Endocrine (2018) 62:292–298
https://doi.org/10.1007/s12020-018-1680-7

MINI REVIEW

Water intake keeps type 2 diabetes away? Focus on copeptin

Giovanna Muscogiuri[1] · Luigi Barrea[1] · Giuseppe Annunziata[1] · Martina Vecchiarini[2] · Francesco Orio[3] · Carolina Di Somma[4] · Annamaria Colao[1] · Silvia Savastano[1]

Received: 23 January 2018 / Accepted: 9 July 2018 / Published online: 19 July 2018

Abstract

Introduction In both diabetic subjects and animal models high levels of vasopressin (AVP) have beendetected. The relationship between AVP and glucose metabolism is mediated through several direct andindirect effects and most of them are still unknown.

Methods We have reviewed 100 manuscripts retrieved from Cochrane Library, Embase and Pubmeddatabases in order to highlight a possible relationship between copeptin and type 2 diabetes and to provideinsights on the molecular mechanism that could explain this association.

Results and conclusions AVP potentiates CRH action at pituitary level resulting in an increased ACTH secretion and in turn in an increased cortisol secretion that escapes the negative feedback loop. Further, AVP regulates insulin and glucagon secretion through V1b receptor and promotes hepatic glycogenolysis and gluconeogenesis through V1a receptor. In addition to worsen glucose metabolism, AVP has been reported to have a role in the pathogenesis of diabetic complications such as cardiovascular diseases, kidney and ocular complications. Due to the very low concentration of AVP in the blood, the small size and poor stability, the assay of AVP is very difficult to perform. Thus, copeptin, the stable C-terminal portion of the prepro-vasopressin peptide has been identified as an easier assay to be measured and that mirrors AVP activity. Although there are promising evidence that copeptin could be involved in the pathogenesis of type 2 diabetes, further studies need to demonstrate the importance of copeptin as clinical marker to predict glucose metabolism derangements.

Keywords Copeptin · Type 2 diabetes · Water · Vasopressin · Insulin resistance · Insulin secretion

Abbreviation

AVP	Arginine vasopressin
PREVEN-D	Prevention of renal and vascular end-stage disease
HIF-1	Hypoxia-inducible factor-1
CAD	Coronary artery disease
HF	Heart failure
SGK1	Serum and glucocorticoid inducible kinase 1
SGLT1	Sodium glucose transporter 1

Introduction

High water intake has been reported to have a beneficial effect in the management of diabetes [1, 2]. However, recent evidence showed that the mechanisms are much more complex and that hide a hormonal milieu. The main actor has been identified in arginine vasopressin (AVP), also termed antidiuretic hormone. AVP is produced in hypothalamus and released by posterior pituitary (neurohypophysis) in a condition of high plasma osmolality, low plasma volume and low blood pressure [3]. Besides preserving the fluid homeostasis, AVP has a role in stimulating hepatic gluconeogenesis and glycogenolysis and the secretion of glucagon and insulin dependent on the extracellular glucose concentration [4–6]. Indeed it has been reported that mice knock out for V1a and/or V1b vasopressin receptors could have metabolic disorders related to glucose metabolism ranging from insulin hypersensitivity and increased glucose tolerance till insulin resistance, obesity, and impaired glucose tolerance [7–9]. Increased AVP levels have been detected in people with diabetes [10] and these

✉ Giovanna Muscogiuri
giovanna.muscogiuri@gmail.com

[1] Dipartimento di Medicina Clinica e Chirurgia, Sezione di Endocrinologia, Università Federico II di Napoli, Naples, Italy

[2] Medicina e Chirurgia, Università Federico II di Napoli, Naples, Italy

[3] Dipartimento di Scienze Motorie e del Benessere, Università Partenope di Napoli, Naples, Italy

[4] IRCCS SDN, Napoli Via Gianturco 113, 80143 Naples, Italy

data were confirmed in animal studies in which spontaneous or streptozotocin-induced diabetes has been associated to an increase of AVP [11, 12]. However, the main limit of the use of AVP as marker to predict impairment of glucose metabolism is represented by its very low concentration in the blood, the small size and poor stability that makes difficult the assay. This issue prompted the researchers to find an alternative marker that could be representative of AVP levels. Copeptin, the stable C-terminal portion of the prepro-vasopressin peptide has been identified as an easier assay that was shown to tightly correlated with AVP levels and mostly with hydration status (a mirror of AVP activity) [13, 14]. Interestingly copeptin has been found to be a marker associated to the risk of developing insulin resistance, metabolic syndrome, and type 2 diabetes [15, 16]. This could be due to AVP that could stimulate the V1b receptors that are located in the anterior pituitary and that contribute to the stimulation of ACTH secretion [17]. As well known, an overstimulation of ACTH secretion results in an increased secretion of cortisol that at high levels has a detrimental effect on glucose metabolism. Besides this indirect mechanism, it has been found a direct action of AVP on liver through V1b receptor having an effect on hepatic glycogenolysis and gluconeogenesis [5, 6]. Thus, the aim of this manuscript is to provide an overview of observational studies that have investigated the association of copeptin with type 2 diabetes and to review the molecular evidence that could explain this link.

