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Vestibular modulation of endocrine secretions – A review

Kumar Sai Sailesh[1], *Joseph Kurian Mukkadan*[2]

Little Flower Medical Research Centre (LFMRC), Angamaly. 1- Research scholar. 2- Research Director.

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Corresponding Author:

Dr. J.K. Mukkadan, Research director, Little Flower Medical Research Centre, Angamaly. Kerala. drmukkadan@sify.com

Abstract:

The need for vestibular stimulation can be observed throughout the life from newborns and infants in the cradle to the aged in a rocking chair. Everyday activities such as running, dancing, swinging, falling aside, or driving cars may exert positive and negative effects on subjective well-being. A thorough review of literature revealed that vestibular system is having extensive interactions with hypothalamic nuclei, autonomic system, dorsal and median raphe nuclei, substantia nigra, hippocampal formation and modulates endocrine secretions. The purpose of this article is to review research reports related to role of vestibular stimulation in modulation of endocrine secretions and to suggest translational research in this area.

Key words: Endocrine secretions; Translational research; Vestibule-hypothalamic connections; Vestibular stimulation; Vestibulo-Sympathetic reflex

Introduction

Vestibular system is the sensory system that provides the leading contribution about movement and sense of balance [1]. Endocrine glands secretes different types of hormones directly into the bloodstream[2]. Electrical and caloric stimulation of vestibular pathways results in a response in PVN (para ventricular neurons) neurons in the guinea pig [3,4]. Retrograde viral tracing in the rat brain has demonstrated the presence of a direct vestibulo-paraventricular projection [5]. The presence of inferior vestibulo hypothalamic connections are testified [6]. These hypothalamic neuro-hormones are known as releasing hormones because their major function is to stimulate the secretion of hormones originating in the anterior pituitary gland. One hypothalamic hormone, somatostatin, has an inhibitory action, primarily inhibiting the secretion of growth hormone although it can also inhibit the secretion of other hormones. The neurotransmitter dopamine, produced in the hypothalamus, also has an inhibitory action, inhibiting the secretion of the anterior pituitary hormone prolactin. The interactions among hypothalamus, pituitary and adrenal glands constitute the HPA axis, a major part of the neuro-endocrine system that controls reactions to stress and regulates many body processes [7]. Thyrotropin Releasing Hormone (TRH) neurons in the paraventricular nucleus of the hypothalamus (PVN) is of key importance for the normal function of the

axis under different physiological conditions including cold stress and changes in nutritional status [8]. The supraoptic nuclei and the para-ventricular nuclei of hypothalamus secretes vasopressin and oxytocin [9]. Vestibular system is also having projections to Suprachiasmatic Nucleus and raphe nucleus [10]. The circadian release of the hormone melatonin is regulated by the suprachiasmatic nucleus (SCN), which feeds back into the nucleus to modulate sleep and circadian phase through activation of the MT (1) and/or MT (2) melatonin receptors [11].

Autonomic responses to vestibular stimulation are regionally selective and have defined a 'vestibulosympathetic reflex' in animals [12]. There is substantial evidence that anatomical connections exists between vestibular and autonomic nuclei. Numerous animal studies have shown functional interactions between vestibular and autonomic systems [13-15]. However, relatively few studies have examined vestibular-autonomic interactions in humans [16,17]. The mechanisms and underlying physiological basis of vestibular-autonomic interactions are not fully defined [18,19]. Vestibular stimulation has been consistently found to reduce blood pressure in animals by reducing sympathetic activity [20]. Vestibular stimulation increased both rate and depth of respiration, as demonstrated by phrenic and recurrent laryngeal nerve recording, and a marked elevation in blood pressure accompanied this effect. When the strength of stimulation was reduced and the evoked respiratory effect weak or questionable, the systemic blood pressure declined [21]. Single shock vestibular stimulation evokes response from the ipsilateral but not from the contralateral vagus nerve [22]. The secretory activity of the gastric D-cell was therefore reciprocally influenced by the sympathetic and parasympathetic nerves [23]. The pancreatic islets are richly innervated by parasympathetic, sympathetic and sensory nerves. Thus, insulin secretion is stimulated by parasympathetic nerves or their neurotransmitters and inhibited by sympathetic nerves or their neurotransmitters [24]. Cells of vestibular origin were labeled by deposits of cholera toxin B (CT-B) centered on the general viscera-sensory division of NTS and dorsal motor nucleus (DMX) [25]. Gastric acid, insulin, and glucagon secretion were elicited by stimulation of the dorsal motor nucleus of the vagus (DMV). The centroid point for gastric acid was in the medial DMV, and the points for insulin and glucagon were in the lateral DMV [26]. Ghrelin release may be influenced directly by vagal stimulation [27].

