

The Tolvaptan Role on Acth Secretion and its Potential Therapeutic Implications

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ABSTRACT

Tolvaptan is an oral arginine vasopressin (AVP) receptor, antagonist. Due to its aquaretic properties, tolvaptan is indicated in the treatment of congestive heart failure, cirrhosis of the liver, syndrome of inappropriate secretion of antidiuretic hormone (SIADH), and autosomal dominant polycystic kidney disease (ADPKD). Studies in Cushing's disease and clinical observation in a patient with palmar hyperhidrosis dictate a tolvaptan role in the central nervous system (CNS) mainly through adrenocorticotrophic hormone (ACTH) suppression. AVP receptors have a wide distribution in the body, including the CNS. Centrally AVP stimulates ACTH secretion by corticotrope cells which express all three vasopressin receptors (V1, V2 and, V3). ACTH is involved in both cortisol secretion and sympathetic nervous system activation. Cushing's disease is caused by prolonged exposure to high cortisol levels engendered by tumors of the pituitary gland secreting ACTH. Palmar hyperhidrosis is a chronic neurologic disorder characterized by excessive sweating of eccrine glands, which worsens during stress. An excessive response of CNS to physiologic stress constitutes the most common etiopathogenetic hypothesis of palmar hyperhidrosis. The current article's data are collateral evidence, emerged from studies that had other study objectives. The tolvaptan role in these diseases probably is sustained by aberrant or overexpression of AVP receptors in corticotrope cells. The physiopathology of tolvaptan action on the central nervous system is reported. An aimed research to evaluate the effect of tolvaptan in both Cushing's syndrome and palmar hyperhidrosis is needed.

Keywords: tolvaptan, vasopressin antagonists, palmar hyperhidrosis, arginine vasopressin, ACTH, Cushing's disease, ACTH-secreting tumors.

INTRODUCTION

Tolvaptan is an AVP antagonist. It is mainly known for its aquaretic properties due to a selective antagonism of AVPR2 in the kidney's collecting duct cells.¹ Tolvaptan efficacy and safety are already known in treating hypervolemic or euvolemic hyponatremia in patients with heart failure, cirrhosis of the liver, and SIADH.^{2,3} Also, Tolvaptan is the first drug treatment for rapidly progressing ADPKD.^{4,5} recent clinical observation and in vitro studies are exploring new properties of tolvaptan as an inhibitor of ACTH secretion in specific pathologic conditions. 6-8 Yang J et al., through an in vitro study, demonstrated that tolvaptan inhibits desmopressin-induced ACTH secretion by the mouse pituitary corticotrophic tumor (AtT-20) cells.⁶ In the study

of Luque RM et al., tolvaptan blunted the ACTH-secretagogue effect of desmopressin in human corticotropinomas cells.⁷ Lastly, we reported a case of palmar hyperhidrosis remission during Tolvaptan treatment for ADPKD.⁸

Cushing's disease, an ACTH-releasing pituitary tumor, is characterized by signs and symptoms of prolonged hypercortisolism.⁹

Palmar hyperhidrosis, excessive sweating of the palms, is a chronic disorder that worsens during stressful situations. Palmar sweating, also known as emotional sweating, is controlled by CNS centers, different from those of thermoregulation. Although the pathology of the condition is not fully understood, it is believed that excessive sweating in palmar hyperhidrosis is a

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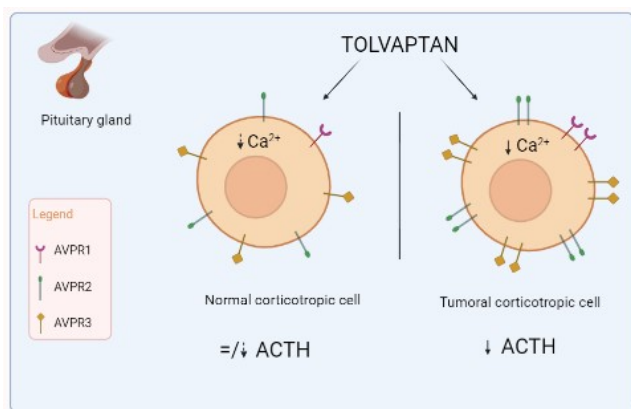
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consequence of an excessive response of CNS to physiologic stress.^{10,11}

CONCLUSION

These data together dictate a role of Tolvaptan in ACTH secretion that is perceptible only in conditions of increased or aberrant AVP receptor expression. (Figure 1)

Figure 1: Schematic illustration of tolvaptan effect on ACTH secretion: tolvaptan has negligible or no effect in normal corticotrophic cells (right); tolvaptan reduces ACTH secretion in corticotropinomas cells (left). Overexpression of AVP receptors probably sustains the tolvaptan ACTH suppressive activity on corticotropinomas cells.



further studies to gain deeper insights into Tolvaptan and ACTH-related diseases are needed. Cushing's disease and palmar hyperhidrosis are two chronic conditions that impair physical and mental health quality. Actual treatments for both Cushing's disease and palmar hyperhidrosis include surgical approaches with a high risk of recurrence.^{10,19,20} Tolvaptan may be a promising treatment for both Cushing's disease and palmar hyperhidrosis.

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