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Traumatic brain injury and resultant pituitary dysfunction: insights from experimental animal models

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Abstract

Purpose Traumatic brain injury (TBI) is a major worldwide cause of disability, often burdening young people with serious lifelong health problems. A frequent clinical complication is post-traumatic hypopituitarism (PTHP) manifesting in several hypothalamus-pituitary axes. The head trauma-induced mechanisms underlying PTHP remain largely unknown. Several hypotheses have been proposed including direct damage to the pituitary gland and hypothalamus, vascular events and autoimmunity. This review aims to provide a summary of the currently limited number of studies exploring hypothalamus-pituitary dysfunction in experimental animal TBI models.

Results Although the impact of different forms of TBI on a number of hypothalamus-pituitary axes has been investigated, consequences for pituitary tissue and function have only scarcely been described. Moreover, mechanisms underlying the endocrine dysfunctions remain under explored.

Conclusions Studies on TBI-induced pituitary dysfunction are still scarce. More research is needed to acquire mechanistic insights into the pathophysiology of PTHP which may eventually open up the horizon toward better treatments, including pituitary-regenerative approaches.

Keywords Pituitary · Traumatic brain injury · Pituitary dysfunction · Hypopituitarism · Stem cells · Regeneration

Introduction

Each year, 69 million people suffer traumatic brain injury (TBI) as caused by motor vehicle accidents, falls, sport-related shocks or other head impacts [1, 2]. TBI temporarily or permanently deteriorates cognitive, physical and behavioral functions [3]. Although pituitary dysfunction was already recognized as a consequence of TBI a century ago [4], post-traumatic hypopituitarism (PTHP) has largely been neglected until recently [5–7]. PTHP has a reported prevalence between 15 and 68%, a broad range due to differing study designs such as varying inclusion/exclusion criteria, analysis time-points, testing methods and trauma severity [8–10]. The pathogenetic mechanisms underlying PTHP remain largely unclarified and are most likely multifactorial including direct pituitary injury because of its location just beneath the brain (Fig. 1), or indirect impact through damage in the hypothalamus or its connection to the pituitary, the infundibulum (Fig. 1), or in other brain areas. Further potential causes negatively impacting pituitary tissue and function include hypotension, regional hypoxia, brain swelling, anemia, lesions of the hypophyseal portal veins and auto-immune reactions [5, 9, 11]. The resultant disruption of hypothalamus-pituitary axes leads to endocrine anomalies, most frequently situated in the somatotropic and gonadotropic axes [8, 11]. In some patients, spontaneous recovery of pituitary function and related endocrine parameters has been observed [5]. Underlying mechanisms are currently unknown but may involve regenerative processes restoring portal vessels or pituitary hormonal cells. It has indeed been shown using transgenic pituitary injury mouse models that the gland possesses the capacity to regenerate cells and function after damage [12–14]. The local pituitary stem cells are activated upon injury and show hormone expression, thereby strongly supporting their contribution to the regenerative response and endocrine cell restoration [12–14].

