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Mini Review

Tumor Necrosis Factor-alpha (TNFα) receptor type 1 (TNFR1) activation during severe inflammation; Can it be a therapeutic target in hypervolemic hyponatremia?

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Abstract

Hyponatremia is a life-threatening situation in severe inflammatory disorders. Managing this disorder is seriously hampered because its underlying pathophysiology has remained elusive. An increase in tumor necrosis factor-alpha (TNFα) during systemic inflammation may be involved in this hyponatremic mechanism as it is known that circulating TNFα exerts potent natriuresis via its action on receptor type 1 (TNFR1). Systemic inflammation also induces non-osmotic release of Antidiuretic Hormone (ADH), commonly known as 'Syndrome of Inappropriate ADH' (SIADH), that would cause water retention to increase in Extracellular Fluid Volume (ECV). Thus, the inflammation-induced TNFR1 activation and sodium loss coupled with SIADH-induced increases in ECV, would lead to the serious condition of hypervolemic hyponatremia. In this brief review, some experimental evidence will be provided that indicates TNFR1 activation during the inflammatory process can be targeted therapeutically to prevent such critical conditions of hypervolemic hyponatremia. The importance of these co-morbidities also extends to several other clinical scenarios of hyponatremia observed in patients with heart failure, liver disease, and renal disease. Besides the pathophysiological insights, the recognition of the propensity for both antidiuresis and natriuresis during inflammation is critically important in selecting the appropriate intravenous fluid regimens in patients with this disorder such as in the coronavirus disease of 2019 (COVID-19).

Introduction

Hypervolemic hyponatremia is a common electrolyte disorder that can be a life-threatening situation in severe inflammatory disorders such as sepsis, acute respiratory distress syndrome (ARDS), and other conditions associated with 'cytokine-storm', including coronavirus disease of 2019 (COVID-19) [1-3]. Nearly a quarter of hospitalized patients in Incentive Care Units (ICU) are suffering from this condition which may induce brain edema and cerebral contusion with high mortality and morbidity [1-4]. The proper management of these terminally ill patients with these clinical conditions is seriously hampered mainly because the underlying pathophysiology of critical hyponatremic disorder is not yet clearly understood. This condition is characterized by a pronounced deficit of free water excretion that leads to inappropriate water retention in comparison with the sodium concentration. This occurs when the kidneys cannot excrete water efficiently due to excess Antidiuretic Hormone (ADH) secretion, but at the same time, causing excess sodium excretion [5]. This imbalance results in an expanded Extracellular Volume (ECV) with dilutional low sodium concentration in plasma. As this condition of electrolyte disorders should be managed carefully by restricting free water ingestion and/or by increasing renal excretion of solute-free water while preventing the loss of sodium in urine, it has been always a critical problem in patients with underlying severe inflammatory conditions. The purpose of this mini-review article is to evaluate experimental findings indicating TNFR1 activation as a mechanism of hyponatremia induced by systemic inflammatory conditions. The evidence that enhanced

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plasma TNFα levels in inflammatory conditions inducing natriuresis, as well as inappropriate ADH secretion resulting in a critical condition of hyponatremia, is highlighted in this article to implicate TNFR1 as a possible therapeutic target to prevent such condition.

Inflammation-induced TNFα release and its natriuretic effect

TNFα is a proinflammatory cytokine produced by immune cells, mainly T-lymphocytes, although other sources include white blood cells, vascular endothelial cells, and renal tubular epithelial and mesangial cells [6]. TNFα has been reported to exert its cytokine signaling function through two different receptors, type 1 (TNFR1, p55) and type 2 (TNFR2, p75) [7,8]. which are differentially expressed and regulated in biological tissues [6]. The circulating TNFα has the maximal high affinity to interact with TNFR1 with no or minimal affinity for TNFR2 [9]. In the kidney, while TNFR2 plays a role in renal inflammation [10], TNFR1 activation induces a natriuretic effect by inhibiting tubular sodium transport and epithelial sodium channel (ENaC) activity [7,8,11]. In our laboratory [7,8], we have demonstrated that intravenous administration of a recombinant TNFα in mice induces a natriuretic effect which is prevented in mice lacking the gene for TNFR1 but not in mice lacking the gene for TNFR2, confirming that such natriuretic action of TNFα is mediated by the activation of TNFR1 in the kidney. Based on the experimental findings using rodents in our laboratory [7,8,11], it can be postulated that TNFα induced TNFR1 activation in the renal tubules caused excessive sodium excretion in urine and thus, may lead to a hyponatremic condition in systemic inflammation.

