INTRODUCTION

Stress is defined as anything that throws the body out of homeostatic balance; for example an acute illness. Any stressor which activates the hypothalamo-pituitary-adrenal (HPA) axis leads to an increase in concentrations of the adrenal stress hormone, cortisol. One of the major hypothalamic stress hormones, which is stimulated by different stressors, is vasopressin (AVP). However, measurement of circulating AVP levels is challenging because it is released in a pulsatile pattern, it is unstable and is rapidly cleared from plasma. AVP derives from a larger precursor peptide (pre-provasopressin) along with copeptin which is released in an equimolar ratio to AVP and is more stable in the circulation and easy to determine. Copeptin levels were found to closely mirror the production of AVP ***(Katan et al., 2008)*.**

Copeptin, a peptide of 39 amino acids, is the C-terminal part of pro-AVP and is released together with AVP during processing of the precursor peptide .Copeptin and AVP are secreted from the neurohypophysis upon hemodynamic or osmotic stimuli). AVP is also involved in the endocrine stress response. Corticotropin-releasing hormone and AVP appear to have a synergistic effect, resulting in adrenocorticotropic hormone (ACTH) and cortisol release. High cortisol levels reflect a higher degree of stress, but are dependent on the integrity of the HPA-axis. Copeptin appears to be superior to cortisol in determination of the stress level, as cortisol is further downstream in the stress response, has a strong circadian rhythm and is also challenging to measure as a free hormone ***(Christian et al., 2012).***

In contrast to AVP and cortisol, copeptin is stable both in serum and plasma at room temperature and can be easily measured *ex vivo* as a 'shadow' fragment of AVP in the circulation ***(Struck et al., 2005; Morgenthaler et al., 2006),*** in manual or fully automated chemiluminescence assays. Copeptin results are available within one hour, which is crucial for any useful biomarker in the emergency department setting.

In stressful situations such as illness, the relationship between plasma osmolality and AVP is lost because AVP with corticotropin-releasing hormone (CRH) leads to the production of adrenocorticotropic hormone (ACTH) and cortisol. Serum cortisol is proportional to stress levels, and by reflecting stress levels, cortisol predicts prognostic outcome in different diseases. However, cortisol is influenced by strong circadian rhythm and its measurement as a free hormone is demanding. These characteristics of cortisol place copeptin as a more reliable hormone for determination of stress levels. Of note, even mild to moderate stress situations contribute to the copeptin release. In recent years copeptin has being studied as a diagnostic and prognostic biomarker in various diseases. Of mention are acute myocardial infarction, heart failure, acute exacerbation of chronic obstructive pulmonary disease, lower respiratory tract infections, acute dyspnea, sepsis, hemorrhagic and septic shock, diabetes mellitus, metabolic syndrome, hyponatremia, vasodilatory shock, diabetes insipidus, autosomal dominant polycystic kidney disease (ADPKD), intracerebral hemorrhage, ischemic stroke and traumatic brain injury ***(Lidijo and Kido, 2013).***

Patients with an unfavorable outcomes and nonsurvivors had significantly increased copeptin levels on admission ***(Katan et al., 2008).***

AIM OF THE WORK

In this Study we seek to determine Copeptin levels in patients presented to the medical emergency room and relate it to the outcome of hospitalization.

DEFINITION OF STRESS

'Stress' may be defined as any situation which tends to disturb the equilibrium between a living organism and its environment. In day-to-day life there are many stressful situations such as stress of work pressure, psychosocial stress and physical stresses due to trauma, surgery and various medical disorders ***(Salam and Reetu, 2011).***

"Stress" represents the effects of anything that seriously threatens homeostasis. The actual or perceived threat to an organism is referred to as the "stressor" and the response to the stressor is called the "stress response." Although stress responses evolved as adaptive processes, that severe, prolonged stress responses might lead to tissue damage and disease ***(Neil et al., 2008).***

Stress thus occurs when the body is exposed to a "stressor" which threatens homeostasis, and the "stress response" is the attempt of the body to counteract the stressor and re-establish homeostasis ***(Mary and Wand, 2012).***

Types of stress:

There are many different kinds of stress to consider: physical exercise, sleep deprivation, psychological stress, environmental stresses (e.g., heat, cold, high altitude, depth, etc.), trauma, and infection ***(Barry et al., 2014).***

A hallmark of the stress response is the activation of the autonomic nervous system and, most importantly, the hypothalamo-pituitary-adrenal (HPA) axis ***(McEwen, 2007).***

The hormonal cascade, initiated by a stressor through brain stem and limbic pathways, involves the release of corticotropin-releasing hormone (CRH) from the paraventricular nucleus of the hypothalamus. CRH stimulates the release of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland. Another hypothalamic hormone which is stimulated by different stressors is vasopressin (AVP) ***(Tanoue et al., 2004).***

AVP seems to exert a potentiating action on CRH and these two agents together are considered the main secretagogues of ACTH ***(Aguilera et al., 2008).***

ACTH, in turn, stimulates the adrenal cortex to produce cortisol. Many factors influence the pattern and magnitude of the response to a stressor, including the duration of the stressor exposure (acute versus chronic), the type of stressor (physical versus psychological), the stress context, age and gender. The variety of unique stress situations is not well served by a single mediator. Rather, the combination of multiple mediators (e.g., AVP, CRH, cortisol, noradrenalin, dopamine or serotonin) address the specific aspects of a stressor ***(Joels and Baram, 2009).***

The pathophysiology of the stress:

The following points are taken into account when explaining the pathophysiological stress that the emotional, behavioral and physiological components of a stress reaction are controlled by corticotropin-releasing hormone and stress response is affected by a combination of cytokines and glucocorticoids ***(Duval et al., 2010)(figure1).***

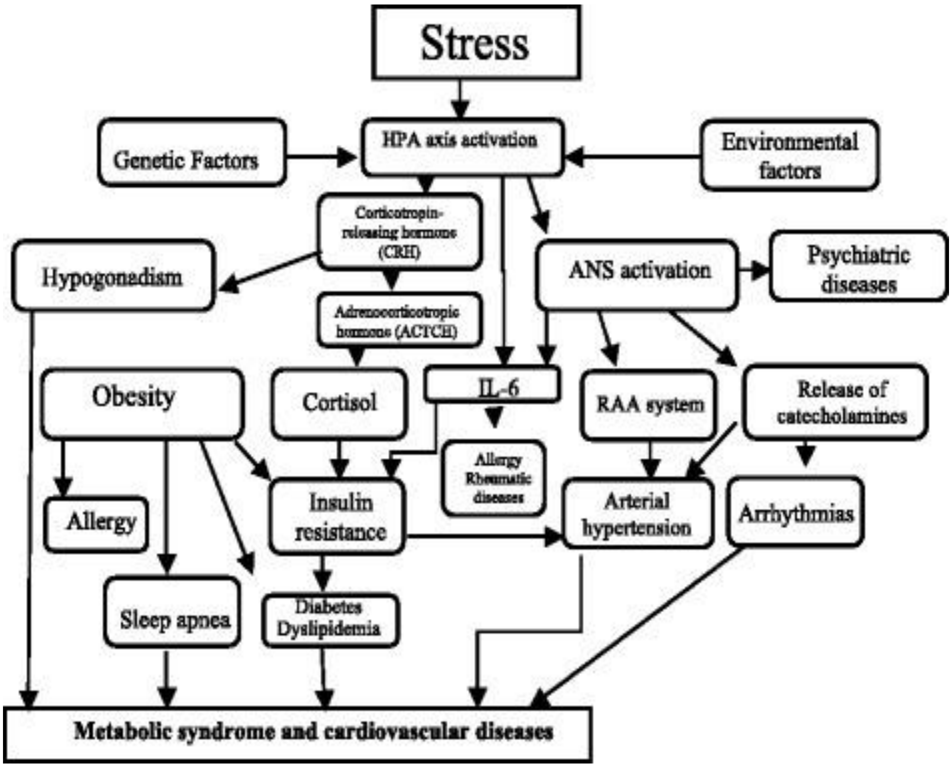

Figure 1: Stress and psychoneuroimmunoendocrinology axis. ANS: autonomic nervous system; HPA: hypothalamic-pituitary-adrenal; IL-6: interleukin 6; RAA: renin-angiotensin-aldosterone ***(Duval et al., 2010)***.

