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Stress Response to Surgery, Anesthetics Role and Impact on Cognition

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Abstract

The stress response to surgery includes a number of hormonal changes initiated by neuronal activation of the Hypothalamo-Pituitary-Adrenal (HPA) axis. Surgery is one of the most potent activators of ACTH and cortisol secretion, and increased plasma concentrations of both hormones can be measured few minutes after the start of surgery. A variable inhibition of ACTH-stimulated production of cortisol by anesthetic drugs has been demonstrated in clinical studies. Endocrine response to stress also includes a release of pituitary hormone prolactin which is poorly affected by anesthesia. These two hormones seem to mostly contribute to memory consolidation processes during anesthesia. This review summarizes the main aspects of interaction between stress response to surgery and cognition during general anesthesia.

Introduction

In recent years, many studies have shown an incomplete abolition of the cognitive faculties -such as memory and learning- during anesthesia despite the dull of consciousness [1-6]. It has been suggested that memory seems to occur more frequently during surgical stimulation regardless of anesthesia depth [7]. The stimulating effect of surgery may be explained by the fact that stress hormones released in response to pain target the hippocampus, prefrontal cortex and amidgala, brain areas involved in the complex memory circuits [8]. The consolidation process of long-term memory mainly takes place in the hippocampus and neocortex [9]. During physiological sleep, functional status of hippocampal-neocortical circuits could be modulated, according to recent hypotheses, by cortisol [10]. High levels of cortisol can disrupt the normal communication between the hippocampus and the neocortex impairing the process of memory consolidation [10]. On the contrary, the decreased levels of cortisol, which occur during slow wave sleep (SWS), are considered critical for memory consolidation. Other neuroendocrine mediators of stress, including prolactin (PRL), could be involved in modulating memory functions [11,12]. PRL increases the expression of corticotrophin-releasing hormone (CRH) which has been shown to enhance learning through hippocampal CRH-R1 regardless of its indirect attenuation of stress-induced hypothalamo-pituitary-adrenal (HPA) axis activity [13,14], probably mediated by modulation of neural pathways to hypothalamic paraventricular nuclei [15]. A variable inhibition of ACTH-stimulated production of cortisol by anesthetic drugs has been demonstrated in clinical studies [16,17]. On the other hand, a marked increase in PRL concentrations were observed independently of the anesthetic procedure [18,19].

The aim of this review was to examine the complex interaction between stress response to surgery, anesthetics and cognition by analyzing the current available literature on this issue.

Sympatho-adrenal response to surgery

The stress response to surgery includes a number of hormonal changes initiated by neuronal activation of the hypothalamic-pituitary-adrenal axis [18]. Hypothalamic activation of the sympathetic autonomic nervous system results in an increased secretion of catecholamines from the adrenal medulla and in a release of norepinephrine from presynaptic nerve terminals. The increased sympathetic activity causes the well-recognized cardiovascular effects of tachycardia and hypertension. In addition, the function of certain visceral organs, including the liver, pancreas and kidney, is modified directly by efferent sympathetic stimulation and/or circulating catecholamines [18]. Anterior pituitary hormone secretion is stimulated by hypothalamic releasing factors [20]. The pituitary synthesizes corticotrophin or adrenocorticotropic hormone (ACTH) as part of a larger precursor molecule, pro-opiomelanocortin. The precursor is metabolized within the pituitary gland into ACTH, β-endorphin and an N-terminal precursor. The amount of growth hormone and PRL secreted from the pituitary gland is also secreted in response to a surgical stimulus. On the contrary, concentrations of the other anterior pituitary hormones, thyroid-stimulating hormone (TSH), follicle- 24 stimulating hormone (FSH) and luteinizing hormone (LH) do not change markedly during surgery. The posterior pituitary produces arginine vasopressin which has a major role as an antidiuretic hormone. It also has an endocrine function, as it stimulates secretion of pro-opiomelanocortin from the anterior pituitary gland in conjunction with CRH.

The stress response to surgery causes an increased production of hormones with catabolic function. The value of this self-healing mechanismis doubtful in the surgical context [18].

