Chapter 16
The Stress Response after Traumatic Brain Injury: Metabolic and Hormonal Aspects

Hervé Quintard, Carole Ichai, and Jean-Francois Payen

Abstract The pathophysiology of TBI can be considered as a dual insult composed of primary and secondary injuries. Growing experimental and clinical evidence suggests that disturbances of cerebral energy metabolism are a key factor in the pathogenesis of secondary cerebral damages. In addition, hormonal dysfunction after TBI, such as adrenal insufficiency, vasopressin, growth hormone, or thyrothropin deficiency, can be associated with poor prognosis. A better understanding of energy metabolism and hormonal disturbances after TBI is necessary to improve the care management at the early phase of TBI.

Traumatic brain injury (TBI) is a common cause of death and disability especially for young adults with various neurological consequences ranging from simple physical disabilities to long-term cognitive, behavioural, psychological, and social defects [1]. The pathophysiology of TBI is considered as a dual insult composed of primary and secondary processes. Primary injury corresponds to anatomic tissue damage at the time of insult. This produces vulnerable cells that are further

H. Quintard
Service de Réanimation, Hôpital Pasteur 2, 30 Voie Romaine, Nice, Cedex 1 06001, France

CNRS UMR6097- Université Nice Sophia Antipolis, Nice F-06000, France

C. Ichai
Service de Réanimation, Hôpital Pasteur 2, 30 Voie Romaine, Nice, Cedex 1 06001, France

IRCAN (INSERM U1081, CNRS UMR 7284), Université Nice Sophia Antipolis, Nice F-06000, France

J.-F. Payen (✉)
Pôle Anesthésie Réanimation, Hôpital Michallon, CHU de Grenoble, Grenoble F-38043, France

Université Grenoble Alpes, Grenoble Institut des Neurosciences, Grenoble F-38042, France
e-mail: Jean-Francois.Payen@ujf-grenoble.fr

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compromised by secondary brain injury. Secondary brain damage occurs at the cellular level and results from a complex biochemical cascade, including excitotoxicity, oxidative stress, inflammation, apoptosis, and mitochondrial dysfunction. Secondary brain damage is a major factor involved in the patient outcome following primary brain insult. Several systemic factors have been found to worsen secondary brain damage [2]. Growing experimental and clinical evidence suggests that disturbances of cerebral energy metabolism are a key factor in pathogenesis of this secondary cerebral damage [3, 4]. In this chapter, we discuss the consequences of TBI on metabolic and hormonal homeostasis.

16.1 Metabolic Disturbances After TBI

16.1.1 Exploration of Brain Metabolism in the ICU

Cerebral microdialysis (CMD) has largely contributed to a better understanding of the pathophysiology of acute brain dysfunction at the bedside [3]. CMD consists in the placement of an intra-parenchymal probe with a semipermeable dialysis membrane. A cerebrospinal fluid-like solution, infused through this catheter, allows hourly sampling of patients' brain extracellular fluid [4]. CMD provides monitoring of dynamic changes of main brain energy substrate (glucose, lactate, and pyruvate). High lactate/pyruvate ratio (LPR) values would reflect either a mitochondrial dysfunction or an imbalance between oxygen supply and its tissue utilisation. A LPR >40 and an extracellular glucose <0.7–1 mmol/L are usually considered as thresholds for abnormality in the clinical setting [5].

16.1.2 Metabolism of Normal Brain

Although brain represents 2 % of the body weight, the cerebral metabolic rate of glucose ($CMR_{glucose}$) accounts for 20 % of the amount of glucose utilised by the body. Brain glucose oxidation is about 4–5 μmol/kg/min. The regulation of glucose metabolism is essential for brain homeostasis in the absence of glycogen storage in the brain. The interaction among neurons, astrocytes, and endothelial cells at the interface blood-brain barrier (BBB) is essential for coupling energy supply with change in neural activity. Neurons and astrocytes are surrounded by interstitial fluid, which contains glucose and lactate, at a concentration of 1 mM. The glucose pool is replenished by blood-derived glucose, whereas lactate is interchanged between astrocytes and glial cells, and cleared by the blood at a low rate [6]. The large blood-brain concentration gradient drives the facilitative transport of glucose across the endothelial membranes via several glucose transporters, in particular glucose transporter 1 (GLUT1). This transporter is localised in astrocyte, while GLUT3 receptors, which have higher affinity and transport capacity for glucose, are localised

