Hormonal dysfunction in neurocritical patients

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Purpose of review
Acute brain injury results in widespread systemic endocrine dysfunction and affects how we care for patients. We review the existing literature on incidence, type and duration of endocrine dysfunction with special focus on the pituitary dependent function.

Recent findings
Acute studies document widespread alterations of the hypothalamic–pituitary–adrenal axis, disruption of the anterior hypothalamus related hormones, and alteration of regulation of sodium and fluid balance. Diagnostic testing and therapeutic intervention are outlined in this review. Relative adrenal insufficiency and cerebral salt wasting are the two main forms of endocrine dysfunction in neurocritical care patients.

Summary
Surveillance for endocrine dysfunction and early treatment with hormonal replacement may be life-saving in neurologic critically ill patients.

Keywords
adrenal dysfunction, brain injury, pituitary, salt wasting, subarachnoid hemorrhage

INTRODUCTION

Critical care of patients with neurocritical illness is difficult because many of the diagnostic clues that typically reveal acute pathophysiology are hidden from detection, and the clinical phenotype of coma is nonspecific. The goals of treatment for neurologic patients are frequently focused on neuroprotection such as to reverse brain ischemia, control intracranial pressure, and prevent seizures. The brain is frequently seen as the recipient end-organ that needs attention but not seen as part of the driving force causing systemic pathophysiology. It is the latter conceptual approach that will be discussed herein, with a special focus on hormonal dysfunction that is caused by or associated with neurologic injury. In short, the brain, especially the hypothalamic–pituitary axis, is a major contributor to normal endocrine homeostasis. Once the brain is injured, frequent disruption of the endocrine system ensues, and may lead to worsening of systemic physiology and even death. This review article features three disease states for discussion: subarachnoid hemorrhage (SAH), traumatic brain injury (TBI), and brain death. We will not discuss hyperglycemia in this review, but this is an important topic to consider elsewhere.

NEUROLOGIC CONTROL OF ENDOCRINE SYSTEM

The hypothalamus has a number of nuclei that are involved in neuroendocrine control of the pituitary system, the autonomic sympathetic nervous system, osmoregulatory system and temperature regulatory system. Distinct cell populations within the hypothalamus are responsible for either hormonal secretion or direct innervation to sympathetic nervous system via descending pathways. The hypothalamic–pituitary–adrenal axis (HPA) is well known to be affected by critical illness and is frequently impacted in neurocritical care patients. Although a full description of the anatomy and blood flow supply is beyond the scope of this review, a few salient points are worth making, which may indicate the vulnerability of the HPA system and the neuroendocrine function more generally. First, the

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KEY POINTS

- Brain injury results in partial or total failure of the hypothalamic–pituitary system.
- Early identification of endocrine dysfunction requires a high degree of suspicion, and specific testing.
- Empiric low dose hormone replacement treatment is frequently needed in neurocritical care patients.
- Sodium and intravascular volume control require attention to cerebral salt wasting in most neurocritical care patients.

pituitary is vulnerable to ischemia. The pituitary is supplied by a very tenuous blood vessel network or rete created by the portal venous system, and the inferior hypophyseal artery that emanate from the circle of Willis. These vessels are small by comparison to major intracranial vessels (i.e. middle cerebral artery) and hence are prone to collapse, compression and traumatic shearing injury [1] (Fig. 1). This can result in infarction of the pituitary acutely after brain injury or ischemia to the hypothalamus and pituitary during vasospasm or systemic shock. The influence of ischemia on inciting HPA axis endocrine insufficiency is theoretically more likely under conditions of cerebral edema and elevated intracranial pressure, as often are present in neurocritical patients. Second, the HPA axis is vulnerable to sedatives that are commonly used in neurocritical patients. Deep anesthesia using propofol, barbiturates or even high dose benzodiazepines may result in temporary impairment of the pituitary [2]. Hence, HPA axis dysfunction may occur during deep anesthesia, and may result in refractory hypotension and temperature dysregulation that may be difficult to interpret. Figure 2 outlines the fundamental interactions between the brain neuroendocrine control and the sympathetic nervous system. Injury to the brain results in downstream negative effects on pituitary and adrenal function.