Search strategy

A comprehensive search of Cochrane Library, Embase and Pubmed was conducted using using at least one of the following terms: obesity and/or type 2 diabetes and/or water and/or glucagon and/or copeptin and/or vasopressin. Reference lists of included studies and review papers were screened for relevance and hand searching of relevant reports done. Articles in the English language were the only ones eligible for inclusion in the manuscript.

Epidemiological evidence

The association of copeptin with the risk of developing type 2 diabetes has been investigated in the Malmo Diet and Cancer Study showing that there was an independent association between copeptin with fasting insulin and blood glucose [18]. These data were not confirmed in the FINRISK97 Study that conversely reported the lack of an association of copeptin with diabetes after adjustment for metabolic risk factors [19]. However, the Prevention of Renal and Vascular End-stage Disease (PREVEND) suggested a sex differences in the association between copeptin and diabetes, that was detected in women but not in men. A sex-related association between copeptin and diabetes was also found by The British Regional Heart Study that 13-years followed up about 3500 patients with no diabetes. Conversely the PREVEND study, The British Regional Heart Study showed an association between the risk of incident diabetes and copeptin only in old men and this risk persisted after adjustment for several diabetes risk factors including metabolic risk factors and C-reactive protein but not in women [20]. This discrepancy could be explained by the fact that The British Regional Heart Study was performed in elderly subjects in which the hypothalamic-pituitary-adrenal axis reactivity could be more responsive to the stimulation of AVP than younger adults [21]. This may explain the positive association between copeptin and diabetes in elderly men (The British Regional Heart Study) but not in young men (the PREVEND study). The lack of a sex-related analysis of the data might also be a bias that could explain the different results coming from The Malmo Diet and Cancer Study and The FINRISK97 study. Indeed, The Malmo Diet and Cancer Study from a Swedish population-based cohort included 4472 participants with 174 incident cases who were older (mean age of 58 years) and included around 60% women [22]. In the The Malmo Diet and Cancer Study study, including a higher number of women who had comparable copeptin levels to those of PREVEND study, a potential sex-related effect on the association of copeptin with diabetes risk was not investigated. The FINRISK97 study from a cohort of 7827 participants with 417 incident cases included similar numbers of women and men. In the FINRISK97 study, a higher but non-significant risk of type 2 diabetes per one standard deviation increase in copeptin has been detected in the total and sex-stratified population. In this latter study, the range of copeptin levels was smaller than in The Malmo Diet and Cancer Study and PREVEND study, for both women and men. Theoretically, this smaller range may also lead to overlap of copeptin levels between individuals with and without type 2 diabetes in the latter study, which could represent a limit for the predictive value of copeptin. The sex-related difference of the association between copeptin and type 2 diabetes lead to hypothesize that there could be differences between men and women in responsiveness to the vasopressin system due to a higher sensitivity of both AVP V1a and V1b receptors to of AVP in women than in men [23, 24]. The gender effect on AVP secretion was suggested in 1979 by Skowsky et al. [25] that reported an increase in plasma AVP 2 weeks after male rats were castrated; this phenomenon was reversed by testosterone administration. The estrogen treatment resulted, instead, in an increase of AVP [25]. Thus, these findings suggested that androgens inhibit and estrogen stimulates

AVP secretion. Opposite results were found by Crofton et al that reported a decrease in AVP following castration of male rats and an increase in AVP with testosterone treatment [26]. The same authors observed no changes in AVP levels in female rats treated with estrogen treatment alone while they detected a decrease when the animals were treated with a combined administration of estrogen and progesterone [26]. A human study reported a midcycle increases in AVP in women even if this was not confirmed in other studies [26–30]. In obese women affected by (Polycystic Ovary Syndrome) PCOS an increase in copeptin levels has been reported compared to lean women. Moreover, copeptin levels were related to (Body Mass Index) BMI, (Waist hip ratio) WHR, hirsutism score, total testosterone, and HOMA-IR, thus suggesting that copeptin could be a predictive factor of the severity of the syndrome and of the cardiovascular risk in this pathological setting [31].

Although the results of the above reported studies were controversial, they suggested the effects of gonadal steroids on AVP secretion and action, in fact gonadal steroids have been reported not only to act on afferents to the AVP neuron but also on the AVP neuron itself and on AVP target tissues [26–29]. Altered vasopressin metabolism, interaction between insulin and vasopressin, both of which act in the renal collecting duct, and the reabsorption of more hypotonic fluid due to slower stomach emptying have been also proposed as possible underlying mechanism [32, 33]. Moreover, the association between hyperglycemia and high copeptin levels has been hypothesized to have a genetic background. In the Data from Epidemiological Study on the Insulin Resistance Syndrome study the CC genotype of rs6084264, the TT genotype of rs2282018, the C-allele of rs2770381, and the CC genotype of rs1410713 have been identified to be associated with incidence of hyperglycemia and high copeptin levels [34]. Although several evidence supported a role for copeptin as a marker of diabetes risk, the current findings were too scarce to prove that there is an actual causal association between elevated copeptin concentration and diabetes risk. Copeptin has been also identified as a predictive marker of diabetic complications (35–47). In addition, type 2 diabetes is often complicated by hepatic steatosis and low AVP levels have been demonstrated to have a protective effect to hepatic steatosis and this seems to be due to the reduced expression of hepatic lipogenic genes. However, this association has been detected in animal studies but needs to be confirmed in human studies [35]. Wang et al. [36] investigated the role of copeptin as predictor marker of functional outcome in patients with ischemic stroke and type 2 diabetes. High levels of copeptin have been associated to a worsen functional outcome and a higher risk of mortality at 3 months follow-up after the event. A prognostic importance of copeptin has been identified in the context of myocardial infarction in type 2 diabetes. Copeptin predicted major cardiovascular events, cardiovascular mortality and total death in people with diabetes followed over a decade for major cardiovascular events in unadjusted analysis [37]. Similar results were reached in the DIGAMI 2 trial that followed up about 400 people with diabetes for 2.5 years in which copeptin has been reported to predict cardiovascular events after myocardial infarction in diabetic subjects [38]. Further, in diabetic individuals, copeptin predicted the combined end point coronary artery disease (CAD), heart failure (HF), and death after adjustment for conventional risk factors [39]. However copeptin is not only a marker of overt cardiovascular disease but also a marker of early cardiovascular derangements. Indeed copeptin has been found to be higher in people with diabetes without known cardiovascular diseases but with peripheral arterial disease [40]. An association of V1-vascular vasopressin receptor gene microsatellite polymorphisms in human essential hypertension has been investigated in humans. Analysis of these polymorphisms were performed in 79 hypertensive and 86 normotensive subjects. No linkage was found in hypertensive patients, thus suggesting that molecular variants of the V(1)R gene are not involved in unselected forms of essential hypertension [41].