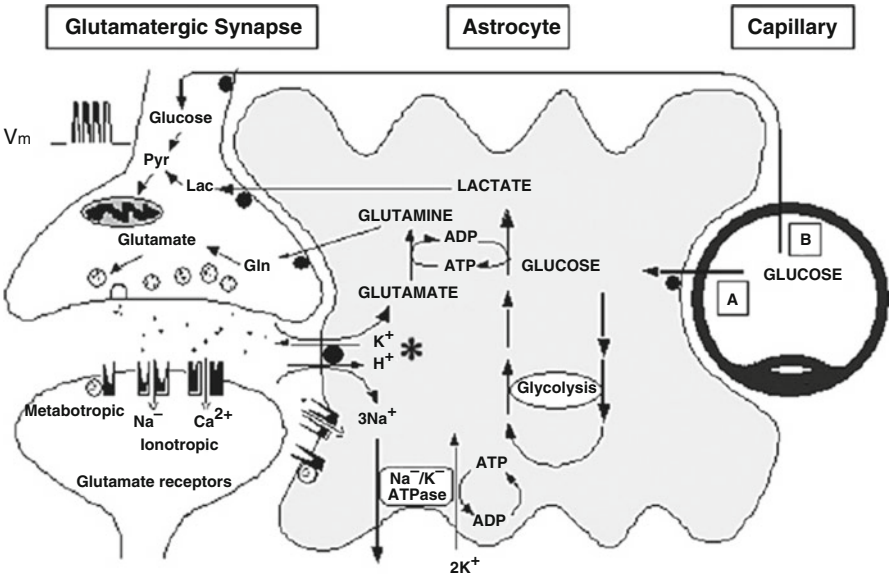

Fig. 16.1 Model for coupling of synaptic activity with glucose utilisation. *A* Glucose uptake by astrocytes in case of neuron activation, *B* direct neuron glucose uptake by resting neuron (Permission conveyed through Copyright Clearance Center, Inc. from [8])

in neurons. The expression of GLUT is regulated by circulating glucose concentration and is upregulated during hypoglycaemia. In resting conditions, blood glucose is raised and metabolised by neurons through the classical glycolytic pathway. During activation, glucose is metabolised by astrocytes, to produce lactate and glutamine. Lactate enters into neurons through the monocarboxylic acid transporter (MCT) to be metabolised by the tricarboxylic acid (TCA) cycle. Glutamine enters into neurons to produce glutamate that is released massively in the synaptic neuronal cleft. Astrocytes reuptake glutamate via a mechanism coupled with sodium reabsorption. ATP produced by glial glycolysis allows the activation of Na/K/ATPase pump to extrude the Na influx coupled to glutamate uptake. This response is illustrative of cell cooperation to metabolic situation. The lactate production is a preferential oxidative fuel when neurons are activated. This interaction between the two types of cells is called "astrocyte to neuron lactate shuttle (ANLS)" [7] (Fig. 16.1). In resting awake brain, brain glucose is mostly oxidised into CO_2 and water, leading to an oxygen/glucose ratio around 5.5–5.8.

16.1.3 Metabolism of Injured Brain

Several studies have found an increased aerobic glycolysis in the acute phase of brain injury, leading to brain lactate accumulation. This hyperglycolysis is reflected by an elevated tissue lactate to glucose ratio using CMD [9]. Because there was no evidence