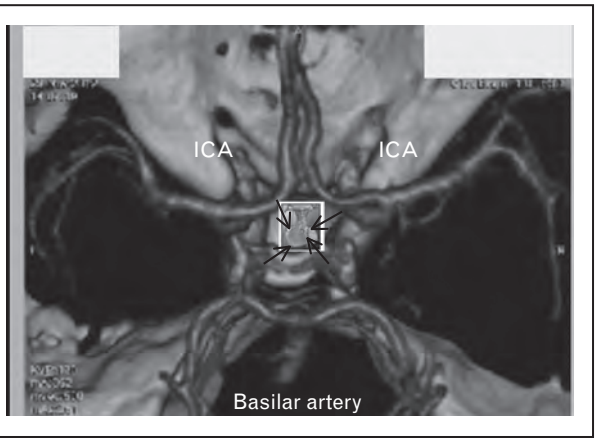

FIGURE 1. An axial computerized tomograph of the skull base showing the arteries at the circle of Willis and an insert of the pituitary gland. The pituitary gland is fed by small vessels coming from the internal cerebral artery (ICA), and basilar artery (arrows). The vascular supply is very tenuous and susceptible to traumatic injury and vasospasm.

NEUROENDOCRINE DISORDERS IN SUBARACHNOID HEMORRHAGE

SAH is a devastating sudden onset disease that occurs in distinct phases, namely acute rupture, vasospasm, and delayed recovery. The neuroendocrine abnormalities that have been most studied in SAH are the HPA axis disorders and sodium regulation disorders. Our focus will be primarily on the acute injury period. Table 1 [2–7,8▪,9–13] outlines clinical studies in SAH and TBI that were considered. There have been six studies of the HPA in acute SAH [2–7]. A deficiency in adrenocorticotrophic hormone (ACTH) and stimulation-induced elevation in cortisol were found in acute SAH [2,4], whereas normal cortisol levels have been reported at baseline [3]. In another report, ACTH and cortisol values were higher in the acute SAH patients than age-matched controls [5]. The degree of cortisol elevation was not associated with the severity of SAH. In contrast, mixed results of normal cortisol with low or normal levels of ACTH were found [7]. In the latter study, the diurnal variation of free cortisol levels was abnormal in some SAH patients, and correlated with poor outcome and longer length of stay as compared with those patients with normal diurnal variation. High levels of cortisol have recently been associated with delayed cerebral ischemia, although the causality of this observation is unclear [14]. More recently, over half of patients with SAH suffer from acute dysfunction of the HPA, specifically dysfunction of the anterior pituitary resulting in low levels of gonadotropin, growth hormone, ACTH, and thyroid stimulating hormone [8▪].

In contrast, a recent study of a particular subgroup of SAH patients who exhibit vasopressor-resistant hypotension suggests that relative adrenal insufficiency may occur [6]. In the latter observational, convenience based study, 18% of SAH patients were found to have vasopressor-resistant blood pressures during the induction of hypertensive therapy. In that subgroup, 69% were found to have relative adrenal insufficiency, as defined by a positive responsive on the cosyntropin stimulation test. This latter study suggests that there may be an