Acute illness as a part of stress:

Stress is defined as anything that throws the body out of homeostatic balance; for example an acute illness. Any stressor which activates the hypothalamo-pituitary-adrenal (HPA) axis leads to an increase in concentrations of the adrenal stress hormone, cortisol. One of the major hypothalamic stress hormones, which is stimulated by different stressors, is vasopressin (AVP) ***(Christ and Crain, 2010).***

Hormonal changes during acute illness:

In response to stress, the level of various hormones changes. Reactions to stress are associated with enhanced secretion of a number of hormones including cortisol, vasopressin, catecholamines, growth hormone and prolactin, the effect of which is to increase mobilization of energy sources and adapt the individual to its new circumstance ***(Herman et al., 2003).***

1- Cortisol:

Activation of the pituitary-adrenal axis is a prominent neuroendocrine response to stress, promoting survival. Stimulation of this axis results in hypothalamic secretion of corticotrophin-releasing factor (CRF). CRF then stimulates the pituitary to adrenocorticotropin (ACTH).

Plasma levels of these hormones can increase two- to fivefold during stress in humans ***(Salam and Reetu, 2011).***

The paraventricular nucleus of the hypothalamus is responsible for the integrated response to stress. Norepinephrine, serotonin and acetylcholine mediate much of the neurogenic stimulation of CRF production.

Effect of acute illness in plasma cortisone:Activate the hypothalamic-pituitary-adrenal (HPA) axis, resulting in corticosteroid release ***(Shishkina et al., 2012).***

2- *Vasopressin:*

Acute stress leads to rapid release of vasopressin from the paraventricular nucleus of the hypothalamus along with corticotrophin releasing hormone CRH. Vasopressin can stimulate secretion of ACTH from the pituitary by acting on the V1b receptor, potentiating the effect of CRH. During chronic stress with corticotroph responsiveness there is preferential expression of hypothalamic vasopressin over CRH ***(Aguilera et al., 2008).***

Stressful situations selectively activate multiple interconnected limbic and hypothalamic brain regions, which in turn ultimately innervate well-defined “premotor” centers that control specific behavioral, neuroendocrine, and autonomic reactions elicited by stress ***(Vianna et al., 2008).***

3- *Catecholamines:*

Stimulation of the pituitary-adrenal axis is associated with release of catecholamines. This leads to increased cardiac output, skeletal muscle blood flow, sodium retention, reduced intestinal motility, cutaneous vasoconstriction, increased glucose, bronchiolar dilatation and behavioral changes ***(Salam and Reetu, 2011).***

4- Growth hormone:

The growth hormone (GH) level is increased during acute physical stress. The level can increase up to two- to tenfold. Because of its insulin-antagonistic effect, growth hormone may enhance metabolic activity. In psychological stress, however, GH responses are rarely seen.

5- Prolactin:

Depending on the local regulatory environment at the time of stress, prolactin level can either increase or decrease.

Vasopressin and peptide histidine isoleucine may be involved in the secretion of prolactin during stress.

Metabolic responses to acute illness:

Metabolic responses to stress and physical activity are extremely complex, involving many interacting variables. These multiple factors include endocrinological, physiological (cardiovascular and neuromuscular), biochemical, nutritional, and central nervous system (CNS) components.Despite differences in the kinds of stress, body responses may have some broad or generalized commonalities, or in other situations, body responses to a given form of stress may be very specific. For example, acute-phase responses associated with various infections or trauma are rather stereotyped, whereas metabolic responses to exercise may be far less specific ***(Willner, 2005).***

STRUCTURE OF COPEPTIN

Copeptin is located in the C-terminal section of the arginine vasopressin (AVP) precursor (pro-AVP) and consists of 39 amino acid glycopeptides.

