paraventricular nuclei of large magnocellular neurons. These neurons send their axons to the posterior pituitary, which retains the peptides in vesicles until action potentials cause their release into the peripheral circulation (for instance, during labour or an imbalance in water homeostasis) **[8]**. The blood brain barrier blocks vasopressin molecules released in this manner from entering the central nervous system (CNS) again; but, extremely minute amounts of peripherally injected peptides (e.g., 1%) do appear to cross through into the cerebral spinal fluid **[9]** has been established that oxytocin and vasopressin concentrations in the brain can be up to 1000X higher than those found in peripheral blood, indicating a potential role for both molecules in the central nervous system (CNS) **[10]**.

While earlier research revealed that children with ASD could have lower plasma levels of the hormones oxytocin and vasopressin than children without the condition **[11]**. Subsequent studies have shown that plasma oxytocin levels tend to be similar among family members, irrespective of an autism diagnosis, but do generally connect with social communication skills **[12]**.



Disorders of neurohypophysis

Diabetes insipidus

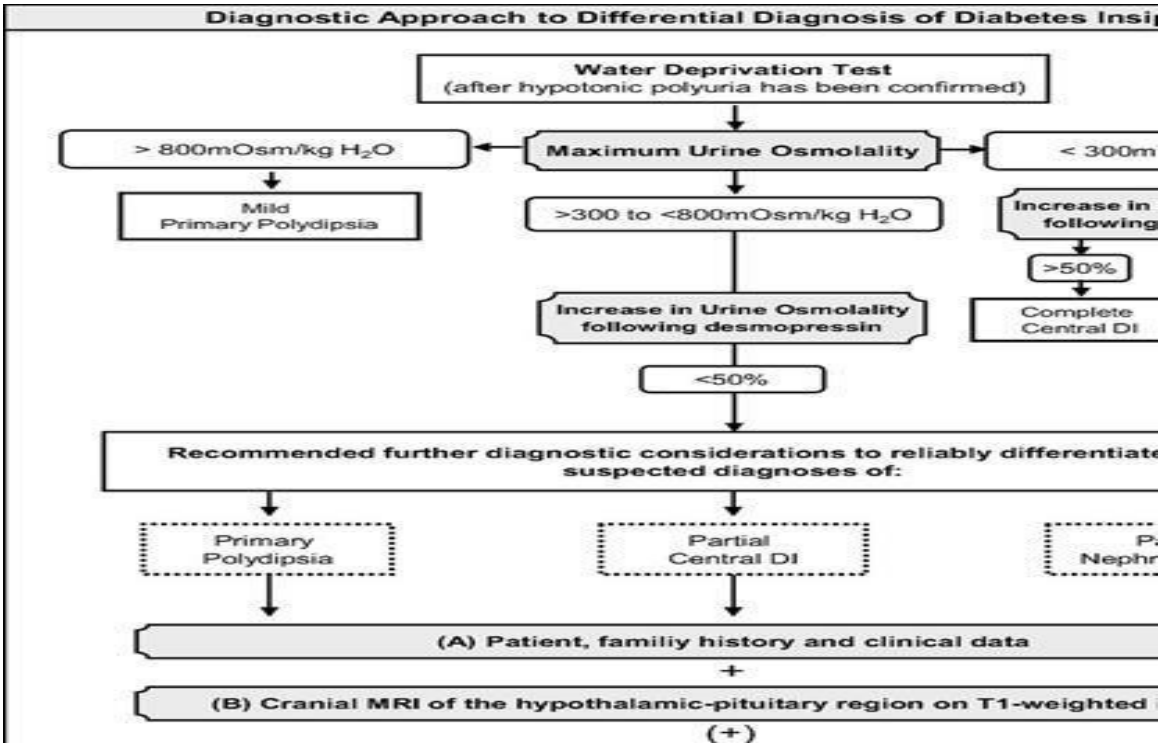
Syndrome of Inappropriate Antidiuretic Hormone (SIADH) pituicytoma **[13]**.