of concomitant reduction in CBF, cerebral hyperglycolysis and concomitant decreased extracellular glucose (<0.2 mmol/l) are considered as reflect of an excessive metabolic demand (brain energy crisis). This increase in the utilisation of brain glucose may be due to seizures and/or episodes of cortical spreading depression (CSD) and/or to the maintenance of ionic pumps and neurochemical cascades in the injured tissue. In addition, a linear correlation between peripheral glucose and brain glucose was found in TBI patients [10]. This underlines the importance of an appropriate glucose supply from blood to the injured brain. TBI patients usually have hyperglycaemia secondary to insulin resistance and to a stress response. This "stress-induced" hyperglycaemia can exacerbate ischaemic damages and worsen the neurological outcome. On the other hand, severe and repetitive hypoglycaemic episodes were found independent risk factors for mortality and morbidity after TBI [11, 12]. Low but also high dialysate glucose levels have been associated with poor outcome and high mortality [5]. A strict glucose control was associated with elevated glutamate and lactate/pyruvate ratio and reduced extracellular glucose, together with increased oxygen extraction fraction [13]. Taken together, these findings suggest that glucose depletion may occur in the injured brain tissue through an excessive metabolic demand, even during non-ischaemic conditions. Therefore, a permissive hyperglycaemia between 6 and 9 mM is recommended to avoid the aggravation of cerebral damages [13, 14].

The brain can use substrates as supplemental fuel other than glucose, e.g., ketone bodies and lactate [15]. Evidence of lactate as an alternative fuel was firstly demonstrated in vitro by limiting neuronal cell death from glucose deprivation induced by ischaemia-reperfusion model [16, 17]. Further studies showed that lactate was preferentially used of lactate by the human brain after TBI [18]. The contribution of lactate to cerebral energy metabolism was increased from 10 to 15 % up to 60 % [19]. Additionally, intracellular lactate inhibits glucose consumption in resting astrocytes in order to redistribute glucose to active areas [20]. Sparing glucose is important to maintain neurotransmission and oxidative stress response in the injured brain. In this context, exogenous lactate supplementation has been studied after trauma. A lactate transfer from blood to brain with a subsequent conversion to pyruvate with spared glucose was described in TBI patients [21]. In a cortical impact model, lactate solution was associated with elevated cerebral blood flow and reduced cortical contusion volume [22]. Besides these metabolic effects, hypertonic sodium lactate administration in severe TBI patients was more effective to lower intracranial hypertension than mannitol [23]. A preventive treatment with hypertonic sodium lactate solution was effective in reducing the number of ICP episodes [24]. Therefore, lactate solution appears as a promising option to treat energetic crisis after TBI by sparing glucose and/or by improving cerebral haemodynamics.

16.2 Hormonal Disturbances After TBI

The hypothalamic-pituitary-adrenal axis (HPA) is altered by numerous causes, particularly after TBI. The primary lesion as well as secondary systemic insults such as arterial hypotension, severe hypoxia, and high intracranial pressure can

induce pituitary dysfunction. The pituitary gland is particularly vulnerable to the blood flow conditions because the anterior lobe is tightly dependent on small vessels from the Willis circle. Somatotropic and gonadotropic cells that are located in the lateral part of the anterior pituitary gland are even more exposed to reduce cerebral blood flow. Other mechanisms involved in hypopituitarism include side effects of sedative drugs used in brain-injured patients and autoimmune mechanisms triggered by TBI [25]. The first report of hypopituitarism post trauma was published in 1918. The prevalence of hypopituitarism in the chronic phase after TBI is 30 % of patients [26]. While the literature about chronic posttraumatic hypopituitarism is abundant, there is still limited data regarding the severity, incidence, and risk factors associated with hypopituitarism in the acute phase after TBI. In those studies, the prevalence of posttraumatic hypopituitarism ranged from 9 to 53 % of patients, including secondary adrenal insufficiency (AI), hypothyroidism, and/or hypogonadism [27, 28]. In many cases, hormonal disturbances have a spontaneous resolution within 6 months after TBI. Indeed, hypopituitarism during a long-term follow-up after TBI was diagnosed in 5.4 % of patients [29]. However, acute AI, central hypothyroidism, SIADH, and diabetes insipidus may cause poor neurological outcomes including death, hypo-/hypernatraemia, hypotension, and increased vasoactive drug requirements [30].

16.2.1 Adrenal Insufficiency

Among clinical conditions of AI, brain trauma is responsible for secondary (central) AI, i.e., suppression of the synthesis of corticotrophin-releasing hormone (CRH) or adrenocorticotrophic hormone (ACTH) [31]. According to the definition used, the prevalence of AI has a broad range from 10 % to more than 75 % of severe TBI patients [32, 33]. There is thus a need to define appropriately AI after TBI.