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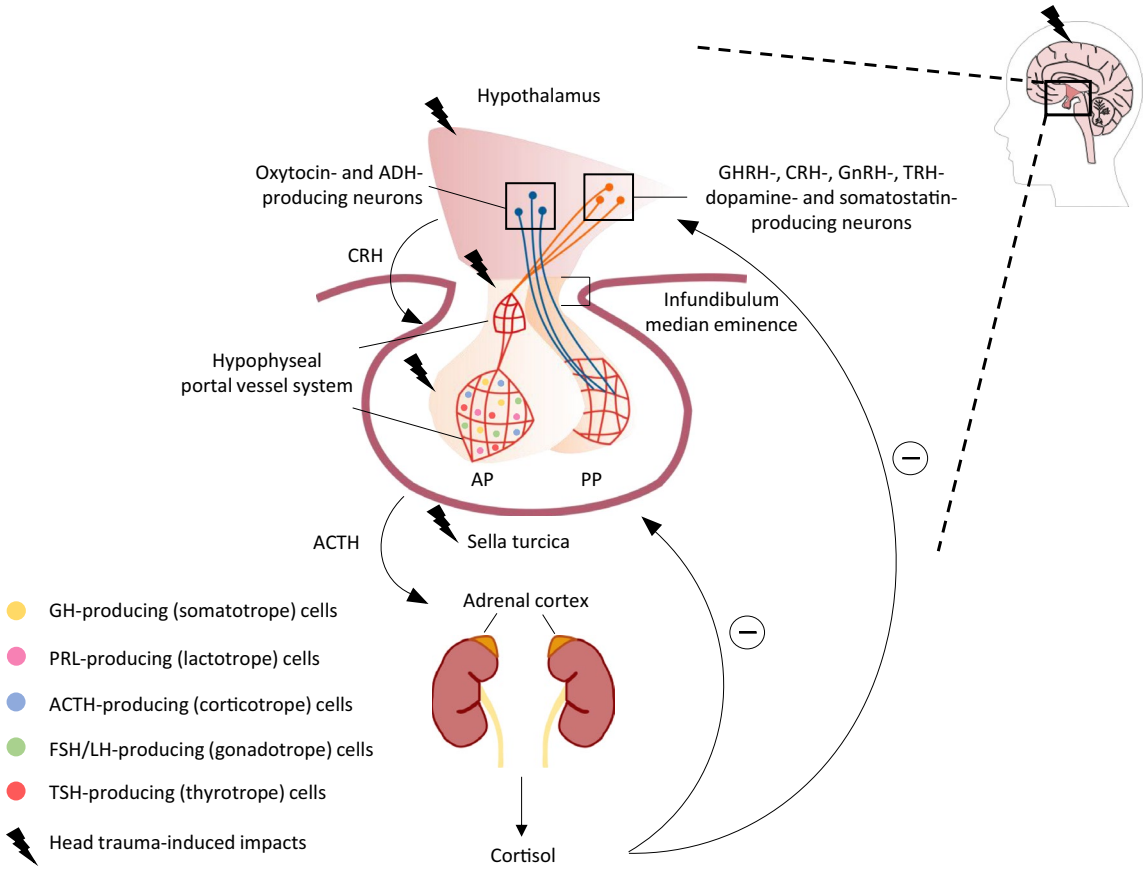

Fig. 1 Potential head trauma-induced impacts on the hypothalamus-pituitary axis. The human pituitary gland is located underneath the brain in a bony enclosure called the *sella turcica* and consists of an anterior and posterior lobe (AP and PP, respectively). The infundibulum connects the pituitary to its brain commanding structure, the hypothalamus. The PP primarily consists of axonal projections from hypothalamic neurons that store and release oxytocin and anti-diuretic hormone (ADH). The hypophyseal portal vessel system transports stimulatory hormones (GHRH, CRH, gonadotropin-releasing hormone (GnRH), thyrotropin-releasing hormone (TRH)) or inhibitory factors (dopamine, somatostatin) from hypothalamic nuclei to the AP to regulate GH, prolactin (PRL), ACTH, luteinizing hormone (LH), follicle-stimulating hormone (FSH) and thyroid-stimulating hormone (TSH) synthesis in the dedicated AP cell types (as indicated), and their release into the circulation. These pituitary hormones will act on several distal target organs, which then produce hormones that in turn negatively feedback to the hypothalamus and pituitary (as illustrated for the HPA axis). Head trauma can jeopardize the pituitary hormonal system through a direct impact or a secondary impact that can result from damage to the hypothalamus or infundibulum, thereby disrupting hypothalamic regulatory communication or transport to the pituitary (hence affecting hypothalamus-pituitary axes such as the HPA), or from swelling of the brain and disruption of the pituitary blood supply, eventually leading to compression or infarction of the gland's tissue

To obtain more insight into the pathophysiology of TBI, and to eventually identify and test potential therapies including regenerative approaches, experimental animal models are needed [15]. So far, most of the animal TBI research has focused on neurological and behavioral endpoints and only a limited number of studies have investigated endocrine changes. Here, we provide an overview of the animal models that have been used so far to study the impact of TBI on the pituitary and different hypothalamus-pituitary axes (summarized in Table 1).

