Schizophrenia Research xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

Review

Brain circuit dysfunction in a distinct subset of chronic psychotic patients

Morris B. Goldman *

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

ARTICLE INFO

Article history:
Received 13 March 2014
Received in revised form 30 May 2014
Accepted 2 June 2014
Available online xxxx

Keywords:
Hippocampus
Stress
Neuroendocrine
Heterogeneity
Oxytocin
Vasopressin
Polydipsia

ABSTRACT

Objective: To identify the mechanism of unexplained hyponatremia and primary polydipsia in schizophrenia and its relationship to the underlying psychiatric illness.
Methods: Briefly review previous studies that led to the conclusion the hyponatremia reflects altered hippocampal inhibition of peripheral neuroendocrine secretion. In greater detail, present the evidence supporting the hypothesis that circuit dysfunction associated with the hyponatremia and the polydipsia contributes to the underlying mental disorder.
Results: Polydipsic patients with and without hyponatremia exhibit enhanced neuroendocrine responses to psychological stress in proportion to structural deformations on their anterior hippocampus, amygdala and anterior hypothalamus. Nonpolydipsic patients exhibit blunted responses and deformations on other hippocampal and amygdala surfaces. The deformations in polydipsic patients are also proportional to diminished peripheral oxytocin levels and impaired facial affect recognition that is reversed by intranasal oxytocin. The anterior hippocampus is at the hub of a circuit that modulates neuroendocrine and other responses to psychological stress and is implicated in schizophrenia. Preliminary data indicate that other measures of stress reactivity are also enhanced in polydipsics and that the functional connectivity of the hippocampus with the other structures in this circuitry differs in schizophrenia patients with and without polydipsia.
Conclusion: Polydipsia may identify a subset of schizophrenia patients whose enhanced stress reactivity contributes to their mental illness. Stress reactivity may be a symptom dimension of chronic psychosis that arises from circuit dysfunction that can be modeled in animals. Hence polydipsia could be a biomarker that helps to clarify the pathophysiology and heterogeneity of psychosis as well as identify novel therapies. Clinical investigators should consider obtaining indices of water balance, as these may help them unravel and more concisely interpret their findings. Basic researchers should assess if the polydipsic subset is a patient group particularly suitable to test hypotheses arising from their translational studies.

1. Overview of impaired water excretion, water intoxication and polydipsia

In the first half of the 20th century, unexplained impaired water excretion (Targowla, 1923; Pfister, 1938) and life-threatening hyponatremia (Barahal, 1938) were observed in patients with chronic psychosis and noted to coincide with psychotic exacerbations. Studies at that time also demonstrated that primary polydipsia was the major unexplained physiologic abnormality in those with severe mental illness (Hoskins and Sleeper, 1933; Sleeper and Jellinek, 1936). During the latter half of the 20th century, these unexplained impairments in water excretion and intake were recognized as common causes of morbidity and a frequent cause of death in schizophrenia pIPatients (Vieweg et al., 1985; De Leon et al., 1994; Hawken et al., 2009). More recent studies suggest that these patients can be relatively easily distinguished from patients whose hyponatremia is attributable to recognized causes (Atsariyasing and Goldman, 2014; Goldman and Ittasakul, 2014). Primary polydipsia and evidence of impaired water excretion are found in 10–25% and 2–5% of chronic psychotic patients respectively, depending on the criteria used to define water imbalance. All of the patients with unexplained hyponatremia appear to have a primary polydipsia (hence about 1/5th of polydipsic patients exhibit impaired water excretion), though the relationship, if any, between the two disorders was initially unknown. See Supplemental Fig. 1 for a primer on water imbalance and Glossary for a definition of terms.

Here, we first briefly summarize studies characterizing the mechanism of the impaired water excretion and its relationship to acute psychosis in hyponatremic polydipsic psychotic patients. Next, we briefly review studies indicating that these patients, and to a somewhat lesser extent those polydipsic patients without impaired water excretion (i.e. normonatremic polydipsics), exhibit diminished anterior hippocampal restraint of peripheral neuroendocrine secretion during psychological stress. This is the opposite of the response seen in nonpolydipsic patients. This work is summarized in greater detail in Goldman (2009).