Absolute AI is considered where serum cortisol is less than 15 μg/dL, and relative AI is defined where serum cortisol cannot exceed 9 μg/dL from baseline using the ACTH test [34] In one study exploring AI in the initial phase of TBI, authors considered AI where baseline serum cortisol was less than 15 μg/dL from 2 blood samples or less than 5 μg/dL from 1 blood sample [28]. Because a normal value of serum cortisol cannot rule out AI for all critically ill patients [35], it was proposed to perform a dynamic test, i.e., the ACTH test (250 μg), to explore the capacity of adrenal glands to produce cortisol. However, due to the nature of AI after TBI, and the absence of confounding factors, a random serum cortisol is usually enough to detect AI. Random serum cortisol less than 10 μg/dL is currently recommended to diagnose AI in critically ill patients [36]. Of note was the delayed diagnosis of AI often mistaken for symptoms of head injury. In the presence of unexplained hyponatraemia and /or large requirements for vasopressors after severe TBI, a dosage of serum cortisol should be considered. It has been suggested that severity of TBI, young age, arterial hypotension, barbiturates, and/or the use of vasopressors could predispose to AI post trauma [28, 37, 38]. Another factor of AI could be the use of etomidate to facilitate tracheal

intubation in these patients [28]. However, this drug-induced disturbance lasts no more than 48 h after the drug administration [39].

The normalisation of serum cortisol level might be a marker of good outcome [40]. In that context, a replacement therapy with low-dose hydrocortisone (200 mg/day) should be initiated in the presence of acute AI. However this proposal has not to be confounded with the abandon of large doses of corticosteroids at the early phase of TBI [41]. In the large Corticosteroid Randomisation after Significant Head Injury (CRASH) trial, a 48-h infusion of methylprednisolone within 8 h of TBI resulted in higher mortality rate compared with placebo group [42].

16.2.2 Vasopressin Dysfunction

The antidiuretic hormone (ADH, or arginine vasopressin) is secreted by the posterior pituitary gland to promote free water reabsorption in the kidney to concentrate urine. ADH acts on vasopressin receptors with three subtypes V1a, V1b, and V2. The water reabsorption depends on the stimulation of V2 receptors that enhances the expression of specific water channel proteins (aquaporins) on the luminal surface of the collecting duct [43]. The secretion of ADH is triggered by the increase in extracellular fluid tonicity that activates osmoreceptors in the hypothalamus. ADH can be secreted, to a lesser extent, during hypovolaemia via the activation of baroreceptors located in the right atrium and carotid sinus.

A failure of homeostatic release of ADH leads to the development of central diabetes insipidus (DI). DI manifests with loss of large volumes of dilute urine in the presence of normal or high plasma osmolality. The criteria to define DI combine urine volume >300 mL/h, urine osmolality <300 mosm/kg, and hypernatraemia >145 mmol/L. The urine specific gravity is less than 1005 (or 1008 if associated glycosuria). DI is usually transient, secondary to hypoperfusion of the posterior pituitary and/or inflammatory oedema. However DI can persist 1 year after TBI in 12 % of patients [35]. The prevalence of DI after severe TBI is around 3 % and is strongly associated with basal skull fracture. Risk factors for DI include low Glasgow coma scale, brain oedema, and severe injury [35]. The development of DI after TBI is associated with higher mortality [44]. The treatment of DI is based on fluid replacement guided by a constant clinical monitoring and a correction rate of hypernatraemia of less than 10 mmol/day. In the case of high ICP, the correction rate should be lowered to exceed no more than 5 mmol/day in order to prevent secondary brain oedema. In conscious patients with DI, intravenous (0.4 μg) or intranasal (100 μg) desmopressin (DDAVP) can be administered and repeated every 12 h. Unconscious patients are treated with fluid replacement with 2.5 % dextrose or water and concomitant DDAVP administration.

