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Review article

Diabetes insipidus: Vasopressin deficiency. . .

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ABSTRACT

Diabetes insipidus is a disorder characterized by hypo-osmotic polyuria secondary to abnormal synthesis, regulation, or renal action of antidiuretic hormone. Recently, an expert group, with the support of patient associations, proposed that diabetes insipidus be renamed to avoid confusion with diabetes mellitus. The most common form of diabetes insipidus is secondary to a dysfunction of the neurohypophysis (central diabetes insipidus) and would be therefore named 'vasopressin deficiency'. The rarer form, which is linked to renal vasopressin resistance (nephrogenic diabetes insipidus), would then be named 'vasopressin resistance'. The etiology of diabetes insipidus is sometimes clear, in the case of a neurohypophyseal cause (tumoral or infiltrative damage) or a renal origin, but in some cases diabetes insipidus can be difficult to distinguish from primary polydipsia, which is characterized by consumption of excessive quantities of water without any abnormality in regulation or action of antidiuretic hormone. Apart from patients' medical history, physical examination, and imaging of the hypothalamic-pituitary region, functional tests such as water deprivation or stimulation of copeptin by hyperosmolarity (induced by infusion of hypertonic saline) can be proposed in order to distinguish between these different etiologies. The treatment of diabetes insipidus depends on the underlying etiology, and in the case of a central etiology, is based on the administration of desmopressin which improves patient symptoms but does not always result in an optimal quality of life. The cause of this altered quality of life may be oxytocin deficiency, oxytocin being also secreted from the neurohypophysis, though this has not been fully established. The possibility of a new test using stimulation of oxytocin to identify alterations in oxytocin synthesis is of interest and would allow confirmation of a deficiency in those patients presenting with diabetes insipidus linked to neurohypophyseal dysfunction.

1. Introduction

Diabetes insipidus (DI) is a disorder characterized by hypo-osmotic polyuria greater than 50 ml/kg bodyweight, accompanied by compensatory polydipsia that is often greater than 3L per day. DI is secondary to abnormal synthesis, regulation, or renal action of antidiuretic hormone, ADH (or arginine vasopressin, AVP) [1,2]. The most common form of DI, central diabetes insipidus, results from central dysfunction of the neurohypophysis and parvocellular and magnocellular hypothalamic neurons. Nephrogenic diabetes insipidus is a rarer form of DI, linked to resistance to the renal action of ADH. In both cases, there is a resultant fluid imbalance due to a deficiency in free water reabsorption in the renal collecting ducts (Fig. 1).

Congenital DI is rare and caused by genetic abnormalities that affect ADH synthesis (*AVP, WFS1* and *PCSK1* genes). Acquired central mechanisms underlying DI are linked to the destruction of the posterior pituitary, due to tumoral, infiltrative, traumatic or vascular causes. Hereditary nephrogenic DI is linked to mutations in the target receptors of ADH (*AVPR2* and *AQP2* gene), while the acquired forms are often iatrogenic (*e.g.* lithium treatment) or linked to infiltrative diseases.

2. Changing the nomenclature

An expert group has recently proposed substituting the term 'diabetes insipidus' for a term that is more representative of the pathophysiology of the disease, with the aim of avoiding confusion between diabetes mellitus and diabetes insipidus [3]. The