The last part of the manuscript reviews evidence that these findings are a facet of circuit dysfunction emanating from the anterior

* Tel.: +1 312 695 2089; fax: +1 708 383 6344.
E-mail address: m-goldman@northwestern.edu.

http://dx.doi.org/10.1016/j.schres.2014.06.001
0920-9964/

hippocampus (AH). Evidence that this dysfunction contributes to the underlying mental disorder, by altering central neuroendocrine activity and/or enhancing stress reactivity, is presented. In addition, we review evidence that nonpolydipsic patients differ markedly on many of these measures suggesting that the pathophysiology(ies) of the mental disorders in polydipsic and nonpolydipsic patients likely differ. The mechanism of the polydipsia and the implications of these findings to current efforts to characterize basic dimensions of behavioral functioning and to 'deconstruct' schizophrenia are then discussed. Additional background on the pathophysiology of water imbalance for the interested reader is provided in Supplemental Information.

1.1. Reset osmostat and its aggravation by psychosis

Hariprasad et al. (1980) provided evidence that hyponatremic polydipsic patients have impaired water excretion attributable to a subtle disorder of antidiuretic function called reset osmostat. Several studies subsequently provided further evidence of reset osmostat in this population and indicated that it was attributable to elevated activity of the antidiuretic hormone, arginine vasopressin (AVP) (Vieweg et al., 1986; Kishimoto et al., 1989; Delva et al., 1990; Vieweg et al., 1990; Ohsawa et al., 1993) (see Supplemental Fig. 2 for further information about reset osmostat). A concurrently conducted study of osmoregulation, which also carefully measured or controlled recognized influences on AVP function, confirmed the finding and showed that resetting could not be attributed to the recognized non-osmotic stimuli for AVP release (Goldman et al., 1988). Subsequent studies further substantiated this conclusion and found that other recognized and putative factors (e.g. oropharyngeal regulation, antipsychotics) could not account for the findings (reviewed in Goldman, 2009). These studies also demonstrated that the resetting appeared to be ameliorated by habituation to the clinical environs (Goldman et al., 1996) and confirmed that they were worsened by psychotic exacerbations (Fig. 1) (Goldman et al., 1997). Recent trials with highly specific AVP antagonists substantiate the conclusion that the variability in the hyponatremia, and thus the resetting, is attributable to enhanced AVP activity (Josiassen et al., 2008, 2012). Together these findings provided a plausible physiologic explanation for the original observations linking acute psychosis to impaired water excretion and the life-threatening hyponatremia in hyponatremic polydipsic schizophrenic patients (Goldman, 2009). The mechanism, however, of the resetting and its aggravation by acute psychosis remained unknown.

AVP is a tightly-regulated and measurable neuropeptide released directly from the brain into the peripheral blood stream where it has precise quantifiable actions (increases urine osmolality) reflecting a precise CNS modulated-function (osmoregulation). In reset osmostat, the precision of the system is unaffected (e.g. plasma osmolality accounts for about 80–90% of the variance in AVP levels), just the set point for AVP release is lowered (Fig. 1). Many factors (i.e. non-osmotic stimuli) can account for this lowering, some of which are associated with limbic functions (Robertson, 2006). The accessibility and precision of these various components of water balance offer a powerful tool for identifying and characterizing aberrations in CNS function attributable to a non-osmotic stimulus. This is one reason the neurohypophysial system has been described as a "veritable Rosetta stone for neuroendocrinology and neuroscience" (Gainer et al., 2002).

2. Reset osmostat and enhanced HPAA and AVP responses to psychologic stress

The association between habituation and acute psychosis to the AVP set point resembled the association between novelty and acute psychosis to variations in other neurohormone levels previously observed in psychiatric patients and attributed to non-specific psychological stress (Coccaro et al., 1984). This observation raised the possibility that psychological stress could be the non-osmotic stimulus that caused the