Fluid percussion injury model

Given its high injury reproducibility and ability to control trauma severity, fluid percussion injury (FPI) is the most widely used approach to model TBI in animals. Injury is induced by a fluid wave onto the intact dura through a craniotomy, generated by a pendulum striking the piston of a fluid reservoir. A midline location of the impact results in diffuse injury while a lateral location induces a focal injury with diffuse component [16]. In the endocrine field, this model has mainly been applied to study stress responses to TBI,

Table 1 Summary of endocrine phenotypes in experimental TBI models

Source	TBI model	Severity	Species	Axis	Main endocrine observations
Roe et al. [17]	Lateral FPI	Moderate	Rat	HPA	↑*CRH* (maximum at 2 h)
Grundy et al. [18]	Lateral FPI	Moderate	Rat	HPA	↑*CRH* (maximum at 4 h), = vasopressin, ↑*Pomc* and corticosterone in sham and FPI
Griesbach et al. [21]	Lateral FPI	Mild	Rat	HPA	↓Corticosterone, ↑ACTH (week 1–2)
Rowe et al. [23]	Midline FPI	Moderate	Rat	HPA Gonadotropic	↓Corticosterone, ↓corticosterone response to stress, = testosterone (day 54)
Taylor et al. [26]	CCI	Mild moderate	Rat	HPA	Corticosterone stress response: ↓day 7–21, ↑day 34–70 corticosterone stress response: ↓day 7–70
Taylor et al. [27]	CCI	Moderate	Rat	HPA	↓Corticosterone response to stress (at 4 weeks)
Osterstock et al. [28]	CCI	Severe	Mouse	Somatotropic	↓GH (day 30), ↓ response to GHRH (day 7 and 30) tanycyte barrier disruption
Kasturi et al. [29]	CCI	Severe	Rat	Somatotropic	↓GH, = IGF1, inflammation hypothalamus (at 8 weeks)
Lavrnja et al. [31]	SCA	Severe	Rat	HPA	↑ACTH (week 1–2), = ACTH (week 4)
Lavrnja et al. [32]	SCA	Severe	Rat	Somatotropic	↓Somatotropes (week 2), = somatotropes (week 4), ↑GHR
Shohami et al. [34]	Weight drop	Severe	Rat	HPA	↑ACTH and corticosterone (2–8 h; normalized at 24 h) ACTH improves recovery from TBI
Greco et al. [36]	RTBI	Mild	Rat	Somatotropic	↓GH (week 4), ↓IGF1 (week 1–4), capillary damage AP
Greco et al. [38]	RTBI	Mild	Rat	Gonadotropic	↓Testosterone (day 1–week 4), ↓peak testosterone in puberty/adolescence, ↓sexual maturation
Tan et al. [39]	IH	Not defined	Rat	/	↑Apoptosis in pituitary > hypothalamus > hippocampus
			Rat	Somatotropic	↓GH (12–24 h)
			Rat	HPA	↑ACTH (12 h), ↓ACTH (24 h)
			Rabbit	/	Effect of stress on apoptosis (↑)
Russell et al. [40]	bTBI	Mild	Mouse	HPA	Male: ↑corticosterone response, ↓CRH neuron activation (7–10 days) Female: ↓corticosterone response, ↑CRH neuron activation, ↓ratio non-neurosecretory/neuroendocrine CRH neurons (7–10 days)

thereby focusing on the hypothalamus–pituitary–adrenal (HPA) axis (Fig. 1).