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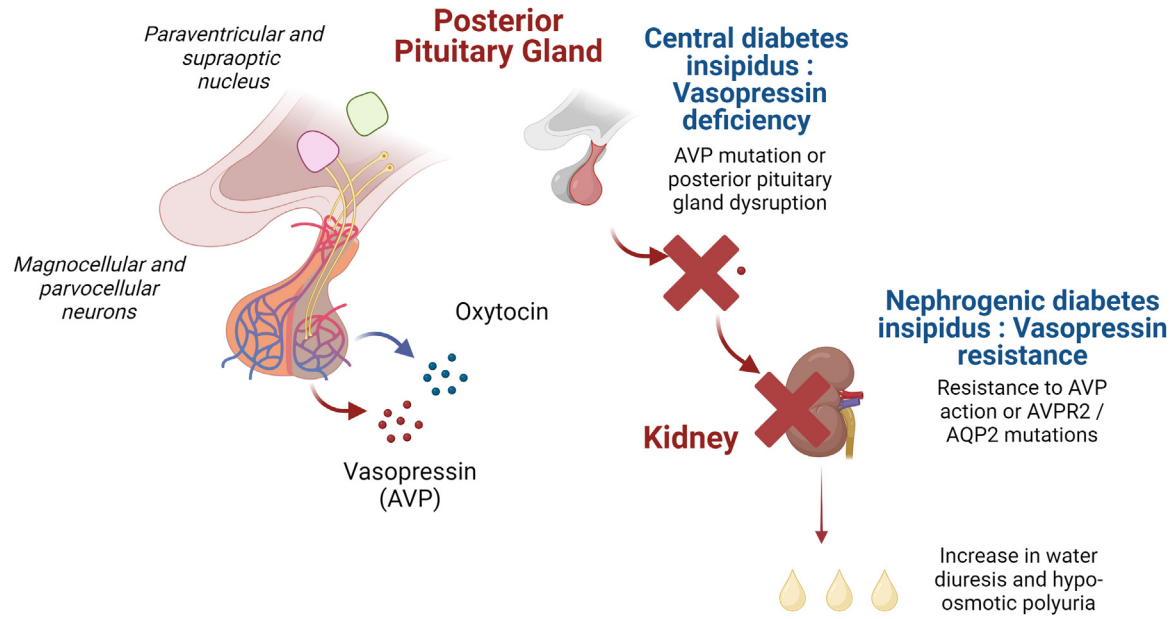

Fig. 1. Diagrammatic representation of ADH (vasopressin) synthesis in the posterior pituitary and its renal action on free water reabsorption. Central diabetes insipidus, or vasopressin deficiency, is characterized by hypo-osmotic polyuria secondary to dysfunction in synthesis or regulation of antidiuretic hormone (ADH or arginine vasopressin, AVP). Nephrogenic diabetes insipidus is secondary to renal resistance to the ADH receptor (AVPR2). In both cases, there is a resultant fluid imbalance linked to a defect in reabsorption of free water from renal collecting tubules. Figure created with Biorender.com.

term 'diabetes' means to 'pass across' in Greek and dates from the first description of a polyuric-polydipsic syndrome by Demetrius of Apamea (1st or 2nd centuries BC) [3,4]. Dr William Cullen was then the first to make a distinction between the different forms of polyuria, and Dr Johann Peter Frank, in the 18th century, added the adjective 'insipid' to describe the hypo-osmotic character of the urine, however, the common term 'diabetes' was retained [4]. A new nomenclature has been proposed with the aim of better reflecting the pathophysiology of DI, using the term 'vasopressin deficiency' to represent central diabetes insipidus and the term 'vasopressin resistance' to represent nephrogenic DI. Apart from being a better reflection of the underlying pathophysiology, the use of the new term would avoid any confusion between diabetes insipidus and diabetes mellitus. In fact, several dramatic cases of incorrect management of patients with DI during hospitalization, resulting in treatment delay or errors in treatment, have been reported, with these being attributed to confusion concerning the two different diseases by medical and paramedical personnel [5].

A recent online survey of patients allowed the size of this problem to be better appreciated. It showed that a quarter of patients included in this survey had already experienced difficulties in accessing desmopressin and water during hospitalization, including an absence of intravenous compensation in patients who were fasting being reported in 40% of cases [6]. Additionally, this survey appeared to confirm the necessity of a new nomenclature, since 85% of patients were in favor of this change and preferred removal of the term 'diabetes' from the name.

Though interesting, this change in terminology is perhaps not sufficient to improve the management of this rare condition by physicians who may have little experience of the disease.