DIAGNOSIS OF DIABETES INSIPIDUS: Diabetes insipidus (DI) belongs to the spectrum of polyuria and polydipsia diseases, a group of hereditary or acquired disorders primarily involve with an inadequate arginine vasopressin (AVP) secretion or renal response to AVP, which clinically expresses as hypotonic polyuria and a compensatory or underlying polydipsia **[14]**. Confirming the existence of hypotonic polyuria is the initial step in diagnosis. Around 15% of individuals who are referred for investigation of polyuria have normal urine volume but report with frequent urination because of infection, prostatism, or an irritated bladder. If the daily volume of urine in an adult patient is less than 2.5 L, no more osmoregulatory function tests are necessary, though urological referral may be suggested **[15]**. Confirming the existence of hypotonic polyuria is the initial step in diagnosis. Around 15% of individuals who are referred for investigation of polyuria have normal urine volume but report with frequent urination because of infection, prostatism, or an irritated bladder. If the daily volume of urine in an adult patient is less than 2.5 L, no more osmoregulatory function tests are necessary, though urological referral may be suggested **[16]**.

The test on water deprivation

In diagnosis DI, the water deprivation test in accordance with the test procedure suggested by Miller *et al*. **[17]** has long been the standard. Since it does not measure the AVP directly, but rather assesses the AVP effect indirectly by measuring the urine concentration throughout a 17-hour period of fluid intake,

it is also sometimes referred to as the indirect water deprivation test. A synthetic AVP analogue is given one hour prior to the test's conclusion, and changes in urine osmolality are taken into consideration for the clinical diagnosis. Complete DI is diagnosed by urine osmolality < 300 mOsm/kg despite water restriction, and patients with central DI exhibit a rise in urine osmolality above 50% after desmopressin injection. Furthermore, there is a significant overlap in the diagnostic cut-offs, especially in the two patient groups of partial central DI and PP. The reduction in renal medullary concentration gradient in long-term PP patients, which makes it difficult to diagnose urine osmolality, best explains this **[18]**. These problems have been identified by two prospective investigations **[19, 20]**, which demonstrated that the water deprivation test had a low diagnostic accuracy of about 70% and performed particularly poorly for detecting PP. The water deprivation test's diagnostic accuracy was further decreased by further copeptin measurement, hence it is not advised **[21]**.



S. No	Category	Osmolalities post water deprivation(mOsm/kg) Plasma.	Urine	Post dDAVP urine osmolality (mOsm/kg)
1.	Normal	283-293	>750	>750
2.	Central DI	>293	<300	>750
3.	Nephrogenic DI	>293	<300	<300
4.	Partial DI or primary polydipsia	>293	300-750	<750

DIAGNOSIS OF SYNDROME OF INAPPROPRIATE ANTIDIURETIC HORMONE (SIADH)

Differential Diagnosis

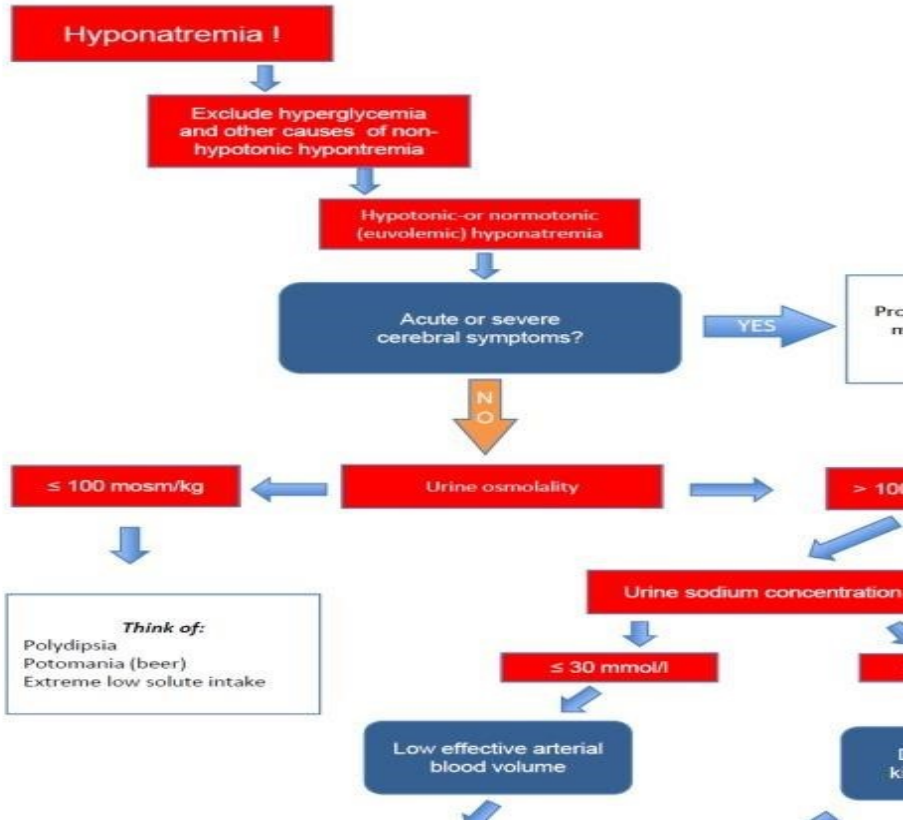
All causes of hyponatremia are included in the differential diagnosis of SIADH. The patient's volume status needs to be evaluated, and the main symptoms should be suspected if the urine osmolality is greater than 100mOsm/kg and the serum osmolality is decreased:

Euvolemic SIADH

Hypervolemia - Cardiac failure, cirrhosis

Hypovolemia - Vomiting, diarrhoea

The diagnosis of SIADH should be confirmed in patients who present with hyponatremia in a state of euvolemia, that is, without overhydration or exsiccosis, after ruling out other illnesses such chronic heart failure. A known and properly managed case of chronic heart failure may manifest as hypervolemia, euvolemia, or - when aggressively managed - hypovolemia. Due to arterial underfilling, which occurs in both chronic heart failure and liver cirrhosis, the renin-angiotensin-aldosterone system and the antidiuretic hormone are activated, causing both salt chloride and water retention. Hyponatremia could result overall if AVP activation predominates. The presence of a sodium-sparing condition may be demonstrated by 24-hour urine collection urine-sodium measurements, which would rule out SIADH **[22]**.



DIAGNOSIS OF PITUICYTOMA: Case Study

CASE 1

A 47-year-old woman with no prior medical history reported having headaches and menstrual irregularities for six months. Apart from a slightly elevated prolactin level of 45 ng/ml, believed to be attributable to the pituitary stalk disinhibition effect, visual function and preoperative neuroendocrine testing were normal. MRI scans revealed a solid mass which measured 16x13x10 mm. The mass had no longer visible neurohypophysis signal and displayed intermediate signal intensity on T1-weighted images, intermediate, slightly increasing signal intensity on T2-weighted images, and marked homogenous enhancement with contrast administration. It seemed to be in the middle of the back lobe. The computed tomography (CT) scans did not show any hyperostosis, necrosis, calcifications, or necrosis.

For tumour resection, a transsphenoidal microsurgical technique was chosen. The neurohypophysis included a small, soft, vascular mass that was reddish in colour. The pituitary stalk was preserved by doing a total resection, and normal hypophysis was seen throughout the procedure. Pituicytoma was the final pathology

conclusion. The adjuvant therapy was not used. MRI scans conducted over an 18 month follow-up period revealed no signs of the tumour remaining or growing again (**Figure 1**).

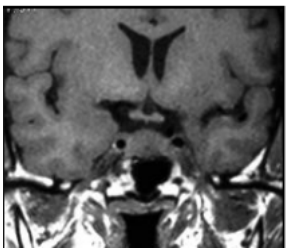


Figure 1

(a and b) T1W 1 - weighted coronal and sagittal MRI scans showing the interstellar mass. (c and d) T 1 - weighted contras t - enhanc sagittal MRI scans f o n the same patient showed no regrowth or residu