Following lateral FPI of moderate severity in rats, the HPA axis was found to be rapidly activated. At the hypothalamic level, corticotropin-releasing hormone (CRH) mRNA expression quickly rose, reaching a peak after 2–4 h [17, 18]. In the pituitary, mRNA levels of pro-opiomelanocortin (POMC), the precursor of adrenocorticotropic hormone (ACTH), and plasma corticosterone levels also promptly increased, reaching a peak after 30 min. Intriguingly, similar effects on *Pomc* and corticosterone (but not *Crh*) were observed in sham-operated animals (undergoing the same surgery but not FPI), as compared to control rats not undergoing any surgical procedure. Thus, just performing anesthesia and cranial surgery promptly activated the HPA axis as a general stress response. Of note, increased ACTH and cortisol levels following head trauma have also been described in human patients [19, 20], but benchmarking with other surgically treated patients yielded conflicting results. For instance, King et al. [19] described higher plasma cortisol levels that were elevated in head injury patients for a longer period of time than in patients undergoing other selective operations, while Bouzarth et al. [20] did not find a difference in plasma cortisol levels between patients operated for head trauma or tumors. In the FPI-impacted rats, plasma corticosterone levels were reduced again after 2 weeks whereas ACTH levels remained elevated, suggesting a dissociation within the HPA axis [21]. A similar dissociation was described in human TBI patients and was proposed to be linked to surgery complications and clinical depression [22]. During these 2 weeks, the FPI-impacted rats were hyperresponsive to restraint-induced stress in terms of a more pronounced increase in plasma corticosterone and ACTH lasting for a longer period of time than in control (including sham-operated) rats. Reduced sensitivity to negative feedback signals in the HPA axis may underlie such hyperresponsiveness to stress. However, dexamethasone could still successfully suppress the elevated ACTH and corticosterone levels in response to stress [21].

Chronic effects in the HPA axis have also been described following a single diffuse midline FPI of moderate severity in rats [23]. A 60% decrease of plasma corticosterone levels was observed 54 days post-injury when compared to sham-operated and unaffected control animals. Moreover,

the corticosterone response to restraint-induced stress was blunted, which is different from the elevated responses occurring acutely in the first 2 weeks following FPI [21]. Administration of dexamethasone could suppress this stress response, indicating the intactness of negative feedback mechanisms in the HPA axis. Thus, TBI seems to chronically dysregulate corticosterone production in this experimental model, which correlates with findings of chronic cortisol deficiencies in human TBI patients [24].

Although TBI-induced dysregulation is most frequently observed in the somatotropic and gonadotropic axes [8, 11, 25], the FPI model has so far not been used to study impacts on the hypothalamic-pituitary-somatotropic axis. Regarding the hypothalamic–pituitary–gonadal axis, rat testosterone levels were not found different from control following midline FPI of moderate severity [23]. However, levels were only measured 54 days after trauma and more acute changes may have been missed.

Controlled cortical impact model

In the controlled cortical impact (CCI) model, mild to severe injury can be induced by an electromagnetic or pneumatic-driven impactor that delivers mechanical damage to the intact dura after craniotomy, thereby causing deformation of the underlying cortex. CCI mainly results in focal injury; time, velocity and depth of impact can be regulated to alter trauma severity [15].

Regarding the HPA axis, the acute corticosterone response to stress in rats that underwent mild or moderate CCI was lower than in sham-operated animals [26], which differs from the initial stress hyper-responsiveness observed in the FPI model [21]. This blunted stress response persisted until day 70 after CCI of moderate severity [26, 27], but recuperated after CCI of mild severity from day 34 onward, suggesting a divergence in recovery according to trauma severity. Mechanisms underlying this difference remain to be clarified.