3. Diagnostic tools

A diagnosis of DI should be suspected where there is polydipsia associated with hypo-osmotic polyuria (osmolality below 300 mOsm/kg) [7]. Once identified, the etiology of the hypo-osmotic polyuria should then be confirmed for an appropriate therapy to be proposed. Confirmation of a central origin is sometimes simple when hypotonic polyuria is accompanied by an obvious involvement of the posterior pituitary resulting from a tumor or infiltrative pathology that is visible on imaging. In the absence of a visible tumor or infiltrative pathology, lack of the posterior pituitary bright spot on T1 image sequences of the posterior pituitary can direct the diagnosis towards central diabetes insipidus and make a peripheral cause or primary polydipsia unlikely. However, according to one study, this hyperintensity, corresponding to storage of ADH in neurons of the neurohypophysis, is absent in only 70% of MRI imaging results of patients presenting with central DI, and is also absent in almost 40% of patients presenting with primary polydipsia [8]. However, it should be noted that this study did not use a stringent MRI procedure (in particular with saturation of fatty tissue to accurately distinguish between posterior pituitary and fatty tissue of the back of the sella turcica) to optimally analyse the neurohypophysis. In fact, few dedicated radiological studies have been carried out to examine the presence or absence of this hyperintensity and thus these numbers could be an under-estimate [8,9]. Lastly, the reduced intensity and size of the signal seen physiologically in patients older than 80 years could equally affect the interpretation of images [10].

Thus, with doubts regarding imaging, the diagnosis of DI and elimination of differential diagnoses can be difficult. Though the diagnosis of nephrogenic DI has become more straightforward thanks to new diagnostic tools such as the copeptin assay (discussed below) [8], the distinction between primary polydipsia and DI is not always clear [2].

In some cases, patients with DI can spontaneously display urine hypo-osmolarity with increased basal sodium levels, higher than 147 mmol/L, and plasma osmolality higher than 295 mOsm/kg. This biochemical profile allows the diagnosis of primary polydipsia to be excluded. In fact, primary polydipsia is more associated with low sodium levels, below 135 mmol/L and a plasma osmolality of less than 280 mOsm/kg (Fig. 2) [11]. However, some patients fall into none of these typical biochemical categories and thus justify the use of stimulation tests.

The current 'gold-standard' is the response to indirect stimulation of ADH by a water deprivation test. This test allows the measurement, indirectly, of ADH activity using its capacity to