The purpose of this article is to review research reports related to role of vestibular stimulation in modulating endocrine secretions, with the intent of clarifying the present knowledge base in this area, and suggesting future research needs.

Materials and methods

Searches of the review study register articles from google.com, pubmed.com, British medical journal.com, Medline, ERIC, frontiersin.org and online standardized journals.

Vestibular stimulation modulates melatonin (the light of night) secretion

Vestibular projections to the intergeniculate leaflet IGL were confirmed by using anterograde tracer injection into the medial vestibular nucleus. The intergeniculate leaflet (IGL) has widespread projections to the basal forebrain and visual midbrain, including the suprachiasmatic nucleus (SCN). IGL may be part of the circuitry governing visuomotor activity and further indicate that circadian rhythmicity might be influenced by head motion or visual stimuli that affect the vestibular system [28]. Intergeniculate leaflet conveys information about nonphotic phase-shifting to the circadian pacemaker in the suprachiasmatic nucleus [29]. Integrity of the IGL is necessary to have a complete integration of photoperiodic changes by the SCN [30]. Vestibular system is having projections to serotonergic dorsal raphe nucleus [31-33]. Vestibular stimulation activates midbrain. Serotonin (5-HT) is strongly implicated in the regulation of mammalian circadian rhythms [34]. Electrical stimulation of the dorsal and median raphe nuclei (DRN and MRN, respectively) induced 5-HT release in the SCN. Electrical stimulation of the DRN induces phase-resetting of the circadian activity rhythm [35].

Recent studies have demonstrated projections from the Medial vestibular nucleus (MVe) to the circadian rhythm system [36, 37]. Unilateral vestibular stimulation increased histamine release from the anterior hypothalamic area of urethan-anesthetized rats [38]. Immunoreactive somatostatin (IRS) is localized in the male and female rats which is submitted to diurnal variations [39]. Pharmacological levels of melatonin have been reported to decrease nerve activity of medial vestibular nuclei in the rat [40].

Vestibular modulation of thyroid hormones

Thyrotrophin releasing hormone (TRH) neurons are located in paraventricular nucleus. Electrical and caloric stimulation of vestibular pathways results in a response in PVN (para ventricular neurons) neurons in the guinea pig. Retrograde viral tracing in the rat brain has demonstrated the presence of a direct vestibulo-paraventricular projection. The hypothalamic pituitary thyroid (HPT) axis plays a critical role in mediating changes in metabolism and thermogenesis. Thus, the central regulation of the thyroid axis by Thyrotropin Releasing Hormone (TRH) neurons in the paraventricular nucleus of the hypothalamus (PVN) is of key importance for the normal function of the axis under different physiological conditions including exposure to cold and changes in nutritional status [41]. The hypothalamic thyrotropin-releasing hormone, in tropic fashion turns on thyroid-stimulating hormone (TSH) secretion by anterior pituitary. TSH is the most important physiologic regulator of thyroid hormone secretion [42]. Vestibular stimulation increases serotonin release from dorsal raphe nucleus [43]. The nucleus raphe dorsalis and median raphe send projections to the arcuate nucleus [44]. NPY innervation of hypophysiotropic TRH neurons in the hypothalamic paraventricular nucleus (PVN) originates primarily from NPY-producing neurons in the arcuate nucleus [45,46].

Increase in NPY/AGRP gene expression in arcuate nucleus neurons contributes to the fall in circulating thyroid hormone levels, presumably by increasing the sensitivity of the TRH gene to negative feedback inhibition by thyroid hormone [47]. Serotonin (5-HT) has been suggested to induce satiety and 5-HT fibers contact NPY neurons in the arcuate nucleus (ARC) and PVN, suggesting that 5-HT could inhibit the ARC-PVN projection [48,49]. Vestibular stimulation increases leptin secretion through vagal stimulation [50]. Leptin stimulates TRH release by 7-folds through both direct and indirect pathways [51]. Central vestibular dysfunction appears to be a rare but reversible neurologic sequelae of hypothyroidism [52].