Evidence demonstrated that copeptin is released from pro-AVP together and equivalent with AVP ***(Dunser et al., 2003)*** *(figure2).*

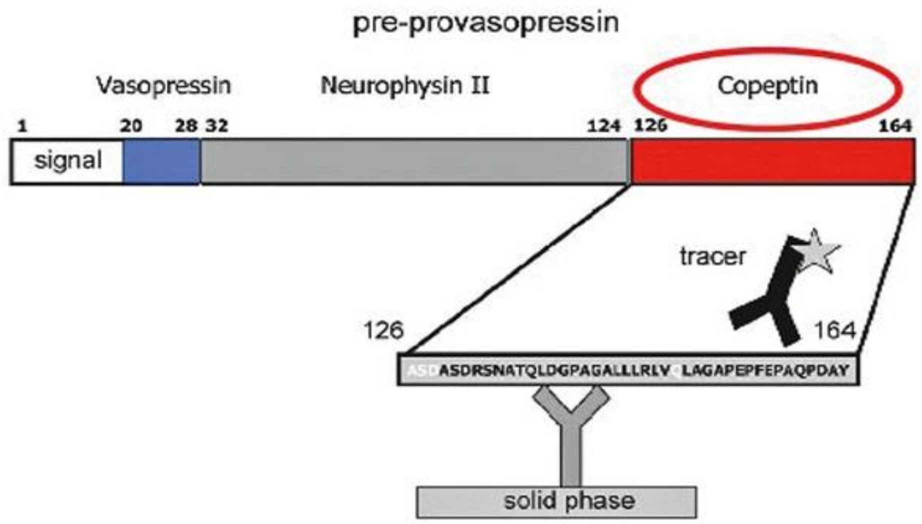

Figure 2: Preprovasopressin and Copeptin Together with AVP, copeptin is derived from a 164-amino acid precursor termed preprovasopressin, which consists of a signal peptide, AVP, neurophysin II and copeptin ***(Dunser et al., 2003)***.

Measurement of copeptin:

Normal values of copeptin in healthy persons range between 1.70–11.25 pmol/L ***(Hoorn et al., 2012).***

Renal function also influences copeptin concentration in healthy individuals ***(Lippi et al., 2012).***

In advanced and acute heart failure the rise in copeptin concentration goes from 20 pmol/L to 45 pmol/L. In terms of life threatening conditions, such as severe sepsis, septic shock, hemorrhagic shock, ischemic stroke and acute myocardial infarction, copeptin increases to concentrations above 100 pmol/L. On the opposite, copeptin decreases in patients with diabetes insipidus and other conditions associated with reduced AVP concentration ***(Lippi et al., 2012).*** It is still however unknown how copeptin is removed from the circulation. It is assumed that it is partially cleared through the kidneys because it is detectable in urine ***(Balanescu et al., 2011).***

Synthesis of AVP and Copeptin:

Copeptin and AVP are secreted from the neurohypophysis upon hemodynamic or osmotic stimuli ***(Figure 3).*** AVP is also involved in the endocrine stress response. Corticotropin-releasing hormone and AVP appear to have a synergistic effect, resulting in adrenocorticotropic hormone (ACTH) and cortisol release**.** High cortisol levels reflect a higher degree of stress, but are dependent on the integrity of the HPA-axis ***(Schuetz et al., 2006).***

Copeptin appears to be superior to cortisol in determination of the stress level, as cortisol is further downstream in the stress response, has a strong circadian rhythm and is also challenging to measure as a free hormone ***(Katan et al., 2008).***