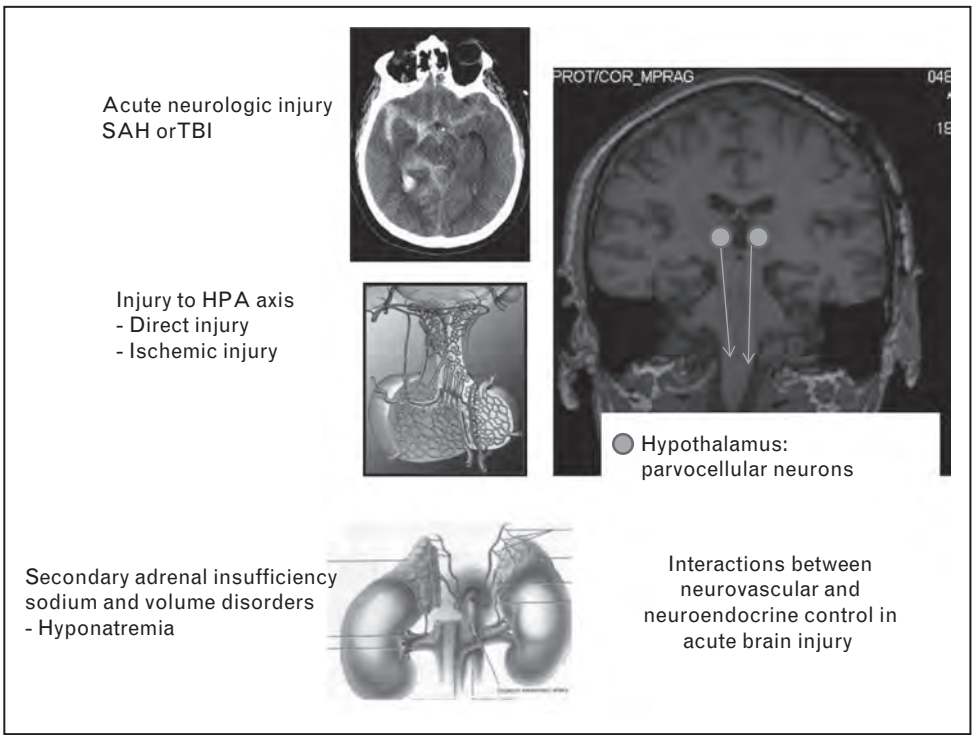

FIGURE 2. Conceptual overview of neurologic injury leading to dysfunction of neuroendocrine function. Subarachnoid hemorrhage shown (top center) leads to ischemia of the blood vessel supply to the hypothalamus and pituitary (middle center). Alteration of pituitary release of hormones leads to secondary adrenal insufficiency and altered renal homeostasis of electrolytes and water (middle bottom). Concurrent changes in the sympathetic nervous system lead to disruption of neuroendocrine control of the adrenal glands and kidneys.

important subgroup of patients with relative adrenal insufficiency requiring hormonal replacement therapy with hydrocortisone to assist with inducing therapeutic hypertensive therapy.

Sodium (Na) regulation disorders in SAH are commonplace with incidence rates ranging from 40 to 80% of patients. Typically, hyponatremia develops early after the SAH and commonly worsens during the period of vasospasm. Hyponatremia is frequently accompanied by reduction of intravascular volume. Controversy exists about whether hyponatremia is due to the syndrome of inappropriate antidiuretic hormone secretion or due to cerebral salt wasting (CSW). The former is a syndrome of normal blood volume with retention of free water resulting in euvolemic hyponatremia. In contrast, CSW is a disorder of salt wasting, hypovolemia, and hyponatremia that is mediated by the secretion of brain natriuretic peptide (BNP). A large number of studies have been done on SAH patients during the acute phase that document elevated levels of BNP without an increase in ADH levels [15–21,22▪,23]. The typical SAH patient does have a high urine output, and high secretion of Na in the urine, despite receiving supplemental intravenous fluids. BNP levels are increased under conditions of elevated intracranial pressure and vasospasm. The secretion of BNP correlates with vasospasm related delayed cerebral ischemia [20], implying that ischemia may be causing both the BNP release and further loss of systemic blood volume in a capricious positive feedback loop. If left uncorrected, patients will develop worsening hyponatremia and worsening cerebral edema as a result.