Vestibular modulation of pancreatic hormones

Direct vestibular nucleus projections to nucleus tractus solitarius (NTS) and dorsal motor nucleus of the vagus nerve (DMX) are observed. The nucleus tractus solitarius (NTS) and dorsal motor nucleus of the vagus nerve (DMV) constitute sensory and motor nuclei of the dorsal vagal complex, respectively. Electrical stimulation of the NTS resulted in evoked excitatory and inhibitory postsynaptic currents (eEPSCs and eIPSCs) in DMV neurons [53]. Anterogradely labeled axons from the caudal medial vestibular nucleus (cMVN) and inferior vestibular nucleus (IVN) could be traced bilaterally to nucleus tractus solitarius (NTS). Cells of vestibular origin were labeled by deposits of cholera toxin B (CT-B) centered on the general viscera-sensory division of NTS and dorsal motor nucleus (DMX). Gastric acid, insulin, and glucagon secretion were elicited by stimulation of the dorsal motor nucleus of the vagus (DMV). The centroid point for gastric acid was in the medial DMV, and the points for insulin and glucagon were in the lateral DMV. Single shock vestibular stimulation evokes response from the ipsilateral but not from the contralateral vagus nerve. Pancreatic insulin secretion is regulated by the vagus nerve. Stimulation of the vagus nerve caused a considerable increase in insulin secretion, no significant change in glucagon secretion, and a decrease in C-peptide secretion. Electrical stimulation of the vagus stimulates pancreatic somatostatin, extrapancreatic somatostatin, and Pancreatic Polypeptide release in vivo in the dog. Both muscarinic and nonmuscarinic mechanisms mediate the PP and pancreatic SLI responses. A nonmuscarinic mechanism mediates the extrapancreatic SLI response; and all three responses are mediated via ganglionic nicotinic receptors [54].

It is concluded that vagal nerve stimulation in the dog produces a moderate increase of glucagon secretion, mediated by a nonmuscarinic (peptidergic?) mechanism, and a marked increase of insulin secretion, mediated by a muscarinic mechanism. Both responses are dependent on nicotinic transmission. Electrical vagal stimulation produced an increase in both insulin and glucagon secretion in proportion to the pulse frequency, but an inhibition in somatostatin release in rat [55]. Atropine inhibits both the glucose and insulin rises following vagal stimulation [56,57]. Diabetes mellitus is a disorder of glucose metabolism that can be associated with vestibular dysfunction [58].

Vestibular modulation of adrenal hormones

Vestibular modulation of adrenal cortical hormones

Controlled vestibular stimulation modulates hypothalamo-pitutary-adrenal (HPA) axis [59]. Swaying appears to decrease salivary cortisol levels in African elephants [60]. Infants who received auditory, tactile, visual and vestibular interventions

showed a significant steady decline in cortisol [61]. Vestibular stimulation is performed twice a day for ten days by using infant water bed in infants, decreased urinary cortisol levels significantly when compared with control group [62].

Noisy galvanic vestibular stimulation promotes GABA release in the substantia nigra in animals [63]. GABAergic inhibition controls the activity of the hypothalamic-pituitary-adrenal (HPA) axis, which mediates the body's response to stress. In addition to the actions of stress-derived steroid hormones on GABA(A)Rs, GABA(A)Rs reciprocally regulate the production of stress hormones [64]. High frequency electrical stimulation of specific vestibular sensory regions of the right labyrinth in anaesthetized guinea pigs induced an evoked field potential in the hippocampal formation bilaterally with a latency with a latency of about 40ms following stimulation onset [65]. Caloric vestibular stimulation in vestibular dysfunction activated hippocampal formation and activated hippocampal formation inhibits stress axis [66].