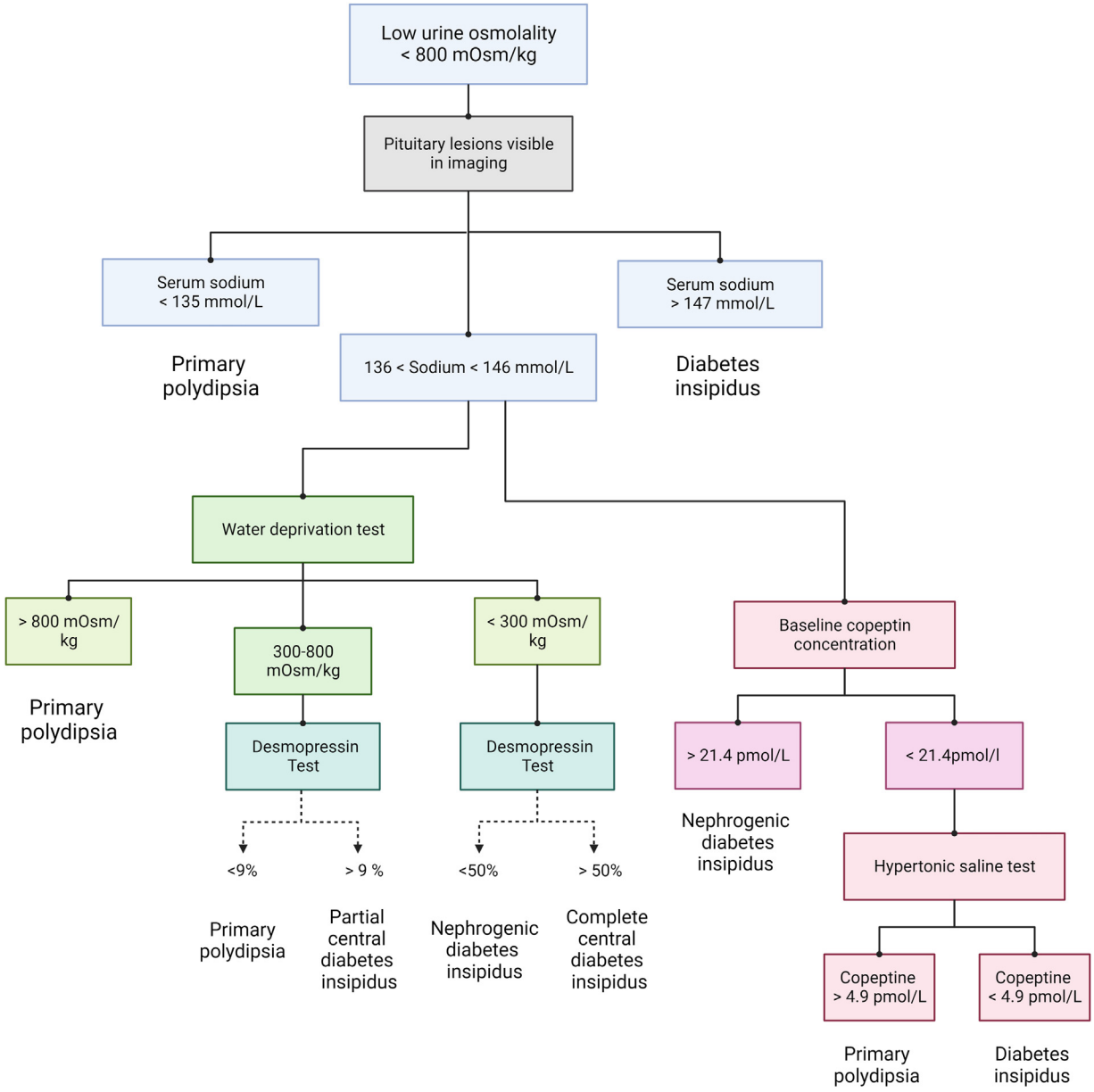

Fig. 2. Algorithm for etiologic diagnosis in the case of primary polydipsia. After confirmation of hypo-osmotic polyuria in the setting of a polyuric-polydipsic syndrome, the use of plasma sodium and plasma osmolarity can direct the etiological diagnosis. If these values are normal, a stimulation test by water restriction followed by hypertonic saline stimulation can be used to distinguish the different etiologies of DI. Figure adapted from [1,2], created with Biorender.com.

reduce renal excretion of free water and thus increase urine osmolarity in response to dehydration induced by restricted access to water over at least 8 hours, with plasma osmolality being measured every 4 hours and urine osmolarity every 2 hours [12]. This test must then be followed by administration of 2 μg desmopressin.

A urine osmolarity of over 800 mOsm/kg during water deprivation is in favor of a diagnosis of primary polydipsia without abnormailty in the synthesis or action of ADH. Conversely, the persistence of urine hypo-osmolarity, less than 300 mOsm/kg, shows a completely altered action of ADH. The profile of the response to administration of desmopressin allows the central form of DI (response of urine osmolarity greater than 50%) to be distinguished from the nephrogenic form of DI (response of urine osmolarity less than 50%) (Fig. 2) [12].

Though the first results on the use of this test were interesting and the test is currently the 'gold-standard' for the diagnosis of DI [7,12], it is important to note that the test is more effective for cases of complete central forms of DI. In this case, the diagnostic precision is close to 70%, with 86% sensitivity and 70% specificity [7,8,13]. However, the diagnostic performance of the test appears lower for distinguishing partial forms of DI in primary polydipsia, dropping to 40%, with 54% sensitivity and 88% specificity [7,8,13].