Case-2

A 51-year-old woman appeared with two months of headaches, six months of diabetes insipidus, and a year's worth of visual symptoms. Testing on the visual field revealed left-temporal hemianopsia. With the exception of an increased prolactin level of 188 ng/ml, the results of the preoperative neuroendocrine testing were normal. A suprasellar and post-chiasmatic mass was detected on the MRI scan, and the tumor's diameter was 9 7 6 mm. The mass had a marked uniform augmentation with contrast administration, intermediate, slightly increased signal intensity on T1-weighted images, and intermediate, slightly increased signal intensity on T2-weighted images. The CT scans detected no hyperostosis, necrosis, calcifications, or necrosis. The mass compressed the left optic chiasm and was connected to the pituitary stalk and infundibulum. It appeared to have originated from the pituitary stalk. The patient underwent a right pterional craniotomy resection. A somewhat vascular, soft, reddish mass was affixed to the pituitary stalk. In order to protect the pituitary stalk, a complete excision was carried out. Following surgery, the visual field defects and visual acuity both improved. After surgery, the diabetic insipidus was regulated, and 0.1 mg/day of desmopressin was administered. After receiving a small dose of dexamethasone, the patient was released. Panhypopituitarism was discovered by endocrinological tests performed after discharge, which required thyroid and adrenal hormone replacement. 11 months following the procedure, a gadolinium-enhanced follow-up MRI scan revealed that there was no residual mass **(Figure 2) [23]**.

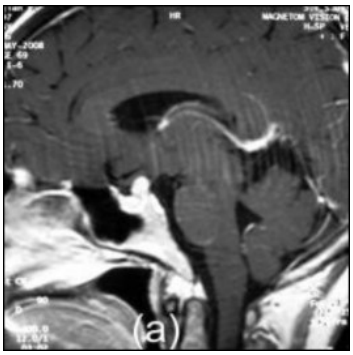


Figure 2

Figure 2 T1W1-weighted contrast-enhanced sagittal and coronal MRI scans showing the heterogeneous enhancement of the suprasellar mass, which appears to have originated from the suprasellar region with welldefined margins and tumor causing compression of the chiasm. The pituitary stalk is not regarded as a structure separate from the mass. T1-weighted contrast-enhanced sagittal and coronal MRI scans for the same patient showed no regrowth or residual mass adherent to the pituitary stalk 11 months post-operatively. CT contrast-enhanced axial scans showing the heterogeneous enhancement of the lesion prior to surgery.

DRUG TARGET ON NEUROHYPOSPHYSIS: Each of the G-protein coupled oxytocin and vasopressin receptors has seven transmembrane alpha helices connected by extracellular and intracellular loops (Kimura *et al*., 1992) (Zingg and Laporte, 2003) or Gimpl and Fahrenholz, 2001 provide extensive reviews of the receptor structure. Each peptide's interaction with its corresponding receptor exhibits cross-reactivity; for instance, oxytocvin binds to the oxytocin receptor with just a 10x stronger affinity than vasopressin (Kimura *et al*., 1994). When a neuropeptide binds to its specific receptor, the receptor structure changes shape, causing G proteins to become activated and then release Ca2+ from intracellular reserves. Activation of nitric oxide synthase, which causes vasodilation, smooth muscle contraction, gene transcription, and increased neuronal excitability are a few examples of potential downstream consequences. Rapid receptor desensitisation via receptor internalisation has been demonstrated for both OXTR and V2 **[24]**. The hypothalamus contains osmoreceptors, and it also receives information from atrial stretch receptors and arterial baroreceptors. Three receptor subtypes—V1a, V1b, and V2—mediate the effects of vasopressin. The phosphoinositol pathway is related to the V1a receptors, which are located in vascular smooth

muscle. They result in an increase in intracellular Ca2+, which causes contraction. The V2 receptor is damaged in the most prevalent genetic form of nephrogenic diabetes insipidus, called X-linked **[25]**. Care must be exercised, and it is important to be aware that individuals with underlying diabetes insipidus may become dehydrated if their access to water is restricted. Evaluation requires comparing the urine osmolality before and after deprivation **[26]**. AVP interacts with three receptors, the V1a (vascular, hepatic, and brain) and V1b (anterior pituitary), which seperate to mobilise calcium through phosphatidylinositol hydrolysis, and the V2 (kidney), which is connected to adenylate cyclase, which explains the diverse activities of AVP **[27]**. Vasopressin interacts to V2 receptors on tubular cells' cell surfaces, starting an intracellular cascade that creates the water channel aquaporin-2. Additionally, preformed aquaporin-2 migrates and binds to the luminal membrane of the tubule cells, acting as a pathway for water to be reabsorbed from the urine, through the cell, and back into circulation. As a result, there is a decline in urine volume, concentration, and renal clearance of free water **[28]**.