Another disturbance in the ADH secretion corresponds to the inappropriate secretion of ADH (SIADH). The diagnosis criteria of SIADH combine plasma osmolality <275 mOsm/kg, hyponatraemia <135 mmol/L and urinary osmolality >100 mOsm/kg, urine sodium >40 mmol/l, euvolemia, and absence of glucocorticoid or thyroid

hormone deficiency. In the presence of hyponatraemia, the differential diagnosis with other conditions may be difficult: secondary AI is classically associated with glucose control disturbances, while the "cerebral salt wasting syndrome" (CSWS) is associated with hypovolaemia and increased serum urea. The presence of SIADH is associated with an increase in length of stay in the ICU. The natural history of SIADH spontaneously resolves after the initial insult. The key issue to manage hyponatraemia in this setting is an accurate diagnosis of the underlying cause. If SIADH is diagnosed, treatment is essentially based in a fluid restriction strategy. Although the use of selective of vasopressin-2 receptor antagonist (vaptan) could be attractive [45], this treatment has not been recommended in recent guidelines [46].

16.2.3 Growth Hormone Deficiency

Growth hormone (GH) deficiency is frequently observed after TBI with an incidence of 2–66 % [47]. Basal serum GH concentrations were increased in TBI patients. Excessive GH response to a stimulation test with GH-releasing hormone (GHRH) was found in patients with poor outcome. Patients with severe and permanent GH deficiency should be treated with hormonal substitution because GH acts on limbic structures with consequences on memory and behaviour. Some studies found benefits of supplementation by GH on motor or cognitive functions at the post-acute phase of trauma [48].

16.2.4 Thyrotropin Deficiency

The incidence of hypothyroidism after TBI varies between 0 and 19 %. A low serum-free T4 concentration (<8 pmol/L) associated with normal or low serum TSH level (<0.1 μUI/mL) is a criterion to diagnose thyrotropin deficiency. No dynamic test is required. Replacement therapy with thyroxine is mandatory, but this treatment requires to rule out CRH deficiency because cortisol clearance is increased by thyroxine. However, there is no evidence that replacement therapy at the acute phase of TBI may improve the outcome. The decrease of thyroid hormonal values was less pronounced during early enteral nutrition compared to delayed enteral nutrition [49].

16.2.5 Gonadotrophin Deficiency

The incidence of gonadal deficiency ranges from 0 to 29 % of TBI patients. A hypothalamic origin has been proposed. The deficit is associated with menstrual irregularities and/or reduced libido. Results between serum testosterone level and

prognosis are conflicting. The level of prolactin is also associated with prognosis with a positive correlation [35]. A complete restoration of hormone levels was observed in 85 % of patients at 1-year post-TBI, but persistent deficiency should benefit for replacement therapy for prevention of osteoporosis and cardiovascular disease.

Traumatic brain injury induces various metabolic and hormonal stress responses that could be associated with poor outcome. A better understanding of these dysfunctions could help us in the management of brain-injured patients during the early phase of trauma.

References

1. Zaloshnja E, Miller T, Langlois JA, Selassie AW (2008) Prevalence of long-term disability from traumatic brain injury in the civilian population of the United States, 2005. J Head Trauma Rehabil 23(6):394–400
2. Jeremitsky E, Omert L, Dunham CM, Protetch J, Rodriguez A (2003) Harbingers of poor outcome the day after severe brain injury: hypothermia, hypoxia, and hypoperfusion. J Trauma 54(2):312–319
3. Hutchinson PJ, Jalloh I, Helmy A et al (2015) Consensus statement from the 2014 International Microdialysis Forum. Intensive Care Med 41(9):1517–1528
4. Hillered L, Vespa PM, Hovda DA (2005) Translational neurochemical research in acute human brain injury: the current status and potential future for cerebral microdialysis. J Neurotrauma 22(1):3–41
5. Timofeev I, Carpenter KL, Nortje J et al (2011) Cerebral extracellular chemistry and outcome following traumatic brain injury: a microdialysis study of 223 patients. Brain 134(Pt 2):484–494
6. Barros LF, Deitmer JW (2010) Glucose and lactate supply to the synapse. Brain Res Rev 63(1–2):149–159
7. Pellerin L, Magistretti PJ (2012) Sweet sixteen for ANLS. J Cereb Blood Flow Metab 32(7):1152–1166
8. Magistretti PJ (2009) Role of glutamate in neuron-glia metabolic coupling. Am J Clin Nutr 90(3):875S–880S
9. Sala N, Suys T, Zerlauth JB et al (2013) Cerebral extracellular lactate increase is predominantly nonischemic in patients with severe traumatic brain injury. J Cereb Blood Flow Metab 33(11):1815–1822
10. Magnoni S, Tedesco C, Carbonara M et al (2012) Relationship between systemic glucose and cerebral glucose is preserved in patients with severe traumatic brain injury, but glucose delivery to the brain may become limited when oxidative metabolism is impaired: implications for glycemic control. Crit Care Med 40(6):1785–1791
11. Finfer S, Chittock D, Li Y et al (2015) Intensive versus conventional glucose control in critically ill patients with traumatic brain injury: long-term follow-up of a subgroup of patients from the NICE-SUGAR study. Intensive Care Med 41(6):1037–1047
12. Kalfon P, Le Manach Y, Ichai C et al (2015) Severe and multiple hypoglycemic episodes are associated with increased risk of death in ICU patients. Crit Care 19:153
13. Vespa P, McArthur DL, Stein N et al (2012) Tight glycemic control increases metabolic distress in traumatic brain injury: a randomized controlled within-subjects trial. Crit Care Med 40(6):1923–1929
14. Meierhans R, Bechir M, Ludwig S et al (2010) Brain metabolism is significantly impaired at blood glucose below 6 mM and brain glucose below 1 mM in patients with severe traumatic brain injury. Crit Care 14(1):R 13