There are multiple causes for this poor diagnostic performance including the test duration, and the need for medical supervision during the test, aimed at combatting the extreme thirst that can distort the test results. Lastly, a lack of effect of desmopressin administration at the end of the test can be secondary to a down-regulation of renal ADH receptor (*AVPR2*) expression as a result of chronic polyuria [14]. A direct assay of vasopressin after stimulation by water deprivation could represent an interesting alternative [15], since vasopressin concentrations are, even before water restriction, very high in patients with nephrogenic DI (due to resistance to AVP), and are increased to a lesser degree by dehydration in patients with primary polydipsia, while they are unchanged in

patients with central DI [15–18]. However, the thresholds allowing these different etiologies to be distinguished require the sensitivity of the vasopressin assay to be around 0.3 pmol/L, a sensitivity which is only obtained with 'artisanal' radioimmunoassays that are specifically prepared for this purpose, but not by the majority of currently-available commercial immunoassays where the detection threshold is around 1 pmol/L. Lastly, the short half-life of vasopressin and its pre-analytical instability make it difficult to use in current practice. The diagnostic performance of this test (water deprivation with AVP assay) in current use is therefore limited, and its diagnostic precision is not higher than 40% [13].

In view of the inherent limitations in these diagnostic tests, the copeptin assay has been proposed as a new marker of vasopressin secretion. Copeptin is a glycoprotein from the C-terminal part of the AVP pro-hormone and is thus a stable reflection of endogenous vasopressin. A basal copeptin level of greater than 21.4 pmol/L favors a diagnosis of nephrogenic DI [8]. The use of copeptin allows primary polydipsia to be distinguished from DI after hyperosmotic stimulation. The copeptin assay provides better results after perfusion with hypertonic solution than it does after fluid restriction [8]. Hyperosmotic stimulation is carried out by intravenous perfusion with a bolus of 250 ml of 3% hypertonic saline solution followed by continuous infusion at a rate of 0.15 ml/kg/min. A concentration of copeptin that stays below the threshold of 4.2 pmol/L, with a sodium level of greater than 150 mmol/L, gives a diagnostic precision of 96.5% for diagnosing complete central DI (and 95.2% for diagnosing partial central DI) (Fig. 2) [1,2,8]. However, use of the copeptin assay, stimulated by intravenous hyperosmotic perfusion, is complicated due to the necessity of reaching a sodium level of greater than 150 mmol/L, putting the patient at risk of metabolic complications, and thus requiring close monitoring of plasma sodium levels, something that is difficult to do in current practice. In view of these difficulties, other copeptin stimulation tests have been proposed. Stimulation using arginine has been proposed but with inferior results regarding diagnostic accuracy compared to hypertonic infusion [19]. Finally, glucagon appear to be an interesting alternative, offering diagnostic efficacies of greater than 90% but this method still need to be validated in prospective studies [20,21].

In conclusion, several tests can be proposed to exclude the diagnosis of primary polydipsia and retain the diagnosis of DI, which will enable appropriate therapies to be proposed. However, the combination of imaging of the hypothalamic-pituitary region and a water deprivation test remains the first choice in current practice. The use of copeptin is a promising alternative for the most difficult cases.

4. Management of central diabetes insipidus

The management of central DI is based on replacement of ADH with desmopressin. This analog has a longer half-life than endogenous vasopressin and acts directly on the renal AVPR2 receptor. It can be administered orally (sublingual), intranasally or subcutaneously, and results in restoration of free water reabsorption. The dose used varies between patients and should be adjusted to the symptoms. The most frequently-reported undesirable effect is the appearance of hyponatremia due to over-dosage and excessive reabsorption of free water. In a retrospective analysis of biochemical data in ambulatory patients over 10 years, carried out on 137 patients with DI, severe hyponatremia was noted in 15% of patients, and less severe hyponatremia in 27% of patients [22]. The occurrence of hyponatremia can be avoided by voluntary omission of desmopressin administration until polyuria occurs, allowing excess free water to be excreted. This strategy, which has not been properly evaluated by clinical studies, leads to a reduction in episodes of hyponatremia. In a survey on more than 1000 patients, 67% of patients spontaneously omitted a dose of desmopressin and episodes of hyponatremia were reported in 17% of these patients, while in the 33% of patients who did not skip doses, 29% reported episodes of hyponatremia (OR = 0,44 [0,31,0,64]) [6].

