available at www.sciencedirect.com

ScienceDirect

www.elsevier.com/locate/brainresrev

BRAIN RESEARCH REVIEWS

Review

The mechanism of life-threatening water imbalance in schizophrenia and its relationship to the underlying psychiatric illness

*Morris B. Goldman**

Department of Psychiatry, Northwestern University, 446 East Ontario, Suite 7-100, Chicago, IL 60611, USA

ARTICLE INFO

Article history:
Accepted 26 June 2009
Available online 9 July 2009

Keywords:
Vasopressin
Oxytocin
HPA axis
Stress
Hippocampus
Polydipsia
Hyponatremia
Schizophrenia
Animal model

ABSTRACT

Impaired water excretion was noted to coincide with psychotic exacerbations in the first decades of the past century. In the ensuing decades, life-threatening water intoxication and elevated plasma levels of the antidiuretic hormone, arginine vasopressin (AVP) were reported in a subset of persons with schizophrenia. Subsequent studies demonstrated that the osmotic set point for AVP secretion was transiently reset in these patients by an unknown process and that this was further exacerbated by acute psychosis. More recent studies indicate that the AVP dysfunction is a manifestation of a hippocampal-mediated impairment in the regulation of both AVP and HPA axis responses to psychological, but not other types of, stimuli. Of potential significance, is that schizophrenic patients without water imbalance exhibit the opposite pattern of responses. Preliminary data indicate those with water imbalance also demonstrate a closely linked deficit in central oxytocin activity which may account for their diminished social function. These latter behavioral deficits are perhaps the most disabling and treatment resistant features of schizophrenia, which recent studies suggest, may respond to oxytocin agonists. Together these findings support the view that schizophrenia is a heterogeneous disorder, and provide novel biomarkers and approaches for exploring the pathophysiology and treatment of severe mental illness.

Contents

* Fax: +1 708 383 6387.
E-mail address: m-goldman@northwestern.edu.

0165-0173/$ – see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.brainresrev.2009.06.004

1. Introduction

1.1. *History of primary polydipsia and water intoxication in severe mental illness*

Impaired water excretion and water intoxication presenting concurrently with psychotic exacerbations were first noted in the initial decades of the 20th century (Targowla, 1923, Barahal, 1938). Investigators observed that over the course of a single day a patient could retain ten or more liters of fluid producing a profound dilutional hyponatremia. Furthermore, primary polydipsia was found to be the most common physiologic abnormality in chronic psychotic patients (Hoskins and Sleeper, 1933). No recognizable factors could account for the water imbalance, and over subsequent years the findings were both reproduced (de Leon et al., 1994; Hobson and English, 1963) and linked to fatal outcomes (Vieweg et al., 1988). Epidemiologic studies demonstrated that 10 to 20% of persons with schizophrenia were polydipsic (intake in excess of ~3 l/day) but only a fifth to a third of these (2–5% of total) experienced symptomatic hyponatremia (i.e. water intoxication: delirium, seizures, coma, lethargy, ataxia) (de Leon et al., 1994). Below we refer to the former group of patients as 'polydipsic normonatremic schizophrenics', the latter group as 'polydipsic hyponatremic schizophrenics (PHS)', and the two groups together as 'schizophrenic patients with water imbalance'. Thus schizophrenics without water imbalance (nonpolydipsic normonatremic schizophrenics) constitute the majority (80–90%) of those with the mental illness. This review focuses primarily on studies addressing the CNS factors which account for the hyponatremia in the PHS and their relationship to the mental illness.

1.2. *Evidence of antidiuretic hormone, arginine vasopressin (AVP) involvement*

With the development of highly sensitive and specific radioimmunoassays, the role of excess levels of the antidiuretic hormone (arginine vasopressin: AVP) in diverse disorders of impaired water excretion became apparent during the latter half of the 20th century (Robertson, 1976). While basal AVP levels and water excretion often appeared to be normal in PHS (Gillum and Linas, 1984), more sensitive assessments of water balance, and other reports, revealed indirect evidence of AVP dysregulation (Hariprasad et al., 1980, Ragavan et al., 1984). Among these were reports of elevated plasma AVP concurrent with acute psychosis (Raskind et al., 1975). While primary polydipsia was commonly found across psychiatric disorders, water intoxication and AVP elevations appeared to be largely restricted to those with psychotic illnesses (de Leon et al., 1994). A recent study demonstrating that an AVP V-2 antagonist almost immediately normalizes plasma sodium and osmolality in PHS (Josiassen et al., 2008) underscores the critical role of the hormone in the hyponatremia.

2. Mechanism of impaired water excretion

2.1. *Why AVP abnormalities are potentially powerful means of probing CNS dysfunction*

The brain maintains the concentration of solute in tissues within a very narrow (~1%) range primarily by controlling the secretion of AVP from the hypothalamus. Plasma AVP levels normally exhibit a tight linear relationship ($r = \sim 0.9$) to plasma