Cortisol: cortisol secretion is increased as a result of adrenal cortical stimulation by means of ACTH. A greater ACTH and cortisol plasma concentrations may be detected few minutes after the start of the surgery and its increase is related to the intensity of surgical stimulus [21]. Other than its known metabolic effects, cortisol exerts anti-

inflammatory activity by reducing inflammatory mediators' production [18]. The physiological feedback mechanism that leads to ACTH synthesis inhibition due to increased cortisol concentration is disrupted during surgery whereas the cortisol secretion may be reduced by anesthetic drugs.

PRL: PRL is a protein hormone of 199 amino acids with a structure similar to that of growth hormone. Secretion of PRL is increased as part of the stress response to surgery. It has a little metabolic activity. The physiological effects of increased secretion of PRL during surgery are unknown. However, PRL is supposed to regulate T-lymphocyte proliferation [22].

Activation of the stress response: The endocrine response is activated by afferent neuronal impulses from the site of injury. These impulses travel along sensory nerve roots through the dorsal root of the spinal cord, up the spinal cord to the medulla in order to activate the hypothalamus. The idea that local substances might influence some of the changes associated with surgery was advanced after the cytokines discovery. The cytokines have local effects of mediating and maintaining the inflammatory response to tissue injury, and are also implicated in some of systemic changes. After major surgery, the main released cytokines are interleukin-1 (IL-1), tumor necrosis factor-α (TNF-α) and IL-6. The initial reaction is the release of IL-1 and TNF-α from activated macrophages and monocytes in the damaged tissues. This process stimulates production and release of further cytokines, in particular, IL-6, the main cytokine responsible for inducing the systemic changes known as acute phase response [23]. The cytokines increase the cortisol secretion by stimulating ACTH release as a result of surgical stimulus but cortisol response to surgery suppresses cytokine production due to a negative feedback system [24]. It has been demonstrated that IL-6 secretion, but not other stress hormones production, may be reduced using less invasive surgical techniques (e.g. laparoscopic approach) [25].

Effect of general anesthesia on the stress response to surgery

Anesthesia exerts a variable action on hypothalamic, pituitary and adrenal hormonal secretion although it has little effect on the cytokine response to surgery because it cannot influence tissue trauma [26]. Blood levels of ACTH, cortisol, epinephrine, norepinephrine and PRL has been used for evaluating stress or nociception level in surgery [18].Most of drugs used, including neuroleptic drugs, opioids, thiopentone, propofol and sevoflurane have been found to stimulate PRL release during anesthesia [18,19,27]. In patients undergoing cardiac surgery, morphine and other opioids (fentanyl, sufentanil and alfentanil) abolished ACTH and cortisol secretion at clinically used doses before the start of cardiopulmonary bypass (CPB) [18]. After CBP start, opioids were unable to completely suppress stress response [18]. In patients undergoing pelvic surgery, fentanyl suppressed ACTH and cortisol secretion when administered before surgical incision but not when given after the start of surgery [28]. Complete inhibition of the stress response in patients undergoing open cholecystectomy using high doses of fentanyl resulted in severe postoperative respiratory depression [29]. Therefore, opioids seem to suppress cortisol production only at high dose. Etomidate suppresses corticosteroids production at the adrenal cortex by reversible inhibition of the enzyme 11-β-hydroxylase and the cholesterol side chain cleavage enzyme. An induction dose (0.3 mg kg^{-1}) blocks the synthesis of aldosterone and cortisol for up to 8 h [30]. Benzodiazepines (midazolam 0.2-0.4 mg 30 kg^{-1} and infusion of 0.9-0.125 mg kg^{-1} h^{-1}) may also inhibit steroid production at the hypothalamic-pituitary level, but the significance of this effect has not been established. Effects of propofol on the synpathoadrenal system are well documented [16,31]. A single induction dose of propofol can suppress cortisol but it do not block cortisol and aldosterone secretion in response to surgical stress [31,32]. Continuous infusion of propofol, at deep anesthesia doses, completely abolished circulating cortisol secretion during surgery [31]. As the ACTH response to surgery during anesthesia maintenance was similar with propofol or inhaled anesthetics, the inhibition of cortisol secretion likely occur on the adrenal glands [16]. In the clinical setting of laparoscopic surgery, also the type of volatile anesthetic significantly affects the stress response: sevoflurane significantly decreased plasma concentrations of ACTH, cortisol and GH when compared to isoflurane [17].