Despite appropriate replacement therapy, in a large survey, 64% of patients still reported an altered quality of life after the diagnosis of DI, and this was in spite of appropriate management and independently of the presence of an anterior pituitary deficiency [6]. Patients also reported increased anxiety, sleep disturbances and mood problems. These problems represented conditions which were being monitored and treated in 11% of cases. Interestingly, 52% of patients also reported problems with social interactions and a reduced ability to experience joy/pleasure, which impacted on their physical and psychological well-being in around 40% of cases. Apart from the effects on quality of life linked to having a chronic disease, a somatic cause could be suggested since there is a possible reduction in oxytocin secretion, oxytocin also being secreted from the posterior pituitary [23]. In addition to its effects on reproduction and metabolism [24,25], oxytocin is implicated in other processes, including some involving the central nervous system (CNS). The action of oxytocin in the CNS involves a number of targets, notably the hippocampus and the amygdala (Fig. 3) [26]. Oxytocin and oxytocin signaling are implicated in the regulation of social behaviors, such as attachment, social interactions, confidence and anxiety, response to fear, and empathy [27,28].

The group of neurocognitive manifestations found in some patients who have posterior pituitary dysfunction, could thus be included with oxytocin deficiency associated with ADH deficiency, secondary to posterior pituitary dysfunction. Surgical treatment of craniopharyngioma is a good example. It can lead to metabolic and neurocognitive problems, which have led to oxytocin deficiency being suspected in this population. Assays of basal oxytocin levels have given contradictory results from one series of patients to another [29–32]. As for a number of hormone deficiencies, insufficiency can sometimes only be diagnosed after a stimulation test, but studies examining the variation of oxytocin levels after stimulation tests (physical exercise, macimorelin, arginine or hypertonic saline) have equally given disappointing results. Even though some variations in oxytocin concentrations have been found to be statistically significant, overlap of the oxytocin levels between the various groups has limited the interpretation and use of these tests in current practice [32–34]. It appears that patients with posterior pituitary dysfunction show altered recognition of emotions compared with healthy controls and compared to patients with an isolated anterior pituitary deficiency [29]. The administration of oxytocin, even though little-studied in this context, can improve some performance on neurocognitive tests [35]. In order to confirm the involvement of oxytocin in these neurocognitive manifestations and the existence of a real oxytocin deficiency in these pathologies, a discriminating stimulation test is needed.

A stimulation test using MDMA (2,4-MethyleneDioxy MethAmphetamine), a psychoactive drug that is the principal ingredient in 'ecstasy', has been proposed. In fact, MDMA favors empathy, attachment, sociability and a sense of well-being. These neuropsychological manifestations are in some degree mediated by oxytocin, and unlike other pyschoactive substances (e.g. amphetamines or LSD), administration of MDMA is accompanied by a significant increase in plasma oxytocin concentrations [36,37]. Thus, in a pilot study, stimulation by administration of 100 mg of MDMA led to an 82% increase in oxytocin concentrations in healthy subjects, while showing no increase in subjects with neurohypophyseal dysfunction and central DI (n = 15 subjects/group) [38]. This absence of an increase in oxytocin was accompanied by an attenuation of the positive effects classically observed in healthy