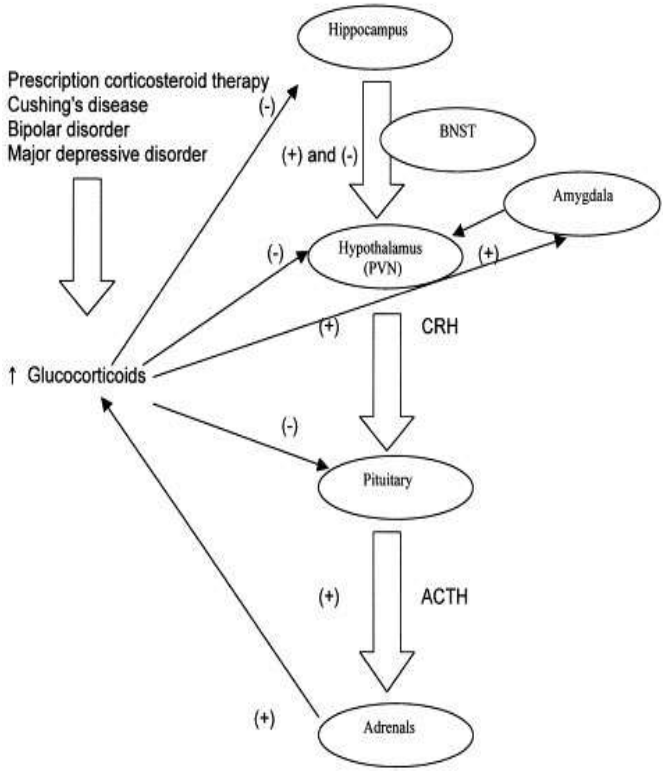

Figure 1: Diagrammatic representation of the interactions between hippocampus, amygdala, glucocorticoids and hypothalamo-pitutary-adrenal axis.

Plasma aldosterone levels are modified in accordance with the cortisol levels by hypophysial influences [67]. Hypothalamic supraoptic and para-ventricular nuclei responds to both electrical stimulation of eighth nerve and caloric stimulation of labryrinth. The response of neurons of supra optic nucleus is characterized by sequence of excitation-inhibition, whereas the neurons of paraventricular nucleus showed different patterns of response with various combinations of excitation and inhibition sequences. Lesions in the nucleus paraventricularis (NPV), the nucleus supraopticus (NSO) caused a substantial decrease in the rate of aldosterone production [68].

Single shock vestibular stimulation evokes response from the ipsilateral but not from the contralateral vagus nerve. Functional studies indicate that electrical vagal stimulation results in reduced cortisol responses in depressed patients [69-72].Vagal stimulation most probably alters synaptic activities at vagal afferent terminations, stimulates deep brain areas, and thus modulates antidepressant neuronal circuits in multiple limbic system structures. Brain imaging studies reveal some of these suspected brain changes. PET measurements of cerebral blood flow in 10 patients with epilepsy before and during acute VNS treatment (both low- and high- stimulation VNS) demonstrated increased blood flow in the rostral, dorsal-central medulla, the right postcentral gyrus, bilaterally in the hypothalami, thalami, and insular cortices, and in the cerebellar hemispheres inferiorly Decreased blood flow was demonstrated bilaterally in hippocampus, amygdala, and posterior cingulate gyri [73-77].

Vagal stimulation has been found to alter concentrations of neurotransmitters that are probably involved in the mechanism of depression. VNS was associated with increased GABA, 5-hydroxyindoleacetic acid and homovanillic acid levels and decreased aspartate and glutamate levels [78,79]. A preliminary study suggests that VNS treatment changes the hypothalamic-pituitary-adrenal (HPA) axis stress system. In patients with chronic depression, corticotrophin-releasing hormone (CRH) challenge causes increased adrenocorticotrophic hormone (ACTH) levels. VNS treatment of depressed patients reversed this abnormally increased ACTH response to CRH challenge [80]. Hypothalamus produces Leutinizing hormone releasing hormone (LHRH), corticotropin-releasing factor (CRF), which reaches the anterior pituitary and stimulates release of luteinizing hormone (LH) and adrenocorticotropic hormone (ACTH) into the blood. LH and ACTH, via the blood, stimulate the testes and adrenal glands, respectively [81].