NEUROENDOCRINE DISORDERS IN TRAUMATIC BRAIN INJURY

There is a significant amount of similarity between SAH and TBI with regards to neuroendocrine dysfunction [24]. The alterations of HPA function and sodium regulation are similar in acute TBI and perhaps more long lasting [25▪]. Acute HPA dysfunction leading to secondary adrenal insufficiency occurs in 50% of patients with severe TBI [9] and acute dysfunction in growth hormone in nearly 20% of severe TBI patients [26,27]. The incidence is similar, 24% in children with TBI [11]; the effects appear to be long lasting and can affect recovery from TBI in the subacute [28] and chronic phases [29]. Early diabetes insipidus can occur as well, with negative fluid balance and hemodynamic instability as a result.

Table 1. Summary of studies that document the incidence, prevalence, and significance of disrupted neuroendocrine function, mostly involving the hypothalamic–pituitary–adrenal axis

Study	Time after injury TBI or SAH	Neuroendocrine abnormality	Impact on outcome
Kelly 2000 [2]	Acute	Pituitary deficiency: TRH, ACTH	Outcome not studied
Savaridas [3]	Acute	Normal ACT, cortisol levels	Outcome not studied
Dimopoulou 2004 [4]	Acute	Pituitary deficiency: ACTH, deficient stimulation of cortisol	Worse outcome in relative adrenal insufficiency
Bendel 2008 [5]	Acute followed by chronic	Supranormal ACTH and cortisol	No effect on outcome; normalization ACTH and cortisol by 3 months
Weant 2008 [6]	Acute	Relative adrenal insufficiency in vasopressor unresponsive patients only	Outcome not studied
Poll 2010 [7]	Acute	Supranormal to normal cortisol levels; no low levels found; variable ACTH levels; abnormal diurnal variation	No effect on outcome
Parenti 2011 [8▪]	Acute	Low levels GH, gonadotropin, ACTH, TSH	Effect on outcome not measured
Cohan 2005 [9]	Acute	Pituitary deficiency: ACTH, cortisol, GH	Worse outcome in relative adrenal insufficiency
Kelly 2006 [10]	Chronic 6–9 months	GH	Worse outcome in GH deficiency
Llompart-Pou 2008 [11]	Acute TBI children	Adrenal insufficiency	10% higher mortality
Llompart-Pou 2007 [12]	Acute	HPA insufficiency with barbiturates	Outcome not studied
Chourdakis 2012 [13]	Acute	RCT of enteral nutrition on HPA, thyroid endocrine function after severe TBI	Enteral nutrition protects against hormonal dysfunction

ACTH, adrenocorticotrophic hormone; GH, growth hormone; HPA, hypothalamic–pituitary–adrenal axis; RCT, randomized controlled trial; TRH, thyrotropin releasing hormone; TSH, thyroid stimulating hormone.

Diagnosis of pituitary dysfunction is enhanced by stimulation/response testing and as many as 70% of patients were found to have hypopituitarism after TBI when tested [29]. Risk factors appear to be related to severity of injury, such as basilar skull fracture, severe brain edema, posttraumatic vasospasm. Diagnostic testing including serial blood levels of ACTH, cortisol, prolactin, and in chronic patients growth hormone and ACTH stimulation testing, are suggested in order to make the diagnosis [30▪▪]. The use of etomidate, propofol and barbiturates were associated with increased incidence of HPA axis dysfunction [9,12]. Long-term outcome is worse in those patients with neuroendocrine dysfunction after TBI [10].

BRAIN DEATH

Progression of neurological deterioration to the state of brain death is frequently accompanied by significant alterations of neuroendocrine function. Diabetes insipidus is a common event and can lead to hemodynamic compromise and loss of systemic circulation, with negative effects on organ donation. At the same time, loss of the HPA axis also occurs, and many patients develop vasopressors refractory hypotension. The combination of hypovolemia and hypotension make caring for these patients during the organ donation phase of care quite challenging. Structured guidelines for the care of the brain dead patient have been created in order to facilitate organ donation [31].