Impact on the somatotropic axis after severe CCI was studied in mice [28] and rats [29]. Initially (after 7 days), GH serum levels remained stable although the pituitary GH response to growth hormone-releasing hormone (GHRH) was already blunted [28]. At a later stage (1–2 months), GH levels were significantly reduced [28, 29] but the main downstream mediator of the GH pathway, insulin-like growth factor-1 (IGF1), was not altered [29]. Remarkably, GH protein and mRNA levels in the pituitary were not changed neither GHRH and somatostatin receptor levels or vascularization of the gland, suggesting that the GH deficiency phenotype following CCI does not find its cause in the pituitary itself [28]. Zooming in on hypothalamus and cortex, a lasting inflammatory reaction was observed in response to the trauma, characterized by higher IgG levels (even in more lateral and rostral brain areas), infiltration of bone marrow-derived cells and increased interleukin-1β levels [29] potentially resulting from inflammatory cells and/or from injury-activated, proliferating glial cells (expressing glial fibrillary acidic protein, GFAP) [28, 29]. The proliferating glial cells were mainly observed near GHRH cell bodies and axon terminals. However, no change in GHRH neuron electrical activity was detected [28]. In the median eminence (Fig. 1), the morphology of the tanycytes (neuroepithelial cells that line the third ventricle and extend into the hypothalamic region) was modified following CCI, suggestive of disruption of this epithelial barrier and altered permeability [28] which may result in an imbalance of out- and in-going signals including hypothalamic factors and immune/inflammatory molecules. Distorted permeability at the tanycyte barrier may represent a more general mechanism of disrupted hypothalamus-pituitary communication and resultant hormonal deficiency, apart from pituitary or pituitary stalk lesions. Together, these data show that cortical impact causes chronic inflammation, even in locations distal from the initial impact site, and long-term GH deficiency. Persistent GH deficiency is also observed in human TBI patients and is negatively associated with recovery from TBI [7, 8, 11, 30].

Suction cortical ablation model

In the suction cortical ablation (SCA) model, part of the cortex is resected by suction through a polypropylene tip, thereby inducing severe TBI [31, 32].

In the HPA axis, sensorimotor SCA (i.e. impacting motor and somatosensory cortical regions) in rats resulted in reduced ACTH immunoreactivity and corticotrope cell volume in the pituitary one week later, while ACTH plasma levels were increased, together suggesting the release of stored ACTH from the pituitary cells [31]. After 2 weeks, the pituitary corticotrope cells regained volume and ACTH plasma levels further increased, possibly indicating de novo ACTH synthesis. A further reduction in ACTH immunoreactivity in the gland suggested further augmented release. One month after SCA, ACTH levels in both plasma and pituitary had normalized again. During the period studied, an inverse correlation was observed between capillary dilation in the gland and corticotrope cell volume. Small cell volume (at one week after injury) accorded with maximum capillary dilation, likely allowing the released ACTH to swiftly enter the bloodstream [31]. Recovery of locomotor ability coincided with the temporal rise of ACTH levels in plasma and pituitary, but a causal connection remains to be demonstrated [31].

Regarding the somatotropic axis, no alterations were observed following SCA in the number and morphology of

somatotrope cells in the pituitary. In contrast, cellular volume and GH immunoreactivity gradually declined during the first week after injury [32]. After 2 weeks, the number of somatotrope cells started to decrease while cellular volume and GH immuno-intensity normalized again. After 30 days, the number of somatotrope cells recovered and no visible differences were present anymore regarding somatotrope cell number, volume and GH immunoreactivity between rats that underwent head injury and control animals [32].

In the brain, SCA induced an acute increase in GFAP, nestin and GH receptor (GHR) expression. GHR expression emerged in reactive astrocytes and in neuronal cell bodies and dendrites lining the injury site. The authors hypothesized that GHR expression was evoked by the changes in somatotrope cell activity in the pituitary and that this upregulation could be involved in the post-traumatic repair of the stressed glial and neuronal cells through the action of GH (as a potential neuroprotector) [32]. However, further studies are needed to support this hypothesis.

Closed head injury model

In contrast to the previously described models, the closed head injury (CHI) model does not involve craniotomy and is designed to mimic concussion and diffuse brain injury [33]. Several variations exist for this model, but the TBI is generally induced by mechanical impact on the exposed skull.

Weight-drop model

In the weight-drop model, head injury is inflicted by dropping a defined weight from a particular distance on the exposed skull of an anesthetized animal.