Besides macrovascular complications, the role of predictive marker of copeptin has been also highlighted in the context of microvascular complications. In a cross-sectional analysis, copeptin was strongly related to diabetic kidney disease and coronary atherosclerosis in adults with type 1 diabetes [42]. In addition, in patients with diabetes, a higher baseline copeptin concentration is significantly associated with kidney function decline during follow-up [43]. Pikkemaat et al. [44] investigated the association of copeptin with development of chronic kidney disease in people with diabetes. People with newly diagnosed type 2 diabetes in 1996–1998 were followed up after about 10 years. Elevated copeptin levels at the baseline predicted the risk of developing chronic kidney disease 10 years later. Similar results were previously found in the the DIABHYCAR trial in which diabetic subjects with albuminuria were followed up for 6 years. Plasma copeptin concentration was tightly associated with the risk of severe renal outcomes (doubling of plasma creatinine concentration and/or end-stage renal disease) in patients with type 2 diabetes and albuminuria. This association was independent of relevant covariates such as age, duration of diabetes, blood pressure, and baseline levels of HbA1c, urinary albumin excretion, and (Estimated glomerular filtration rate) eGFR [45]. As evidenced that AVP plays a direct role in the pathophysiology of kidney dysfunction, DDAVP (a selective vasopressin V2 receptor agonist) was infused in healthy subjects and in normal rats [46] resulting in an increased urinary albumin excretion (UAE). Furthermore, treatment with a selective