15. Valente-Silva P, Lemos C, Kofalvi A, Cunha RA, Jones JG (2015) Ketone bodies effectively compete with glucose for neuronal acetyl-CoA generation in rat hippocampal slices. NMR Biomed 28(9):1111–1116
16. Schurr A, Payne RS, Miller JJ, Rigor BM (1997) Brain lactate, not glucose, fuels the recovery of synaptic function from hypoxia upon reoxygenation: an in vitro study. Brain Res 744(1):105–111
17. Cater HL, Chandratheva A, Benham CD, Morrison B, Sundstrom LE (2003) Lactate and glucose as energy substrates during, and after, oxygen deprivation in rat hippocampal acute and cultured slices. J Neurochem 87(6):1381–1390
18. Gallagher CN, Carpenter KL, Grice P et al (2009) The human brain utilizes lactate via the tricarboxylic acid cycle: a 13C-labelled microdialysis and high-resolution nuclear magnetic resonance study. Brain 132(Pt 10):2839–2849
19. Boumezbeur F, Petersen KF, Cline GW et al (2010) The contribution of blood lactate to brain energy metabolism in humans measured by dynamic 13C nuclear magnetic resonance spectroscopy. J Neurosci 30(42):13983–13991
20. Sotelo-Hitschfeld T, Fernandez-Moncada I, Barros LF (2012) Acute feedback control of astrocytic glycolysis by lactate. Glia 60(4):674–680
21. Bouzat P, Sala N, Suys T et al (2014) Cerebral metabolic effects of exogenous lactate supplementation on the injured human brain. Intensive Care Med 40(3):412–421
22. Berthet C, Castillo X, Magistretti PJ, Hirt L (2012) New evidence of neuroprotection by lactate after transient focal cerebral ischaemia: extended benefit after intracerebroventricular injection and efficacy of intravenous administration. Cerebrovasc Dis 34(5–6):329–335
23. Ichai C, Armando G, Orban JC et al (2009) Sodium lactate versus mannitol in the treatment of intracranial hypertensive episodes in severe traumatic brain-injured patients. Intensive Care Med 35(3):471–479
24. Ichai C, Payen JF, Orban JC et al (2013) Half-molar sodium lactate infusion to prevent intracranial hypertensive episodes in severe traumatic brain injured patients: a randomized controlled trial. Intensive Care Med 39(8):1413–1422
25. Kelly DF, Gonzalo IT, Cohan P et al (2000) Hypopituitarism following traumatic brain injury and aneurysmal subarachnoid hemorrhage: a preliminary report. J Neurosurg 93(5):743–752
26. Schneider HJ, Schneider M, Saller B et al (2006) Prevalence of anterior pituitary insufficiency 3 and 12 months after traumatic brain injury. Eur J Endocrinol 154(2):259–265
27. Agha A, Sherlock M, Phillips J, Tormey W, Thompson CJ (2005) The natural history of post-traumatic neurohypophysial dysfunction. Eur J Endocrinol 152(3):371–377
28. Cohan P, Wang C, McArthur DL et al (2005) Acute secondary adrenal insufficiency after traumatic brain injury: a prospective study. Crit Care Med 33(10):2358–2366
29. Kokshoorn NE, Smit JW, Nieuwlaat WA et al (2011) Low prevalence of hypopituitarism after traumatic brain injury: a multicenter study. Eur J Endocrinol 165(2):225–231
30. Powner DJ, Boccalandro C, Alp MS, Vollmer DG (2006) Endocrine failure after traumatic brain injury in adults. Neurocrit Care 5(1):61–70
31. Prigent H, Maxime V, Annane D (2004) Science review: mechanisms of impaired adrenal function in sepsis and molecular actions of glucocorticoids. Crit Care 8(4):243–252
32. Koiv L, Merisalu E, Zilmer K, Tomberg T, Kaasik AE (1997) Changes of sympatho-adrenal and hypothalamo-pituitary-adrenocortical system in patients with head injury. Acta Neurol Scand 96(1):52–58
33. Bernard F, Outtrim J, Menon DK, Matta BF (2006) Incidence of adrenal insufficiency after severe traumatic brain injury varies according to definition used: clinical implications. Br J Anaesth 96(1):72–76
34. Cooper MS, Thickett DR, Stewart PM (2013) Reduced cortisol metabolism during critical illness. N Engl J Med 369(5):480
35. Agha A, Phillips J, O'Kelly P, Tormey W, Thompson CJ (2005) The natural history of post-traumatic hypopituitarism: implications for assessment and treatment. Am J Med 118(12): 1416
36. Marik PE (2009) Critical illness-related corticosteroid insufficiency. Chest 135(1):181–193