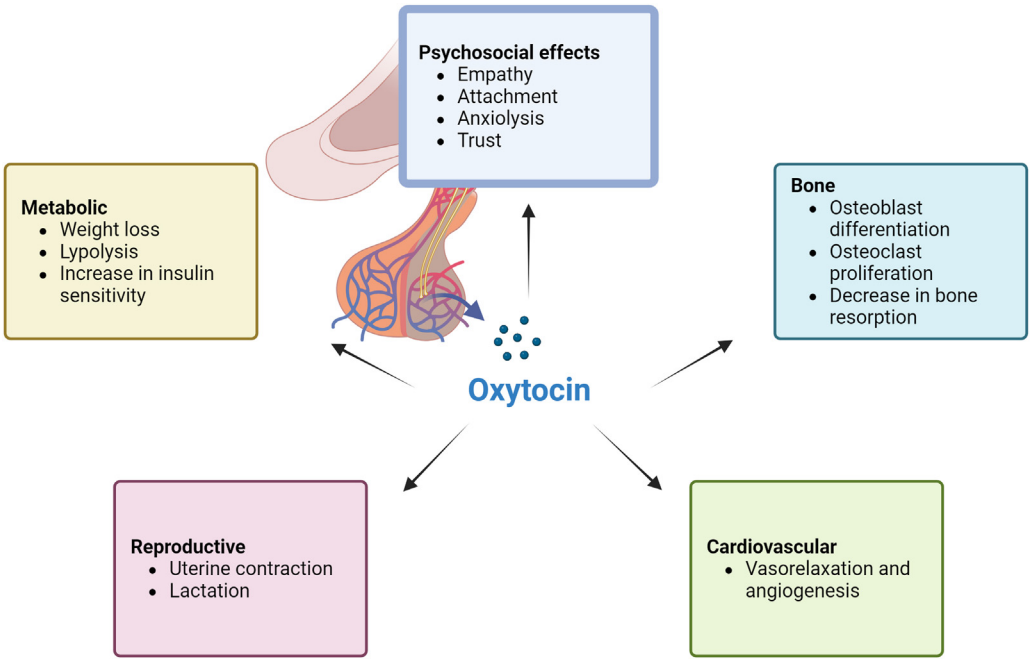

Fig. 3. Different actions of oxytocin. Dendritic release of oxytocin has an effect in the central nervous system via local diffusion that can reach different regions in the brain. In addition, parvocellular neurons project to various regions of the brain including the amygdala, hippocampus, striatum, suprachiasmatic nucleus, bed nucleus of the stria terminalis and the cerebral trunk, where oxytocin can act as a neuromodulator or neurotransmitter. Figure adapted from [23,26], created with Biorender.com.

subjects after MDMA administration. These preliminary results appear to point to an oxytocin deficiency in patients with known neurohypophyseal dysfunction, and thus suggest an interest in use of a replacement therapy.

Treatment using oxytocin is generally via intravenous injection in the setting of inducing labor in pregnancy and the treatment of post-partum hemorrhage, while intranasal delivery has also been used in other indications with satisfactory tolerance [23,39]. In patients operated for craniopharyngioma, administration of oxytocin did not show strong effects, though studies were performed on a small number of patients. However, administration of oxytocin did result in an improvement in some sociocognitive characteristics when it was used for other indications, such as Prader-Willi syndrome [35,39]. Currently, two studies are underway, in Switzerland and the United States, which will examine the effects of oxytocin substitution in patients presenting with vasopressin deficiency (Clinical Trials NCT06036004 and NCT04789148).

Oxytocin deficiency in patients with DI is likely and thus certain socio-cognitive consequences of the pathology could be integrated with this somatic component, though published data are thus far insufficient to reach a firm conclusion. The prospect of a new oxytocin stimulation test is therefore interesting but needs to be validated in a larger number of subjects and in further studies.

5. Conclusion

Central diabetes insipidus (vasopressin deficiency) remains a rare clinical entity that can be difficult to diagnose. Dynamic tests to confirm the diagnosis can be required in order to eliminate differential diagnoses, mainly primary polydipsia. For this purpose, the reference test remains water deprivation. The use of the copeptin assay after stimulation with hypertonic saline perfusion allows the diagnosis to be refined is some difficult cases, but does expose patients to metabolic risks. Some promising alternative tests are now in the process of being validated and may provide new tools for the diagnosis of diabetes insipidus.

The clinical management of central DI is straightforward thanks to the use of desmopressin, but does require patient education to ensure their autonomy and also to avoid the appearance of complications, particularly in the care setting. Lastly, the place of oxytocin in this disease remains to be demonstrated but does offer interesting future perspectives.

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Author contributions

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Disclosure of interest

The authors declare that they have no competing interest.

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