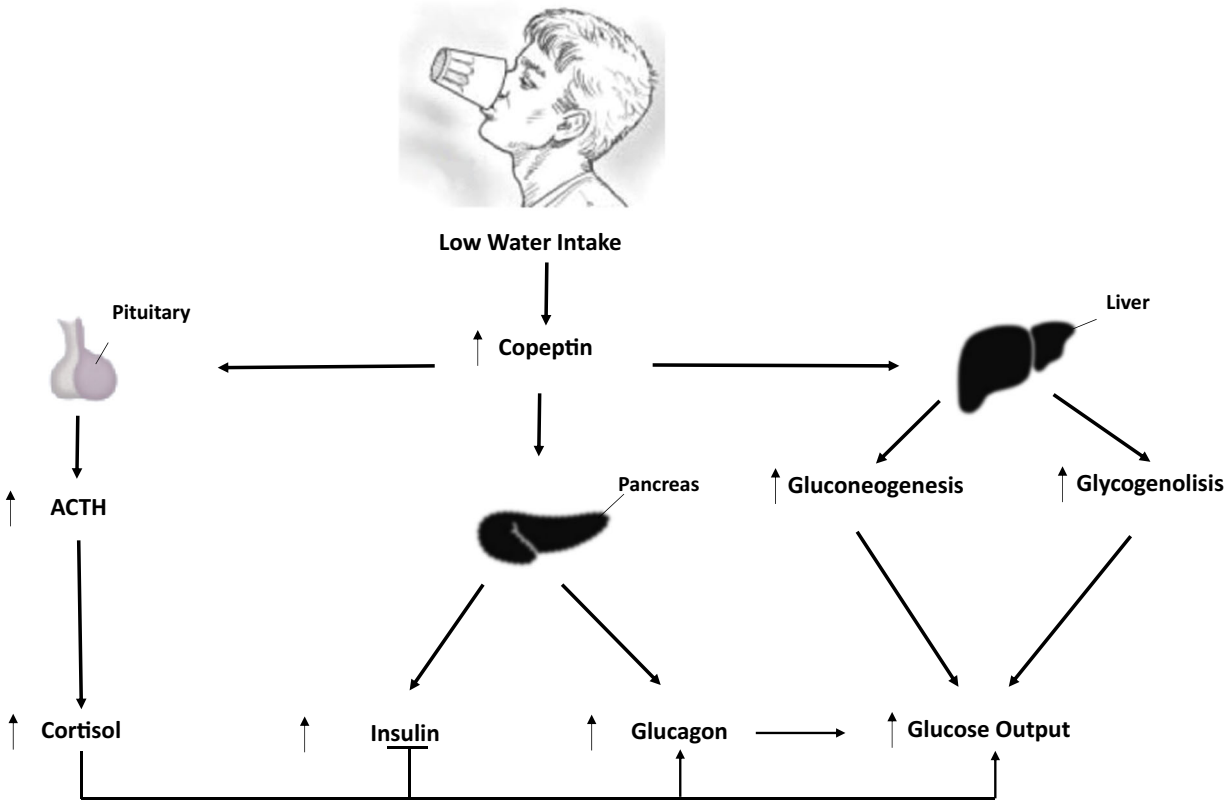

Fig. 1 Mechanism of action of copeptin. Low water intake stimulates the secretion of copeptin that in turn potentiates CRH action resulting in an increased ACTH and cortisol secretion. Copeptin acts on liver stimulating glycogenolysis and gluconeogenesis. Further, pancreas is another target of copeptin, which contributes to the regulation of insulin and glucagon secretion

vasopressin V2 receptor antagonist prevented the increase in albuminuria in rats with streptozotocin-induced diabetes [47].

Basic evidence

A low water intake (< 1.2 litres/day of total fluid intake) results in an increased plasma AVP in order to preserve fluid homeostasis [48]. AVP may bind V1b receptor at pituitary level stimulating ACTH secretion as well as enhancing the effect of CRH [8, 49–51]. This may results in a Cushing's Syndrome like increase in the secretion of cortisol. Interestingly, the AVP stimulated secretion of cortisol lacks a negative feed-back loop, which may initiate a vicious circle of cortisol release [51]. In fact, low drinkers have been reported to have significantly higher plasma cortisol levels [48]. The pleiotropic effects of glucocorticoids include the upregulation of the serum and glucocorticoid inducible kinase 1 (SGK1) that stimulates the intestinal Na + coupled glucose transporter (SGLT)-1 [52]. The increased activity of this carrier plays an important role in the development of obesity; an increased post-prandial glucose absorption due to the upregulation of SGLT-1 represents a powerful stimulus to insulin secretion and subsequent fat deposition [53, 54]. SGK1 has also a direct action on adipocyte differentiation and adipogenesis [55]. In addition to these pituitary effects, AVP regulates insulin and glucagon secretion through V1b receptor and promotes hepatic glycogenolysis and gluconeogenesis through V1a receptor [4–6] (Fig. 1). Moreover, cortisol potentiates glucagon-stimulated gluconeogenesis in an additive manner, thus contributing to increase glucose output [56]. Further, hyperosmolality, which is a consequence of the low water intake and at the same time a stimulus for AVP secretion, could per sè contribute to the onset of insulin resistance [57]. Although AVP has been reported to stimulate insulin secretion [58, 59], this beneficial effect on glucose metabolism may not be able to counteract the several negative effects related to the increased cortisol secretion, glycogenolysis, and gluconeogenesis, thus resulting in a final hyperglycemic effect of AVP. Despite it has been demonstrated these direct effect of AVP on target organs that are involved in glucose homeostasis, the contribution of AVP to glucose metabolism seems to be rather complex. Mice with selective deletion of V1a R developed elevated glucose levels, predisposition for obesity and diabetes, low triglycerides levels, and enhanced lipid

metabolism [7, 60], whereas mice lacking V1b R showed a phenotype characterized by low glucose levels and increased insulin sensitivity [61]. In humans, the rs1042615 polymorphism of the *V1aR* gene was associated with obesity and metabolic complications such type 2 diabetes and low triglycerides resembling the phenotype of the mouse with V1aR deletion [62, 63]. In addition, AVP promotes water reabsorption through stimulation of V2 receptors, thus increased levels of AVP limit glucose-induced water loss in patients with diabetes [64]. Increased levels of AVP may, however, have long-term deleterious renal and cardiovascular effects [36–39, 43–46]. In animal studies it has been demonstrated that AVP causes hyperfiltration, albuminuria, and renal hypertrophy in diabetes [45, 65]. In fact, drinking water or treatment with V2 receptor antagonist in rats with renal failure has been reported to have a renal protective effect both in diabetic and non-diabetic condition [46, 66, 67]. The involvement of AVP in diabetic cardiovascular complications could be explained by the fact that high concentrations of plasma AVP has been demonstrated to bind V1a receptors preferentially [68], which results in coronary vasoconstriction [69], increasing afterload, ventricular stress, and cardiac hypertrophy [70, 71].

Conclusions

In summary, a large number of studies identified high levels of copeptin as a novel risk factor for the development of diabetes. The most likely pathophysiological mechanism is insufficient fluid intake that leads to increased AVP secretion, which in turn stimulates the secretion of ACTH and cortisol resembling a Cushing syndrome like-phenotype. Thus, encouraging water intake, which is linked to the decrease of copeptin appears a broadly, applicable, safe, cost-effective, and easy-to implement primary preventive intervention, especially in patients at high risk of developing type 2 diabetes. Strategy intervention to implement water intake should be evaluated in future large randomized controlled clinical trials in order to investigate if the assumption of adequate intake of water could represent a preventive factor to metabolic diseases. Further, there is need to identify the optimal water intake that should be recommended as prevention/treatment of the different metabolic diseases, adjusted for gender and age.