LIST OF TREATMENT METHODS FOCUSSED ON NEUROHYPOPHYSEAL DISORDERS:

Diabetes Insipidus Desmopressin is the prescription drug that is advised for both acute and chronic central DI **[29, 30]**. With a half-life of 8 to 20 hours, desmopressin, D-amino D-arginine vasopressin (DDAVP), is administered intravenously, orally, and intranasally. In order to ameliorate the patient's polyuria and polydipsia without jeopardising the plasma serum electrolytes, it is imperative to determine the dose **[31]**. Replace the water that was lost. Whether the patient is conscious or unconscious must be determined in acute DI following a TBI. Drinking should be encouraged if the patient is awake. In order to enforce fluid consumption if the patient is unable to drink, daily weighing should be used as a guidance. Intravenous dextrose 5% fluids are administered if the patient is unconscious. DDAVP is used as a treatment and is given subcutaneously or intravenously in doses ranging from 0.4 to 4 mcg to 10 mcg. One or two nasal puffs every 12 hours are often used for maintenance. It is important to treat hypokalemia if it is present. Monitoring is necessary for serum electrolytes, plasma osmolality, urine osmolality, fluid balance, and other variables. Having a normal urine production and electrolyte balance are the objectives. It is critical to keep an eye on sodium levels after desmopressin

administration. Dextrose or nasogastric water must be used to reduce plasma sodium content at a rate of 0.5 mEq/L/hr or less in order to effectively treat hypernatremia in DI **[32]**. Desmopressin, a synthetic ADH, is the most used treatment for CDI and gestational DI (DDAVP). Thiazide diuretics have an odd way of treating the central and nephrogenic subtypes of DI **[33]**. Other medications, such as hydrochlorothiazide, may be used to treat people with incomplete CDI and lingering vasopressin activity. Hydrochlorothiazide and water can be added to the formula as a treatment for babies with diabetes insipidus, which can be particularly difficult. In this age group, DDAVP should be taken with caution because newborns need to drink a lot of liquids to get enough calories for growth. Other medical care is supportive and symptomatic **[34]**. Desmopressin ,which operates on the kidneys in a similar manner to treat neurogenic DI, is typically used to concentrate urine and boost blood volume. Hormone replacement is the method of treatment **[35]**.

SIADH Secretion

The main therapy for SIADH secretion is fluid restriction. Reduce your daily fluid intake to 500–800 ml. The goal of correction should be to raise serum sodium to 130 mEq/L. Salt pills and furosemide 20 mg twice daily should be given to the patient if hyponatremia continues. Fluids that are isotonic will not make up the deficit, hence for severe hypernatremia, 3% hypertonic (513 mOsm/kg) should be administered. A 100 ml bolus is administered after three hours, and subsequent boluses might be given as necessary depending on the serum electrolytes. Hypertonic saline will also aid in lowering intracranial pressure in TBI. To avoid osmotic demyelination syndrome, correction should not exceed 8 mEq/L over 24 hours or 0.5 to 1 mEq/L every hour. Oral tolvaptan or iv conivaptan (v2 receptor antagonist) are given for chronic hyponatremia **[36]**. Tolvaptan is hepatotoxic and should not be administered to anyone who have liver problems. It is possible to provide demeclocycline, a tetracycline vasopressin inhibitor, although doing so may result in reversible azotemia, cirrhosis, and photosensitive skin rashes **[37]**. The use of urea to reduce natriuresis and reverse hyponatremia in SIADH secretion has been compared to that of vaptans **[38]**. The hyponatraemia of enduring SIAD has been treated with oral urea at doses of 30 g/day. An intelligent strategy for managing hyponatraemia brought on by SIAD is the use of V2-R antagonists (Vaptans). Since they increase renal water excretion without affecting

renal electrolyte loss, they are aquaretic. There are two types of V2-R antagonists: selective (V2-R specific) and non-selective (V2- and V1a-R antagonism) **[39]**.

Based on the degree of hyponatremia, the existence of symptoms, and associated illnesses, postoperative SIADH is managed. The basis of therapy is fluid restriction, with salt administration on occasion. Serial salt and fluid output monitoring allows for outpatient treatment for the majority of patients **[40]**.

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