Finally, there are evidences that perioperative use of dexmedetomidine reduces serum cortisol levels although the decrease in cortisol levels was not statistically different from the comparator anesthetics [33].

Interaction between stress hormones and cognition

Hormones released in response to stress play crucial roles in cognition. The influence of stress hormones on hippocampal function has been acknowledged for several decades. Stress is best described as a disturbance of physiological and psychological homeostasis ultimately controlled by HPA axis activity and resulting in secretion of corticosteroids from the adrenal cortex. The hippocampus has the highest concentration of corticosterone receptors in the brain that is responsible for the profound effects of stress on learning and memory processes [34]. Identification of the mechanisms by which stress modulate hippocampal function has been the subject of intense interest. A predictable finding is that high levels of glucocorticoids have a profound inhibitory effect on hippocampal cells activity, whereas low levels of glucocorticoids enhance cellular activity. Therefore, high concentrations of circulating glucocorticoids, consistent with marked stress, inhibit long-term potentation (LTP) while low concentrations of glucocortocoids enhanced LTP [35]. Within the central nervous system (CNS), two kinds of receptors are activated by cortisol: so-called glucocorticoid receptors (GRs; type II), and mineralocorticoid receptors (MRs; type I). When a neuron contains receptors of both types, as many within the hippocampus do, cortisol level affects the hippocampal function in an inverted U-shaped fashion [36]. For example, Diamond et al. [37] demonstrated that glucocorticoids facilitate LTP at low levels but impair it at high levels. The mechanisms producing this complex interaction are interesting. Type I (MR) receptors have a considerably higher affinity for cortisol than type II (GR) receptors do. Until all the MRs are occupied, there is a little occupancy of GRs. With extensive activation of the MR receptors, the possibility of activation of GRs emerges. Thus, impairment of hippocampal function by high levels of cortisol depends on the co-localization of MRs and GRs. Some study has confirmed that MRs and GRs are co-localized in the dentate gyrus and in the CA1 field, but much less so in the CA2 and CA3 fields, where concentrations of GR are greatly diminished [38,39]. This difference has potentially critical functional implications. Most prominently, it means that at high levels of cortisol, communication between the hippocampus and the neocortex, which is mediated by CA1 → subiculum → rhinal cortex connectivity, will be altered or disrupted. At the same time, communication within parts of the hippocampus itself, most prominently CA3, could remain intact. Thus, as the night progresses and cortisol levels increase, hippocampal-neocortical communication will eventually be altered. Note that levels between 10

and 30 μg/dL are associated with memory impairment during wake [40,41]. However, neither cortical-cortical activity itself nor activity within the CA3 circuits of the hippocampal formation will necessarily be disrupted. This interruption of hippocampal-neocortical communication could halt the consolidation of some type of memory, e.g. episodic memory [42,43], but it do not affect neuronal CA3 circuits activity or consolidation within procedural memory circuits [44]. High levels of cortisol during late night REM sleep could do more than interfere with episodic memory consolidation [45], as it weaken hippocampal system communication with the neocortex that is critical for episodic memory [46]. Neocortical circuits can thus generate only "episode-like" fragments that can be rather bizarre. It is worth noting the similarities between the nature of dreams and the kind of memories created during stress or trauma [47]. Fragmentation is an important feature of Post-Traumatic Stress Disorder (PTSD), in which patients sometimes describe gaps in recalled experiences, not only of trauma but of other personal experiences as well [48,49]. There are clinical evidences that high levels of cortisol alter memory function. Patient populations with chronically elevated levels of cortisol, such as Cushing's syndrome, major depression, and schizophrenia, as well as asthmatic patients treated with the glucocorticoid prednisone are characterized by impaired memory function [50,51]. Experimental studies of acute stress and memory have been carried out in animals [52], and several well-controlled studies have recently been conducted in humans. Kirschbaum et al. [40] demonstrated that a single, low dose of hydrocortisone (10 mg) leads to a deficit in verbal episodic memory. In this study, subjects who received hydrocortisone recalled fewer words (via a cued recall test) from a previously learned word list than control subjects did when recall interview occurred 60 min after receiving the drug. Further, Lupien et al. [53] demonstrated that prolonged cortisol elevations in older adults are associated with reduced hippocampal volume and impairments in hippocampally dependent memory tasks. Exactly how stress or glucocorticoids suppress LTP is still not well understood. It has been proposed that stress/glucocorticoids induce a variety of effects, including a change of the after-hyperpolarization amplitude, calcium current, or glutamate transmission, which impair LTP activation [54]. However, each stress hormone seems to affect LTP in a different manner. It has been demonstrated that noradrenaline and CRH increase LTP [55]. PRL, that pass the blood-brain barrier [56,57] and is also synthesized in the brain [57-60], acts as neuromodulator of HPA axis activation indirectly affecting LTP. PRL activates the mitogen activated protein kinase/extracellular signal-regulated kinase (MAPK/ERK) pathway facilitating CRH transcription in CRH neurons, This suggest that the in vivo reported inhibitory effect of PRL on HPA axis activity is indirect and probably mediated through modulation of afferent pathways to the PVN. PRL thus enhances CRH expression which has been shown to enhance learning through hippocampal CRFR1 [11].