Author contributions G.M. wrote the manuscript, L.G., G.A., M.V., and F.O. helped to draft the manuscript, C.D.S. and A.C. reviewed the manuscript, and S.S. conceived the manuscript

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. R. Roussel, L. Fezeu, N. Bouby, B. Balkau, O. Lantieri, F. Alhenc-Gelas, M. Marre, L. Bankir, D.E.S.I.R. Study Group Low water intake and risk for new-onset hyperglycemia. Diabetes Care **34**, 2551–2554 (2011)
2. C. Taveau, C. Chollet, L. Waeckel, D. Desposito, D.G. Bichet, M. F. Arthus, C. Magnan, E. Philippe, V. Paradis, F. Foufelle, I. Hainault, S. Enhorning, G. Velho, R. Roussel, L. Bankir, O. Melander, N. Bouby, Vasopressin and hydration play a major role in the development of glucose intolerance and hepatic steatosis in obese rats. Diabetologia **58**, 1081–1090 (2015)
3. G.L. Robertson, Thirst and vasopressin function in normal and disordered states of water balance. J. Lab. Clin. Med. **101**, 351–371 (1983)
4. D.A. Hems, L.M. Rodrigues, P.D. Whitton, Rapid stimulation by vasopressin, oxytocin and angiotensin II of glycogen degradation in hepatocyte suspensions. Biochem. J. **172**, 311–317 (1978)
5. P.D. Whitton, L.M. Rodrigues, D.A. Hems, Stimulation by vasopressin, angiotensin and oxytocin of gluconeogenesis in hepatocyte suspension. Biochem. J. **176**, 893–898 (1978)
6. E.A. Abu-Basha, S. Yibchok-Anun, W.H. Hsu, Glucose dependency of arginine vasopressin-induced insulin and glucagon release from the perfused rat pancreas. Metabolism **51**, 1184–1190 (2002)
7. T. Aoyagi, J. Birumachi, M. Hiroyama, Y. Fujiwara, A. Sanbe, J. Yamauchi, A. Tanoue, Alteration of glucose homeostasis in V1a vasopressin receptor-deficient mice. Endocrinology **148**, 2075–2084 (2007)
8. Y. Fujiwara, M. Hiroyama, A. Sanbe, T. Aoyagi, J. Birumachi, J. Yamauchi, G. Tsujimoto, A. Tanoue, Insulin hypersensitivity in mice lacking the V1b vasopressin receptor. J. Physiol. **584**, 235–244 (2007)
9. K. Nakamura, T. Aoyagi, M. Hiroyama, S. Kusakawa, R. Mizutani, A. Sanbe, J. Yamauchi, M. Kamohara, K. Momose, A. Tanoue, Both V(1A) and V(1B) vasopressin receptors deficiency result in impaired glucose tolerance. Eur. J. Pharmacol. **613**, 182–188 (2009)
10. R.L. Zerbe, F. Vinicor, G.L. Robertson, Plasma vasopressin in uncontrolled diabetes mellitus. Diabetes **28**, 503–508 (1979)
11. D.P. Brooks, D.F. Nutting, J.T. Crofton, L. Share, Vasopressin in rats with genetic and streptozocin-induced diabetes. Diabetes **38**, 54–57 (1989)
12. S.S. Yi, I.K. Hwang, Y.N. Kim, I.Y. Kim, S.I. Pak, I.S. Lee, J.K. Seong, Y.S. Yoon, Enhanced expression of arginine vasopressin (Avp) in the hypothalamic paraventricular and supraoptic nuclei of type 2 diabetic rats. Neurochem. Res. **33**, 833–841 (2008)
13. N.G. Morgenthaler, J. Struck, C. Alonso, A. Bergmann, Assay for the measurement of copeptin, a stable peptide derived from the precursor of vasopressin. Clin. Chem. **52**, 112–119 (2006)
14. S. Balanescu, P. Kopp, M.B. Gaskill, N.G. Morgenthaler, C. Schindler, J. Rutishauser, Correlation of plasma copeptin and vasopressin concentration in hypo-, iso-, and hyperosmolar states. J. Clin. Endocrinol. Metab. **96**, 1046–1052 (2011)
15. U. Saleem, M. Khaleghi, N.G. Morgenthaler, A. Bergmann, J. Struck, T.H. Mosley Jr., I.J. Kullo, Plasma carboxy-terminal provasopressin (copeptin): a novel marker of insulin resistance and metabolic syndrome. J. Clin. Endocrinol. Metab. **94**, 2558–2564 (2009)
16. F.X. Zhu, H.L. Wu, K.S. Tu, J.X. Chen, M. Zhang, C. Shi, Serum levels of copeptin are associated with type 2 diabetes and diabetic complications in Chinese population. J. Diabetes Complicat. **30**, 1566–1570 (2016)