Vestibular modulation of adrenal medullary hormones

Vestibular system regulates sympathetic nerve activity in humans [82]. Numerous animal studies have shown functional interactions between vestibular and autonomic systems. However, relatively few studies have examined vestibular-autonomic interactions in humans. In response to electrical activation of vestibular afferents, firing of sympathetic nerves located throughout the body is altered [83]. Otolith organs but not the horizontal semicircular canals participate in the regulation of SNA in humans [84]. Vestibular stimulation reduces sympathetic activity [85,86] However the response of sympathetic nerve varies with the intensity of vestibular stimulation [87]. Vestibular system project to the diencephalon and diencephalon alters sympathetic nerve activity [88]. Plasma nor-epinephrine should show an intensity-dependent increase during sympathetic stimulation and decrease during sympathetic inhibition [89].

Vestibular modulation of pituitary hormones

Vestibular modulation of anterior pituitary hormones

The secretion of growth hormone (GH) is mainly by two neuroendocrine hormones, GH-releasing hormone and somatostatin [90]. Growth hormone-release-inhibiting hormone (somatostatin) was localized in the external zone of the median eminence, the subcommissural organ, the organum vasculosum of the lamina terminal is and the pineal gland [91]. Vestibular stimulation modulates pineal gland secretions. Vestibular stimulation evokes response from the ipsilateral but not from the contralateral vagus nerve. The influence of vagal stimulation on somatostatin release varies with species. Vagal stimulation inhibits somatostatin release in rat [92].

Portal vein somatostatin was decreased following vagal stimulation, indicates that the release of somatostatin from another large source of somatostatin, presumably the fundic region of the stomach or the pancreas, was decreased by vagal activation [93]. In contrast vagal stimulation increased somatostatin release in dogs. Vestibular system regulates sympathetic nerve activity in humans [94]. In isolated perfused human pancreas, celiac neural bundle stimulation causes inhibition of somatostatin secretion through an alpha-adrenergic effect. Beta-adrenergic fibers stimulate somatostatin secretion; cholinergic fibers have a negligible effect on somatostatin secretion. Splanchnic innervation of the pancreas has a potent regulatory role in somatostatin release in vitro human model [95].

Vestibular system is having projections to serotonergic dorsal raphe nucleus. Vestibular stimulation activates midbrain [96]. The nucleus raphe dorsalis and median raphe send projections to the arcuate nucleus [97]. In conscious rats, serotonin microinjected into the basal hypothalamus caused secretion of GH maximal within 10-25 min. .It is concluded that activation of serotonin receptors, probably type I, on or near GH releasing factor neurons in the arcuate nucleus causes secretion of GH [98,99]. Serotonin also increases prolactin release [100]. Hypothalamic extracts stimulated the release of prolactin and growth hormone from pigeon and chicken pituitary glands incubated in vitro [101].

Noisy galvanic vestibular stimulation promotes GABA release in the substantia nigra in animals. Intraventricular injections of the highly specific gamma-amino-butyric acid (GABA) agonist muscimol (5 nmol/animal) stimulated pituitary prolactin release and inhibited LH release from pituitary gland in ovariectomized (ovx) and in ovx estrogen-progesterone (OEP) primed rats, supports the hypothesis that preoptic-anterior-hypothalamic GABA neurons involves in the regulation of pituitary LH and prolactin release [102]. Unilateral electrical vestibular stimulation activate the histaminergic neuron system in the brain. Histamine release from anterior hypothalamus was increased to approximately 180% of the basal release by the electrical stimulation of the inner ear with 1 Hz, 500 microA, and 200 ms for 20 min [103]. Histamine receptors present in the preoptic-anterior-hypothalamic area are involved in the PRL release due to estrogen and that both H1 and H2-histamine receptors may be mediators of this response [104]. GnRH neurons receive a major input from-aminobutyric acid (GABA)ergic neurons, and GABA type A receptor activation may play a role in their regulation by steroids [105]. Noisy galvanic vestibular stimulation promotes GABA release in the substantia nigra in animals.

Increasing endogenous GABA concentration in rats and non-human primates prevents ovulation and pulsatile LH release, and blunts the LH surges by actiong on the preoptic-anterior hypothalamic area where the cell bodies of LHRH neurons are located, and the medial basal hypothalamus which contains the nerve endings of the LHRH system [106]. GnRH neurons receive a major input from-aminobutyric acid (GABA)ergic neurons, and GABA type A receptor activation may play a role in their regulation

by steroids. GABA plays a physiological role in the control of AP hormone secretion, mainly via a hypothalamic action. GABA can stimulate LH, growth hormone (GH) and, at high doses, prolactin (Prl) release, whereas low doses inhibit Prl and al doses inhibit TSH release [107].