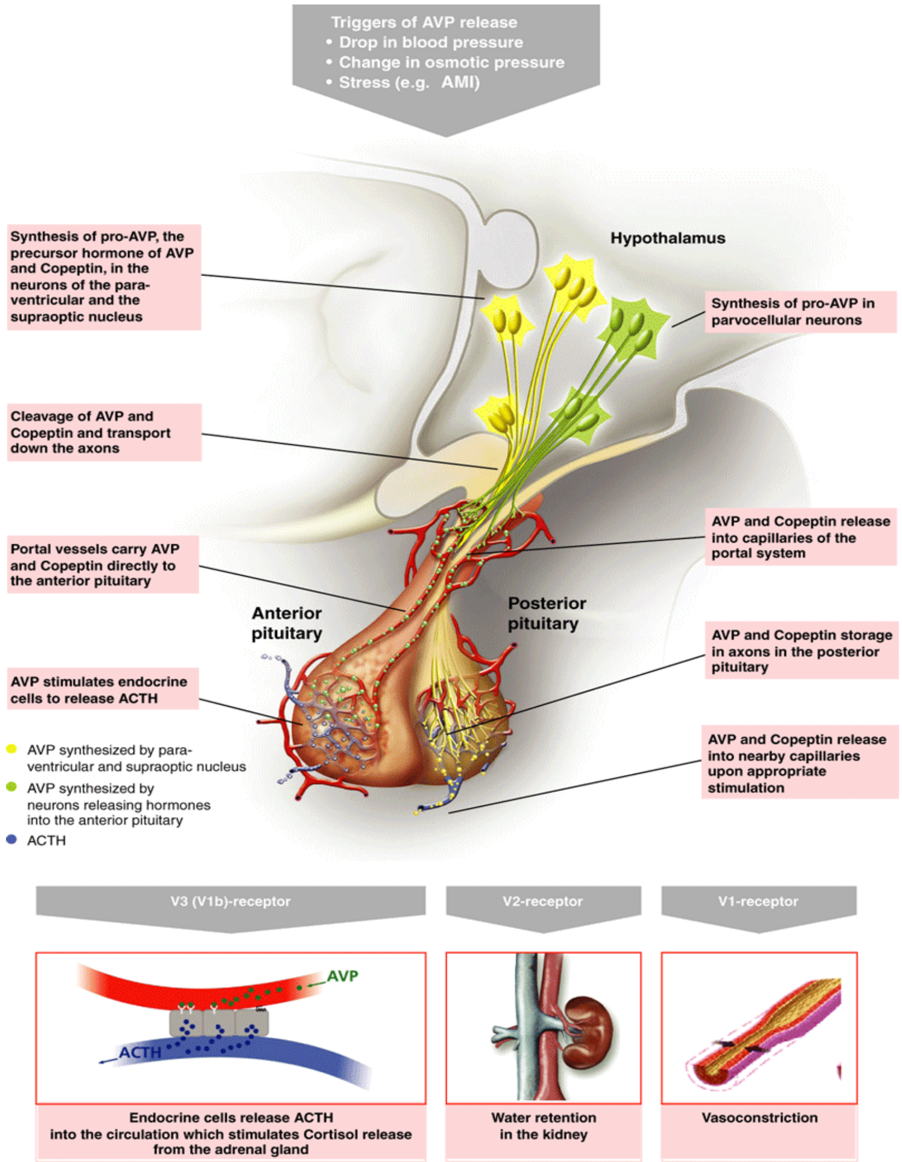

Figure 3: Synthesis and release of AVP and copeptin in hypothalamus and pituitary. Pro-AVP is processed in the hypothalamus, followed by two distinct release-mechanisms for the anterior and posterior pituitary. During stress, a drop in blood pressure, or a change in osmotic pressure ***(Nickel et al., 2013).***

Copeptin and AVP in the Circulation:

Copeptin responds to changes in plasma osmolality with a kinetic increase/decrease similar to that reported for AVP ***(Morgenthaler et al., 2006)***.

Patients with diabetes insipidus and reduced AVP have very low plasma levels of copeptin while patients with hyponatremia and the syndrome of inappropriate ADH secretion (SIADH) have elevated copeptin in their circulation ***(Katan et al., 2007)***.

While the normal range of copeptin mirrors the physiologic AVP secretion needed to maintain plasma osmolality, in severe diseases or states, such as shock, sepsis, stroke, or cardiovascular diseases, the nonosmotic release of AVP is depicted by a sharp increase in plasma copeptin, which has diagnostic and prognostic value ***(Fenske et al., 2009).***

Plasma AVP levels increase apparently during the process of some acute and chronic diseases, and the measurement of AVP would be useful for the prognosis of diseases ***(Zhan et al., 2016).*** However, because of the pulse release mode and the short half-life of AVP, the clinical application of AVP is restricted ***(Bolignano et al., 2014).***