Inflammation-induced non-osmotic release of ADH

Recent studies also point to a key role for pro-inflammatory cytokines in the non-osmotic release of ADH by the hypothalamic-pituitary axis [12-14] commonly known as the syndrome of inappropriate ADH (SIADH). Although an anti-inflammatory effect of ADH on induced generalized inflammation as in sepsis condition has been suggested [15], the opposite was also noted that pro-inflammatory cytokines such as TNFα, released from inflammatory stress condition can activate the hypothalamus to produce ADH [14,15]. It has been demonstrated that TNFR1 is the major mediator of the actions of TNFα that implicates in glutamate-dependent neural communication that potentiates NMDA receptor-mediated signaling [16] and thus, it is conceivable that TNFR1 activation participates in ADH release by the hypothalamus. SIADH is generally a common phenomenon in various lung infections including acute and chronic respiratory failures [17,18]. When such severe inflammatory conditions with lung congestion occur in patients with Congestive Heart Failure (CHF), decompensated liver cirrhosis, and nephrotic syndrome, an increase in the non-osmotic release of ADH would further aggravate the function of these organs (heart, lungs, and kidney) due to increase in circulatory plasma volume by enhanced water permeability in the renal collecting duct cells [19,20]. ADH-dependent antidiuresis leads to water retention and increases the extracellular fluid volume in CHF resulting in dilutional (hypervolemic) hyponatremia [2,19]. Thus, it is critically important to understand the role of TNFα and its effect via TNFR1 activation in such non-osmotic release of ADH in CHF [19,20]. A complicated treatment regime to deal with replacing the loss of electrolytes while preventing or combating fluid excess poses a critical situation in the management of these patients [21]. Thus, identifying a mechanistic pathway for inducing this condition would be a breakthrough discovery to effectively manage and prevent the unusually high mortality and morbidity in these critical patients with electrolyte disorders.

TNFR1 activity as a therapeutic target in the management of hyponatremia

Experimental results from our laboratory [6-8,10,11,22,23] have demonstrated that the activation of TNFR1 receptor in the kidney resulted in a natriuretic response. Such a response could lead to hyponatremia in chronic inflammatory conditions that induce the production of this cytokine. Moreover, TNFR1 activation in the hypothalamus in generalized inflammatory conditions induces non-osmotic ADH release which acts on the kidney to mediate anti-diuretic action leading to fluid retention to increase in ECV. Thus, a combination of such dual actions (anti-diuresis and natriuresis) of TNFR1 activation would lead to this severe electrolyte disorder of hypervolemic hyponatremia. This postulated mechanism of hypervolemic hyponatremia due to TNFR1 activation is illustrated as given in Figure 1. In generalized inflammatory conditions, an increase in TNF level would activate TNFR1 in different organs including the kidney and hypothalamus. Thus, based on this postulated mechanism, it is expected that the specific inhibition of TNFR1 during cytokine storm would prevent this life-threatening electrolyte disorder and will have tremendous therapeutic benefits in such critical conditions. It may be mentioned here that a lack of commercially available specific TNFR1 antibodies should be challenged in finding this solution. All the available TNF receptor antibodies are either non-specific or have greater affinity to type 2 (TNFR2) receptors [24]. There are currently five approved TNF biologics that work by completely blocking the interaction of TNFα with its receptors non-specifically,

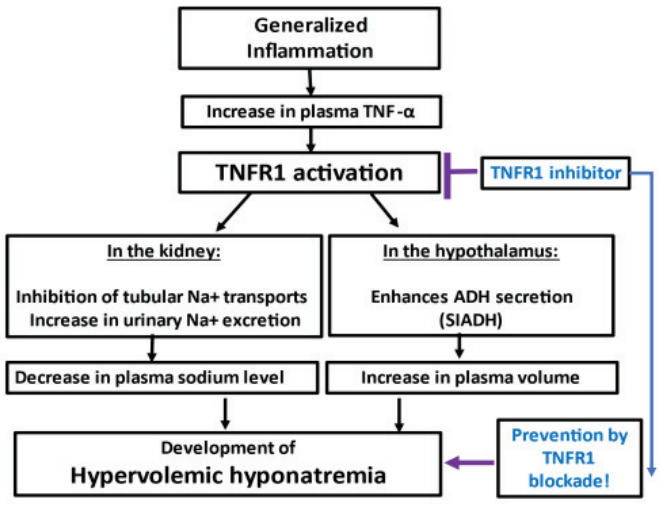

Figure 1: Postulated mechanism of hypervolemic hyponatremia due to TNF receptor type 1 (TNFR1) activation.

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but to date, there are no small molecule therapeutics available that disrupt the high-affinity TNFα–TNFR1 interaction [24]. Future research will validate the beneficial effect of specific TNFR1 inhibition in preventing hyponatremic conditions in generalized inflammatory disorders.

Conclusion

The experimental evidence so far strongly suggests that an increase in TNFα during systemic inflammation induces natriuretic as well as antidiuretic responses via its action on TNFR1 in renal tubules and in the hypothalamic-pituitary axis in the brain. Such sodium loss coupled with SIADH-induced fluid retention by the kidney would lead to the serious condition of hypervolemic hyponatremia in generalized inflammatory conditions. These results suggest a therapeutic benefit of specific blockade of TNFR1 activity in clinical management that will resolve the long-standing life-threatening condition of hyponatremia in many inflammatory disorders.

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