HORMONAL REPLACEMENT THERAPY IN NEUROCRITICAL CARE PATIENTS

Hormonal replacement in neurocritical care patients could take one of several forms, namely replacement of corticosteroids, mineralocorticoids, supplemental sodium, and early enteral nutrition. Table 2 has a summary of treatments and suggested dosages. The settings of treatment depend on the clinical presentation. There are very few prospective studies on the influence of hormonal replacement therapy in patients with acute brain injury. In SAH, there have been two prospective studies on the use of fludrocortisone [32,33], one on hydrocortisone [34,35], and one on methylprednisolone [36]. Treatment with fludrocortisone was weakly associated with decreased delayed cerebral ischemia [relative risk (RR) 0.65; 95% confidence interval (CI) 0.33–1.27] and lower mortality (RR 0.33; 95%

Table 2. Summary of treatments for neuroendocrine dysfunction

Problem	Drug	Dosage	Diagnostic clues to trigger use
Hyponatremia	3% Nacl	Infusion 25–100 cc/hr	Decreasing Na in setting of high urine output; vasospasm
Hyponatremia	Fludrocortisone	0.1–0.2 mg q 12 hrs	Lack of response to 3% Nacl infusion
Hypotension refractory to vasopressors	Hydrocortisone	50–100 mg IV q 8 h	Refractory hypotension during vasospasm or during worsening cerebral edema and elevated ICP
Hypotension refractory to vasopressors	Vasopressin	0.01–0.04 units/min	Refractory hypotension during vasospasm or during worsening cerebral edema and elevated ICP
Hypernatremia	Desmopressin	1–2 micrograms SQ	High urine output in patient in deep coma progressing towards brain death

ICP, intracranial pressure; IV, intravenous; SQ, subcutaneously.

CI 0.03–3.20). The wide CI in results outlines the modest effects of this treatment. Mineralocorticoids are frequently used in the treatment of hyponatremia and thought to be important for correction of cerebral salt wasting [37▪].

The use of corticosteroids has been sparsely studied as well. The use has been presumptively for neuroprotection, rather than for acute adrenal insufficiency. In the single trial of hydrocortisone, there was an increased 1-month mortality rate (RR 1.49; 95% CI 0.40–3.19) and higher incidence of hyperglycemia. The recent study by Gomis *et al.* [36] was a single center, randomized controlled trial of high dose methylprednisolone (18 mg/kg per day for 3 days) in 95 patients with SAH. In this study, patients exposed to methylprednisolone experienced a similar incidence of key outcome variables as compared with the placebo group, including symptomatic vasospasm (28 vs. 31.5%, $P < 0.7$), modified Rankin Scores at 12 months ($P < 0.08$), delayed ischemic neurologic deficits on CT (24.4 vs. 18.4%, $P < 0.8$), and death (18.3 vs. 17.3%, $P < 0.8$). Gomis *et al.* highlight that the functional outcome, determined using a modified version of the mRS that excludes all patient deaths, was better in the methylprednisolone group.

The use of supplemental sodium to correct hyponatremia is a mainstay of treatment [37▪]. For practical purposes, continuous infusions of hypertonic saline in conjunction with mineralocorticoids are necessary to correct hyponatremia.

An interesting small randomized controlled trial of early enteral nutrition in TBI was recently reported [13]. In this study, early enteral nutrition resulted in less negative downregulation of thyroid-related hormones and less elevation of acute cortisol levels. Patients had no difference in mortality but the study sample was small and not powered to detect a difference. This study suggests the potential for other treatments of acute endocrine dysfunction after brain injury.

CONCLUSION

Critical care of the neurologic patient often focuses on intracranial hemodynamics and intracranial pressure. One should be cognizant of potential severe dysfunction of the endocrine system, principally, the HPA in acute brain injury. Supplemental treatment with targeted, low dose hormone replacement therapy may be life-saving, and needs to be part of the treatment approach. Longer lasting endocrine problems may occur in the subacute phase of illness, and may be cause for readmission to the ICU.

Acknowledgements

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Conflicts of interest

There are no conflicts of interest.

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- ▪ of special interest
- ▪▪ of outstanding interest

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