In the HPA axis, corticosterone and ACTH levels were found to acutely (in 2–8 h) rise as a result of the concussive injury, and to normalize again from 24 h onward [34]. To explore potential involvement of the HPA axis in recovery from this particular TBI, adrenalectomy (ADX) was performed, CHI inflicted and recuperation measured using the neurological severity score (that assesses a multitude of reflexes, beam walking distance and beam balancing time). ADX and the resulting high ACTH levels were found to have a beneficial effect; cortical edema development was significantly lower and neurological recovery was improved. These positive effects were not due to the absence of corticosteroids after ADX, since administration of corticosteroid receptor antagonists to non-ADX rats did not have any beneficial effect on edema development and neurological recovery. ACTH appeared to have a protective influence since removal of the pituitary (hypophysectomy) resulted in lower resistance to CHI. Indeed, mortality was observed in 1/3rd of the animals whereas no death was encountered in the non-hypophysectomized group. Moreover, CHI-induced mortality could be efficiently prevented by exogenous ACTH administration to the hypophysectomized animals. In addition, ACTH administration positively influenced recovery and reduced edema in animals with intact HPA axis [34]. Taken together, the findings point to a neuroprotective role of ACTH following brain injury, which has also been suggested before in studies using ACTH analogs or fragments (reviewed in McDaniel [35]).

Repetitive TBI

To establish repetitive TBI (RTBI), a pneumatic piston cylinder can be used as mechanical impactor and the infliction repeated for a defined number of times.

RTBI in adolescent rats (as established by 4 consecutive insults with 24-hour interval) resulted in reduced weight gain and body growth as compared to single TBI-impacted and sham-operated animals [36]. By week 4, RTBI-impacted animals still had lower body weight but differences in length were not observed anymore. In the pituitary, capillaries were damaged following RTBI, resulting in higher permeability that may be involved in the pathology and symptoms [36].

In the somatotropic axis, no acute changes in GH serum levels were observed after RTBI, but one month later GH levels were significantly declined and lower than the levels measured in single TBI-impacted animals. In contrast, IGF1 levels were already decreased one week after RTBI and remained chronically reduced (as analyzed one month later) [36]. This study suggests that multiple, repetitive head insults in adolescent rats induce a large, cumulative effect on the GH/IGF1 axis. In analogy, pronounced GH deficiency has been observed in a young (14-year old) patient who suffered 4 consecutive head traumata in a 4-month period, eventually resulting in decreased muscle strength and physical growth [37].

Impact of RTBI on the gonadotropic axis has also been studied [38]. RTBI in male pubertal rats caused an acute decrease in plasma testosterone levels that persisted till 4 weeks after trauma and suppressed the peak testosterone production that is normally seen during this adolescent period of life. At later time points, no significant differences were observed anymore in testosterone levels which attained normal adult concentrations. One of the consequences of lowered testosterone levels in the first weeks after trauma was a delay (by 3 days) in the testosterone-driven onset of puberty. Also reproductive organ growth was compromised following RTBI, likely due to the lower

testosterone levels, showing a decreased weight of penis, prostate and testis at 1 and 2 months post-trauma when compared to sham-operated rats. Development of the epididymis, which is testosterone-independent, was found normal. RTBI-impacted rats further displayed erectile dysfunctions and altered sexual behavior [38]. Taken together, RTBI suffered during the critical phase of puberty/adolescence negatively affects sexual maturation and functioning. Hence, it is important to acknowledge hormonal deficiencies after repetitive TBI in young patients (being at high risk because of their particular lifestyle), as they may have lasting (reproductive) complications and abnormalities if untreated [36–38].

Intracranial hypertension model

In the intracranial hypertension (IH) model, autologous blood is injected in the animal's epidural space, mimicking epidural hematoma [39].