17. O. Melander, Vasopressin, from regulator to disease predictor for diabetes and cardiometabolic risk. Ann. Nutr. Metab. **68**(Suppl 2), 24–28 (2016)
18. S. Enhörning, T.J. Wang, P.M. Nilsson, P. Almgren, B. Hedblad, G. Berglund, J. Struck, N.G. Morgenthaler, A. Bergmann, E. Lindholm, L. Groop, V. Lyssenko, M. Orho-Melander, C. Newton-Cheh, O. Melander, Plasma copeptin and the risk of diabetes mellitus. Circulation **121**, 2102–2108 (2010)
19. V. Salomaa, A. Havulinna, O. Saarela, T. Zeller, P. Jousilahti, A. Jula, T. Muenzel, A. Aromaa, A. Evans, K. Kuulasmaa, S. Blankenberg, Thirty-one novel biomarkers as predictors for clinically incident diabetes. PLoS ONE **5**, e10100 (2010)
20. S.G. Wannamethee, P. Welsh, O. Papacosta, L. Lennon, P.H. Whincup, N. Sattar, Copeptin, insulin resistance, and risk of incident diabetes in older men. J. Clin. Endocrinol. Metab. **100**, 3332–3339 (2015)
21. J.D. Veldhuis, A. Sharma, F. Roelfsema, Age-dependent and gender-dependent regulation of hypothalamic-adrenocorticotropic-adrenal axis. Endocrinol. Metab. Clin. North. Am. **42**, 201–225 (2013)
22. A. Abbasi, E. Corpeleijn, E. Meijer, D. Postmus, R.T. Gansevoort, R.O. Gans, J. Struck, H.L. Hillege, R.P. Stolk, G. Navis, S.J. Bakker, Sex differences in the association between plasma copeptin and incident type 2 diabetes: the Prevention of Renal and Vascular Endstage Disease (PREVEND) study. Diabetologia **55**, 1963–1970 (2012)
23. N.S. Stachenfeld, A.E. Splenser, W.L. Calzone, M.P. Taylor, D.L. Keefe, Sex differences in osmotic regulation of AVP and renal sodium handling. J. Appl. Physiol. **91**, 1893–1901 (1985)
24. E. Kajantie, D.I. Phillips, The effects of sex and hormonal status on the physiological response to acute psychosocial stress. Psychoneuroendocrinology **31**, 151–178 (2006)
25. W.R. Skowsky, L. Swan, P. Smith, Effects of sex steroid hormones on arginine vasopressin in intact and castrated male and female rats. Endocrinology **104**, 105–108 (1979)
26. J.T. Crofton, P.G. Baer, L. Share, D.P. Brooks, Vasopressin release in male and female rats: Effects of gonadectomy and treatment with gonadal steroid hormones. Endocrinology **117**, 1195–1200 (1985)
27. N.S. Stachenfeld, L. DiPietro, C.A. Kokoszka, C. Silva, D.L. Keefe, E.R. Nadel, Physiological variability of fluid-regulation hormones in young women. J. Appl. Physiol. **86**, 1092–1096 (1999)
28. W.F. Trigoso, J.M. Wesly, D.L. Meranda, Y. Shenker, Vasopressin and atrial natriuretic hormone response to hypertonic saline during the follicular and luteal phases of the menstrual cycle. Hum. Reprod. **11**, 2392–2395 (1996)
29. T.J. Vokes, N.M. Weiss, J. Schreiber, M.B. Gaskill, G.L. Robertson, Osmoregulation of thirst and vasopressin during normal menstrual cycle. Am. J. Physiol. **254**, R641–R647 (1988)
30. T.D.M. Williams, A. Edwards, K.M. Fairhall, I.C.A.F. Robinson, G.M. McGarrick, S.L. Lightman, Influence of endogenous and exogenous oestrogens on posterior pituitary secretion in women. Clin. Endocrinol. (Oxf.) **22**, 589–596 (1985)
31. M.I. Taskin, E. Bulbul, E. Adali, A.A. Hismiogulları, U. Inceboz, Circulating levels of obestatin and copeptin in obese and nonobese women with polycystic ovary syndrome. Eur. J. Obstet. Gynecol. Reprod. Biol. **189**, 19–23 (2015)
32. L. Bankir, P. Bardoux, M. Ahloulay, Vasopressin and diabetes mellitus. Nephron **87**, 8–18 (2001)
33. M. Bustamante, U. Hasler, O. Kotova, A.V. Chibalin, D. Mordasini, M. Rousselot, A. Vandewalle, P.Y. Martin, E. Féraille, Insulin potentiates AVP-induced AQP2 expression in cultured renal collecting duct principal cells. Am. J. Physiol. Ren. Physiol. **288**, F334–F344 (2005)