There is only one study in which the relationship between memory and stress hormones under anesthesia has been investigated [61]. From this study it emerges that listening to a recording during surgical anesthesia is associated with a lower PRL increase, compared to baseline values, indicating that the perception of auditory stimulus during general anesthesia may affect neurohormonal response. In this study, hormonal changes were related to dream recall with a cortisol increase -compared to baseline values- determining a lower probability to recall dreams after awakening and higher levels of PRL leading to an increased rate of dream recall [61]. The interaction between a decrease in PRL levels induced by auditory presentation and memory impairment should be taken into consideration in order to ensure postoperative amnesia [61].

It is well known that there are no direct methods to measure stress level during general anaesthesia [62]. The common measured signs of autonomic reactions, such as blood pressure or heart rate, have been used for assessing stress level during anaesthesia, accepting their low specificity [62]. Some electroencephalographic (EEG-) derived variables, such as entropy [63] and bispectral index [64], are useful for monitoring depth of anaesthesia and preventing conscious recall but they do not always indicate inadequate analgesia and should be interpreted carefully during anaesthesia. The so-called surgical pleth index (SPI), a novel multivariate index using two continuous derived cardiovascular variables, has been proposed as a method to evaluate intraoperative stress level during general anaesthesia and a moderate correlation to the stress hormones (ACTH, cortisol, epinephrine, and norepinephrine) has been found during general anaesthesia in a recent study [65].

The incomplete abolition of memory and learning during anaesthesia, due to unimpaired stress response, may lead to an awareness episode with consequent PTSD, which is the most dangerous result of light anaesthesia [66]. HPA axis hyper-responsiveness in response to acute stress seems also involved in postoperative delirium pathophysiology [67].

As previously stated, the other aspect of stress response induced by maior surgery is inflammatory process that has a main role in the development of postoperative cognitive dysfunction (POCD) [68]. It has been demonstrated that surgery causes a persistent and possibly irreversible decrement in memory and learning in a murine model of Alzheimer disease, primarily through a transient activation of neuroinflammation [69] However, also metabolic endocrine stress, measured as perioperative cortisol secretion, has be found to correlate with incidence of POCD after major surgery [70]. Neuro-monitoring may help to prevent both PTSD [66] and POCD [71,72], but response to stress induced by surgery needs to be abolished in order to prevent memory consolidation and neuro-inflammation processes.

Conclusions

Anaesthetic drugs exert a variable action on response of HPA axis to surgical trauma and only little effects on cytokine production linked to tissue trauma. It is essential to blunt the stress hormones secretion in order to prevent postoperative complications, such as PTSD, POCD and delirium. Up to date, there is not a safe method to discriminate if response to stress is suppressed under anaesthesia; however, the use of drug at dose known to produce adequate anaesthesia and the support of neuro-monitoring may help to prevent an excessive HPA axis activation.

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