IH infliction in rats resulted in a gradual (from 12 to 24 h post-surgery) increase in cell apoptosis and cleaved caspase-3 levels (marker of apoptosis) in the hippocampus, hypothalamus and pituitary [39]. The pituitary gland seemed most sensitive to the elevated intracranial pressure since showing highest apoptosis rates (defined as the percentage of Terminal Deoxynucleotidyl Transferase (TdT)-Mediated dUTP Nick End Labeling (TUNEL)-positive cells). Of note, the surgery itself (as analyzed in sham-operated animals) also increased apoptosis in the 3 tissue structures although to a lower extent than in IH-impacted animals. Using a rabbit stress model in which animals were subjected to restraint and/or electrical shocks, not involving any brain injury, it was demonstrated that a general stress reaction per se also induced apoptosis in the pituitary and hypothalamus, and that apoptosis rates positively correlated with the intensity of suffered stress [39].

Regarding the HPA axis, IH caused an initial increase in ACTH levels (12 h post-surgery), which later dropped to levels lower than in control animals (24 h post-surgery). However, an acute increase in ACTH levels was also observed in sham-operated animals, in line with the idea of a generalized stress response to the trauma of surgery and anesthesia [39].

In the somatotropic axis, GH levels significantly declined following IH, which was also observed, although to a lower extent, in sham-operated animals [39].

Taken together, this study shows that increased apoptosis in the hypothalamus-pituitary axis can be caused by intracranial hypertension, along with the stress of the trauma, which may contribute to the distorted pituitary function.

Blast-injury model

The blast-injury model was developed to mimic mild TBI that is caused by blast waves from explosive devices, which has a phenotype distinct from other TBI forms [15]. Blast injury is especially common among soldiers and can cause long-term behavioral, emotional and cognitive problems [40]. In this experimental animal model, blast impact injury is inflicted by an air pressure wave.

Russell et al. [40] investigated the impact of a mild blast TBI (bTBI) on the HPA axis in male and female mice. The HPA axis was disrupted in both genders, although in a different manner. In male mice, the corticosterone response to restraint stress was elevated and CRH neuron activation decreased after bTBI, while the opposite was observed in female mice. This gender dichotomy was not due to differences in *Pomc* and CRH receptor-1 (*Crhr1*) gene expression in the pituitary, or in *11β-OHase*, *11β-HSD1* and *Mc2r* expression (needed for corticosterone synthesis in response to ACTH activity) in the adrenal gland which were not at all altered after bTBI. Also negative feedback loops were still intact following bTBI, as supported by suppression of the HPA axis after dexamethasone administration and sustained expression of the mineralocorticoid and glucocorticoid receptors in the paraventricular nucleus (PVN) of the hypothalamus after the blast impact. The ratio of non-neurosecretory CRH neurons (proposed to be involved in autonomic responses such as stress) to neuroendocrine CRH neurons in the PVN was found to be decreased following bTBI in female mice, but not in male mice. This decline may dysregulate autonomic responses to stress in female mice. The authors hypothesized that there might be a greater disruption of limbic pathways involved in HPA axis regulation in male *versus* female mice, but no evidence was provided. Taken together, it appears that traumatic blast impact on the HPA axis is sexually dimorphic which may be clinically and therapeutically important.

Conclusion

TBI and the concurring hypopituitarism have serious consequences for the manifold (young) people impacted every year. Not much is known on the mechanistic basis leading to the pituitary endocrine disruption. Several experimental TBI models have been developed to cover the heterogeneous phenotype of the disorder, but pituitary consequences and effects in physically or functionally associated structures have only scarcely been studied. Moreover, these investigations were mainly observational, and did mostly not look into the possible mechanisms causing the PTHP. Thus, more

research efforts are needed to uncover development of pituitary hormone dysregulation following TBI, at the same time asking for more pliable study models. Moreover, given the spontaneous restoration in some patients, it would be worthwhile to explore the underlying reparative mechanisms, and in particular the occurrence of tissue regeneration including the reaction of the local pituitary stem cells to TBI. Understanding this regenerative process may open up new treatment options for PTHP.

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Compliance with ethical standards

Conflict of interest Authors AV and HV declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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