34. R. Roussel, R. El Boustany, N. Bouby, L. Potier, F. Fumeron, K. Mohammedi, B. Balkau, J. Tichet, L. Bankir, M. Marre, G. Velho, Plasma copeptin, AVP gene variants, and incidence of type 2 diabetes in a cohort from the community. J. Clin. Endocrinol. Metab. **101**, 2432–2439 (2016)
35. C. Taveau, C. Chollet, L. Waeckel, D. Desposito, D.G. Bichet, M. F. Arthus, C. Magnan, E. Philippe, V. Paradis, F. Foufelle, I. Hainault, S. Enhorning, G. Velho, R. Roussel, L. Bankir, O. Melander, N. Bouby, Vasopressin and hydration play a major role in the development of glucose intolerance and hepatic steatosis in obese rats. Diabetologia **58**, 1081–1090 (2015)
36. C.B. Wang, M. Zong, S.Q. Lu, Z. Tian, Plasma copeptin and functional outcome in patients with ischemic stroke and type 2 diabetes. J. Diabetes Complicat. **30**, 1532–1536 (2016)
37. M.I. Smaradottir, V. Ritsinger, V. Gyberg, A. Norhammar, P. Näsman, L.G. Mellbin, Copeptin in patients with acute myocardial infarction and newly detected glucose abnormalities–A marker of increased stress susceptibility? A report from the Glucose in Acute Myocardial Infarction cohort. Diab. Vasc. Dis. Res. **14**, 69–76 (2017)
38. L.G. Mellbin, L. Rydén, K. Brismar, N.G. Morgenthaler, J. Ohrvik, S.B. Catrina, Copeptin, IGFBP-1, and cardiovascular prognosis in patients with type 2 diabetes and acute myocardial infarction: a report from the DIGAMI 2 trial. Diabetes Care **33**, 1604–1606 (2010)
39. S. Enhörning, B. Hedblad, P.M. Nilsson, G. Engström, O. Melander, Copeptin is an independent predictor of diabetic heart disease and death. Am. Heart J. **169**, 546–556 (2015)
40. D. Bar-Shalom, M.K. Poulsen, L.M. Rasmussen, A.C. Diederichsen, N.P. Sand, J.E. Henriksen, M. Nybo, Plasma copeptin as marker of cardiovascular disease in asymptomatic type 2 diabetes patients. Diab. Vasc. Dis. Res. **11**, 448–450 (2014)
41. M. Thibonnier, M.K. Graves, M.S. Wagner, N. Chatelain, F. Soubrier, P. Corvol, H.F. Willard, X. Jeunemaitre, Study of V(1)-vascular vasopressin receptor gene microsatellite polymorphisms in human essential hypertension. J. Mol. Cell. Cardiol. **32**, 557–564 (2000)
42. P. Bjornstad, D.M. Maahs, T. Jensen, M.A. Lanaspa, R.J. Johnson, M. Rewers, J.K. Snell-Bergeon, Elevated copeptin is associated with atherosclerosis and diabetic kidney disease in adults with type 1 diabetes. J. Diabetes Complicat. **30**, 1093–1096 (2016)
43. W.E. Boertien, I.J. Riphagen, I. Drion, A. Alkhalaf, S.J. Bakker, K.H. Groenier, R.T. Gansevoort, Copeptin, a surrogate marker for arginine vasopressin, is associated with declining glomerular filtration in patients with diabetes mellitus (ZODIAC-33). Diabetologia **56**, 1680–1688 (2013)
44. M. Pikkemaat, O. Melander, K. Bengtsson Boström, Association between copeptin and declining glomerular filtration rate in people with newly diagnosed diabetes. The Skaraborg Diabetes Register. J. Diabetes Complicat. **26**, 1062–1065 (2015)
45. G. Velho, R. El Boustany, G. Lefèvre, K. Mohammedi, F. Fumeron, L. Potier, L. Bankir, N. Bouby, S. Hadjadj, M. Marre, R. Roussel, Plasma copeptin and renal outcomes in patients with type 2 diabetes and albuminuria. Diabetes Care **36**, 3639–3645 (2013)
46. P. Bardoux, D.G. Bichet, H. Martin, Y. Gallois, M. Marre, M.F. Arthus, M. Lonergan, N. Ruel, N. Bouby, L. Bankir, Vasopressin increases urinary albumin excretion in rats and humans: involvement of V2 receptors and the renin-angiotensin system. Nephrol. Dial. Transplant. **18**, 497–506 (2003)
47. P. Bardoux, P. Bruneval, D. heudes, N. Bouby, L. Bankir, Diabetes-induced albuminuria: role of antidiuretic hormone as a revealed by chronic V2 receptor antagonism in rats. Nephrol. Dial. Transplant. **18**, 1755–1763 (2003)