37. Bondanelli M, De Marinis L, Ambrosio MR et al (2004) Occurrence of pituitary dysfunction following traumatic brain injury. J Neurotrauma 21(6):685–696
38. Llompart-Pou JA, Perez-Barcena J, Raurich JM et al (2007) Effect of barbiturate coma on adrenal response in patients with traumatic brain injury. J Endocrinol Invest 30(5):393–398
39. Vinclair M, Broux C, Faure P et al (2008) Duration of adrenal inhibition following a single dose of etomidate in critically ill patients. Intensive Care Med 34(4):714–719
40. Barton RN, Stoner HB, Watson SM (1987) Relationships among plasma cortisol, adrenocorticotrophin, and severity of injury in recently injured patients. J Trauma 27(4):384–392
41. Alderson P, Roberts I (2000) Corticosteroids for acute traumatic brain injury. Cochrane Database Syst Rev (2):CD000196
42. Roberts I, Yates D, Sandercock P et al (2004) Effect of intravenous corticosteroids on death within 14 days in 10008 adults with clinically significant head injury (MRC CRASH trial): randomised placebo-controlled trial. Lancet 364(9442):1321–1328
43. Treschan TA, Peters J (2006) The vasopressin system: physiology and clinical strategies. Anesthesiology 105(3):599–612
44. Boughey JC, Yost MJ, Bynoe RP (2004) Diabetes insipidus in the head-injured patient. Am Surg 70(6):500–503
45. Schrier RW, Gross P, Gheorghiade M et al (2006) Tolvaptan, a selective oral vasopressin V2-receptor antagonist, for hyponatremia. N Engl J Med 355(20):2099–2112
46. Spasovski G, Vanholder R, Allolio B et al (2014) Clinical practice guideline on diagnosis and treatment of hyponatraemia. Intensive Care Med 40(3):320–331
47. Bushnik T, Englander J, Katznelson L (2007) Fatigue after TBI: association with neuroendocrine abnormalities. Brain Inj 21(6):559–566
48. Devesa J, Reimunde P, Devesa P, Barbera M, Arce V (2013) Growth hormone (GH) and brain trauma. Horm Behav 63(2):331–344
49. Chourdakis M, Kraus MM, Tzellos T et al (2012) Effect of early compared with delayed enteral nutrition on endocrine function in patients with traumatic brain injury: an open-labeled randomized trial. JPEN J Parenter Enteral Nutr 36(1):108–116