Vestibular stimulation increases leptin secretion through vagal stimulation [108]. Leptin also interacts with and regulates the hypothalamic-pituitary-adrenal, the hypothalamic-pituitary-thyroid and the hypothalamic-pituitary-gonadal axes [109]. Leptin modulates pituitary hormones including LH, FSH and ACTH, probably via the hypothalamus. Leptin has a direct effect on the pituitary to enhance GHRH-induced GH secretion [110,111].

Vestibular modulation of posterior pituitary hormones

Hypothalamic supraoptic and para-ventricular nuclei responds with excitation and inhibition sequences to both electrical stimulation of eighth nerve and caloric stimulation of labryrinth. However the response is depended on the intensity of stimulation. Electrical vestibular stimulation with more than 200 microA increased the plasma levels of VP in a current intensity-dependent manner, and stimulation with 500 microA increased the plasma VP levels to 350% of the normal control group, which received no stimulation.

Caloric vestibular stimulation with cold water increased the plasma VP levels to 262% of the control group, which received caloric stimulation with water at 37 degrees C, and stimulation with warm water tended to increase the plasma VP levels [112]. Vestibular stimulation increases serotonin (5-HT) release from dorsal raphe nucleus. 5-HT is involved in the mediation of the vasopressin and oxytocin response to stress. 5-HT receptors involved in the 5-HT-induced increase of mRNA expression of vasopressin and oxytocin in the hypothalamic paraventricular nucleus (PVN) and supraoptic nucleus (SON).

The neurotransmitter serotonin (5-HT) stimulates the secretion of vasopressin and oxytocin. stimulation with 5-hydroxytryptophan or 5-HT agonists increases mRNA expression of oxytocin in the PVN and the SON via stimulation of at least 5-HT1A, 5-HT1B, 5-HT2A and 5-HT2C receptors. Vasopressin mRNA in the PVN was increased only via the 5-HT2 receptor, whereas vasopressin mRNA in the SON does not seem to be affected by 5-HT stimulation. Corticotropin-releasing hormone appears to be partly involved in the mediation of 5-HT induced vasopressin and oxytocin secretion. Vasopressin levels are elevated briefly following 5-HT intracerebroventricular (i.c.v) [113].

Single shock vestibular stimulation evokes response from the ipsilateral but not from the contralateral vagus nerve. Abdominal vagal afferents causes secretion of vasopressin in the rabbit via a central pathway that includes neurons in the A1 area [114]. Afferent electrical stimulations of both sciatic and vagal nerves at 5 V, 0.2-2 ms and 3-10 Hz caused immediate significant elevations of oxytocin levels [115].

Vestibular modulation of thymic hormones

Vestibular stimulation influences growth hormone secretion. The development and aging of the thymus appear to be dependent on the serum level of GH which is under the balance of positive (GHRH) and negative (GHRIH) signals from the hypothalamus. The thymus became hypertrophic and serum level of growth hormone (GH) markedly increased, when the anterior portion of the hypothalamus (AHTL) was destroyed in rats at 1 month of age and older. AHTL removed the cells secreting GHRIH (growth hormone release inhibitory hormone), but not GHRH (growth hormone releasing hormone), leading to increased pituitary secretion of GH which is responsible for hypertrophy of thymus [116].

Vestibular modulation of gastro-intestinal hormones

Vestibular stimulation increases vagal activity. Vagal stimulation suppresses somatostatin release from delta cells. The vagus nerve plays a central role in the regulation of gastrin release [117]. Activation of the vagal nerves causes release of vagally controlled gastrointestinal hormones such as gastrin and cholecystokinin [118]. Electrical stmulation of vagus nerve caused significant increase in both GRP and gastrin but a decrease in somatostatin [119].

Limitations

This hypothesis has not proved experimentally. But work is in progress in our Research centre to prove or disprove this hypothesis.

Conclusion

From the above discussion we conclude that vestibular stimulation modulates endocrine

secretions. It is the need of time to identify the importance of vestibular stimulation and to start translational research in this area.

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