48. E. Perrier, S. Vergne, A. Klein, M. Poupin, P. Rondeau, L. Le Bellego, L.E. Armstrong, F. Lang, J. Stookey, I. Tack, Hydration biomarkers in free-living adults with different levels of habitual fluid consumption. Br. J. Nutr. **109**, 1678–1687 (2013)
49. A. Tanoue, S. Ito, K. Honda, S. Oshikawa, Y. Kitagawa, T.A. Koshimizu, T. Mori, G. Tsujimoto, The vasopressin V1b receptor critically regulates hypothalamic-pituitary-adrenal axis activity under both stress and resting conditions. J. Clin. Invest. **113**, 302–309 (2004)
50. I. Tatsuno, D. Uchida, T. Tanaka, H. Koide, A. Shigeta, T. Ichikawa, H. Sasano, Y. Saito, Vasopressin responsiveness of subclinical Cushing's syndrome due to ACTH-independent macronodular adrenocortical hyperplasia. Clin. Endocrinol. (Oxf.). **60**, 192–200 (2004)
51. J. Hensen, O. Hader, V. Bähr, W. Oelkers, Effects of incremental infusions of arginine vasopressin on adrenocorticotropin and cortisol secretion in man. J. Clin. Endocrinol. Metab. **66**, 668–671 (1988)
52. C. Rabadan-Diehl, G. Aguilera, Glucocorticoids increase vasopressin V1b receptor coupling to phospholipase C. Endocrinology **139**, 3220–3226 (1998)
53. G.L. Firestone, J.R. Giampaolo, B.A. O'Keeffe, Stimulus-dependent regulation of serum and glucocorticoid inducible protein kinase (SGK) transcription, subcellular localization and enzymatic activity. Cell. Physiol. Biochem. **13**, 1–12 (2003)
54. F. Lang, A. Görlach, V. Vallon, Targeting SGK1 in diabetes. Expert Opin. Ther. Targets **13**, 1303–1311 (2009)
55. F. Lang, C. Böhmer, M. Palmada, G. Seebohm, N. Strutz-Seebohm, V. Vallon, (Patho)physiological significance of the serum- and glucocorticoid-inducible kinase isoform. Physiol. Rev. **86**, 1151–1178 (2006)
56. N. Di Pietro, V. Panel, S. Hayes, A. Bagattin, S. Meruvu, A. Pandolfi, L. Hugendubler, G. Fejes-Tóth, A. Naray-Fejes-Tóth, E. Mueller, Serum-and glucocorticoid-inducible kinase 1 (SGK1) regulates adipocyte differentiation via forkhead box O1. Mol. Endocrinol. **24**, 370–380 (2010)
57. L. Lecavalier, G. Bolli, J. Gerich, Glucagon-cortisol interactions on glucose turnover and lactate gluconeogenesis in normal humans. Am. J. Physiol. **258**(4 Pt 1), E569–E575 (1990)
58. P.R. Bratusch-Marrain, R.A. DeFronzo, Impairment of insulin-mediated glucose metabolism by hyperosmolality in man. Diabetes **32**, 1028–1034 (1983)
59. A.M. O'Carroll, G.M. Howell, E.M. Roberts, S.J. Lolait, Vasopressin potentiates corticotropin-releasing hormone-induced insulin release from mouse pancreatic beta-cells. J. Endocrinol. **197**, 231–239 (2008)
60. M. Lu, S.P. Soltoff, G.C. Yaney, A.E. Boyd 3rd, The mechanisms underlying the glucose dependence of arginine vasopressin-induced insulin secretion in beta-cells. Endocrinology **132**, 2141–2148 (1993)
61. M. Hiroyama, T. Aoyagi, Y. Fujiwara, J. Birumachi, Y. Shigematsu, K. Kiwaki, R. Tasaki, F. Endo, A. Tanoue, Hypermetabolism of fat in V1a vasopressin receptor knockout mice. Mol. Endocrinol. **21**, 247–258 (2007)
62. Y. Fujiwara, M. Hiroyama, A. Sanbe, J. Yamauchi, G. Tsujimoto, A. Tanoue, Mutual regulation of vasopressin- and oxytocin-induced glucagon secretion in V1b vasopressin receptor knockout mice. J. Endocrinol. **192**, 361–369 (2007)
63. S. Masuki, M. Mori, Y. Tabara, T. Miki, A. Sakurai, M. Morikawa, K. Miyagawa, K. Higuchi, H. Nose, Shinshu University Genetic Research Consortium Vasopressin V1a receptor polymorphism and interval walking training effects in middle-aged and older people. Hypertension **55**, 747–754 (2010)
64. S. Enhörning, M. Leosdottir, P. Wallström, B. Gullberg, G. Berglund, E. Wirfält, O. Melander, Relation between human vasopressin 1a gene variance, fat intake, and diabetes. Am. J. Clin. Nutr. **89**, 400–406 (2009)
65. L. Bankir, S. Fernandes, P. Bardoux, N. Bouby, D.G. Bichet, Vasopressin-V2 receptor stimulation reduces sodium excretion in healthy humans. J. Am. Soc. Nephrol. **16**, 1920–1928 (2005)
66. P. Bardoux, H. Martin, M. Ahloulay, F. Schmitt, N. Bouby, M.M. Trinh-Trang-Tan, L. Bankir, Vasopressin contributes to hyperfiltration, albuminuria, and renal hypertrophy in diabetes mellitus: study in vasopressin-deficient Brattleboro rats. Proc. Natl Acad. Sci. USA **96**, 10397–10402 (1999)
67. N. Bouby, S. Bachmann, D. Bichet, L. Bankir, Effects of water on the progression of chronic renal failure in the 5/6 nephrectomized rat. Am. J. Physiol. **258**, F979–F979 (1990)
68. T. Sugiura, A. Yamauchi, H. Kitamura, Y. Matsuoka, M. Horio, E. Imai, M. Hori, High water intake ameliorates tubulointerstitial injury in rats with subtotal nephrectomy: possible role of TGF-beta. Kidney Int. **55**, 1800–1810 (1999)
69. W. Fenske, C. Wanner, B. Allolio, C. Drechsler, K. Blouin, J. Lilienthal, V. Krane, German Diabetes, Dialysis Study Investigators Copeptin levels associate with cardiovascular events in patients with ESRD and type 2 diabetes mellitus. J. Am. Soc. Nephrol. **22**, 782–790 (2011)
70. M.F. Maturi, S.E. Martin, D. Markle, M. Maxwell, C.R. Burruss, E. Speir, R. Greene, Y.M. Ro, D. Vitale, M.V. Green, Coronary vasoconstriction induced by vasopressin. Production of 470 myocardial ischemia in dods by constriction of nondiseased small vessels. Circulation **83**, 2111–2121 (1991)
71. J. Fukuzawa, T. Haneda, K. Kikuchi, Arginine vasopressin increases the rate of protein synthesis in isolated perfused adult rat heart via the V1 receptor. Mol. Cell. Biochem. **195**, 93–98 (1999)