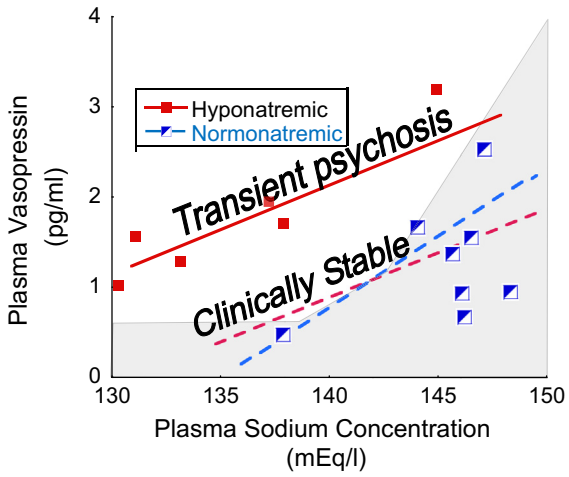

Fig. 1. Acute psychosis aggravates reset osmostat in hyponatremic polydipsic patients. Following three weeks of optimal treatment on an inpatient psychiatric research unit, osmoregulation (dotted lines) in six hyponatremic polydipsic (red) and eight matched normonatremic polydipsic (blue) patients was similar and near normal. A transient psychotic exacerbation was then induced with intravenous methylphenidate. While severity of induced psychosis was similar, peak arginine vasopressin (AVP) plasma levels were higher in those subjects with hyponatremia (solid squares) despite their lower sodium levels. Moreover, as the figure illustrates, these peak AVP levels in the hyponatremic subjects (but not the normonatremics half-filled squares) were proportional to concurrent plasma sodium (solid red line: $P_{Na} = 10.2P_{AVP} + 114$ mEq/l; $r = 0.80$), consistent with reset osmostat. The resetting appears so severe (i.e. new set point = 114 mEq/l) that it would induce water intoxication in the presence of even modest polydipsia. Thus these findings provide a plausible explanation for the observations first made in the early 20th century that acute psychosis in some chronic psychotic patients impairs water excretion and contributes to water intoxication. See Supplemental Information for primer on water imbalance and reset osmostat. Normal range of AVP relative to concurrent plasma osmolality is shown in gray. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

reset osmostat. Consistent with this interpretation, hypothalamic–pituitary–adrenal axis (HPAA) activity (a generally reliable measure of psychological stress) was elevated on admission in polydipsic relative to nonpolydipsic patients (Goldman et al., 1993).

The problem with this interpretation, however, is that AVP secretion is insensitive to psychological stress in humans (Edelson and Robertson, 1986) and other mammals (Onaka and Yagi, 1988). This insensitivity was attributed to neural inhibition by limbic pathways (Onaka and Yagi, 1990) and in this manner resembled the constraint of HPAA secretion by the hippocampus during psychological stress. The HPAA constraint involved a projection from the ventral subiculum (the rodent analogue of the lateral anterior hippocampus (AH) in primates) to the anterior hypothalamus (Herman et al., 1998). Indeed, this same projection enervated adjacent neurons in the anterior hypothalamus responsible for peripheral AVP secretion (Risold and Swanson, 1996; Tasker et al., 1998). Lesion studies demonstrated that this pathway enhanced both peripheral AVP and HPAA responses to psychological stimuli (Nettles et al., 2000) (see Fig. 2 for model). This observation was reproduced in an animal model of schizophrenia that disrupts the neurodevelopment of this hippocampal segment (Chrapusta et al., 2003; Mitchell and Goldman, 2004), substantiating the possibility that this pathway may be altered in persons with schizophrenia.

The potential relevance of these observations to the impaired water excretion in hyponatremic patients was assessed in a series of studies in four subject groups (matched polydipsic schizophrenic patients with and without hyponatremia, nonpolydipsic schizophrenic patients and healthy controls). The first study compared neuroendocrine responses to physical and psychological stress. Results demonstrated that AVP responses to psychological (but not physical) stress were a) enhanced in hyponatremic polydipsic patients relative to the three other groups, were b) similar in healthy controls and normonatremic polydipsic patients and were c) blunted in nonpolydipsic patients relative to the

Please cite this article as: Goldman, M.B., Brain circuit dysfunction in a distinct subset of chronic psychotic patients, Schizophr. Res. (2014), http://dx.doi.org/10.1016/j.schres.2014.06.001