Neuropharmacological Targets for Drug Action in Vestibular Sensory Pathways

Choongheon Lee\(^1\) and Timothy A. Jones\(^2\)

\(^1\)Department of Otolaryngology, Washington University School of Medicine, Saint Louis, MO, USA
\(^2\)Department of Special Education and Communication Disorders, University of Nebraska-Lincoln, Lincoln, NE, USA

The use of pharmacological agents is often the preferred approach to the management of vestibular dysfunction. In the vestibular sensory pathways, the sensory neuroepithelia are thought to be influenced by a diverse number of neuroactive substances that may act to enhance or inhibit the effect of the primary neurotransmitters [i.e., glutamate (Glu) and acetylcholine (ACh)] or alter their patterns of release. This review summarizes various efforts to identify drug targets including neurotransmitter and neuromodulator receptors in the vestibular sensory pathways. Identifying these receptor targets provides a strategic basis to use specific pharmacological tools to modify receptor function in the treatment and management of debilitating balance disorders. A review of the literature reveals that most investigations of the neuropharmacology of peripheral vestibular function have been performed using \textit{in vitro} or \textit{ex vivo} animal preparations rather than studying drug action on the normal intact vestibular system \textit{in situ}. Such noninvasive approaches could aid the development of more accurate and effective intervention strategies for the treatment of dizziness and vertigo. The current review explores the major neuropharmacological targets for drug action in the vestibular system.

\textbf{KEY WORDS:} Dizziness · Vertigo · Peripheral vestibular system · Neuroactive substance · Vestibular suppressant.

Introduction

Dizziness may be caused by many disturbances in central and peripheral neural function. Vertigo, dizziness, and disequilibrium consistently rank among the most common complaints experienced by individuals with vestibular dysfunction. Moreover, vestibular deficits appear to be among the most common causes of disequilibrium symptoms requiring medical intervention. Decreased function of the peripheral vestibular system can result in decreased visual acuity during head movements and a degradation of postural control. The management of dizziness related symptoms has mostly involved the use of pharmacological agents during the early acute phase of symptom onset. The common objective of drug treatment is to suppress vestibular sensory input. This is thought to reduce conflicting sensory input, control undesirable perceptions, and improve the quality of life of patients.

Vestibular signals originate from the sensory organs of the three semicircular canals and two macular organs within the petrous portion of the temporal bone (Fig. 1). The vestibular neuroepithelium including hair cells, supporting cells as well as afferent and efferent neurons are thought to interact with a diverse number of neuroactive substances (neurotransmitters and neuromodulators), which bind to specific receptors at the postsynaptic membrane. During normal chemical synaptic transmission, these neurotransmitters and modulators are synthesized and stored in presynaptic vesicles and are released into the synapse to bind and act on postsynaptic cell receptors during the transmission and processing of sensory information. Glutamate (Glu) or a glutamate-like excitatory amino acid...
Pharmacological Targets for Vestibular Disorders

(EAA) and acetylcholine (ACh) are widely accepted as being the primary neurotransmitters released by vestibular hair cells and efferent neural terminals respectively [1,2]. In the peripheral vestibular system, there are a variety of other neuroactive molecules that are thought to be present and may act as modulators at these synapses including γ-aminobutyric acid (GABA), substance P, calcitonin gene-related protein (CGRP), and opioid peptides. These neuromodulators may affect the response of neurons by facilitating or inhibiting the effect of the primary neurotransmitters or by altering patterns of release. Neuroactive substances bind with numerous corresponding postsynaptic and presynaptic receptors to mediate neural transmission or modulate the response of postsynaptic neurons. Pharmacologic agents can act at these receptors to alter synaptic messaging. In this way, pharmacological agents have a diverse array of cellular targets that provide a means for modifying sensory transmission. In Fig. 2, many of the possible targets of pharmacological agents in the peripheral vestibular sensory neuroepithelium are summarized.

Neuroactive Substances and Receptors

Molecular biological, biochemical, and electrophysiologic evidences suggest that glutamate, ACh, histamine, enkephalins, GABA, CGRP, and substance P are all released to some extent as neurotransmitters or modulators in the peripheral vestibular system [3,4]. In central vestibular circuits, the vestibular nuclei integrate vestibular, somatosensory, proprioceptive, and visual inputs. These diverse synaptic inputs to the nuclei are also represented by glutamatergic, GABAAergic, histaminergic, serotoninergic, and dopaminergic neurons [4]. These neural projections to vestibular nuclei arise mainly from vestibularafferent neurons, spinal afferents, cerebellum, and more rostral descending visual and motor control systems [5]. The following provides an overview of neurotransmitter and neuromodulator receptors identified in the peripheral vestibular neuroepithelium and ganglion as well as in central vestibular nuclei.

Glutamate receptors

In the vestibular system, glutamate is an EAA and the major neurotransmitter of the vestibular sensory hair cells [1].
Glutamate interacts with ionotropic receptors such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), N-methyl-D-aspartic acid (NMDA), and kainic acid (KA) as well as metabotropic receptors such as metabotropic glutamate receptor 1-8 (mGluR1-8) [1,6]. Ionotropic and metabotropic glutamate receptors are located on the vestibular primary afferent dendrites. These receptors mediate the input signals from vestibular hair cells and also between primary afferents and second order vestibular nuclei neurons (see below).

AMPA is a major glutamate receptor in the inner ear. The AMPA response to glutamate produces a postsynaptic increase in intracellular cations including especially Na\(^+\) post-synaptically; these cations thus play a functional role in AMPA-mediated depolarization of vestibular afferent neurons [7]. Immunohistochemical studies have suggested that AMPA receptor subunits GluR1, GluR2-3, and GluR4 are expressed in mammalian vestibular hair cells and calyx afferents [3,7]. The application of a specific AMPA/KA antagonist (1.5 mM DNQX) to the mouse vestibular afferents blocked AMPA responses [7]. The neurons of the vestibular nuclei also express AMPA EAA receptors. Popper, et al. [8] used immunohistochemistry in the vestibular nuclei of the chinchilla and found ionotropic AMPA receptor subunits (GluR2-3) in the most neurons, (GluR1) in some neurons, and (GluR4) in the fewest number of neurons.

There is evidence in support of the presence of the NMDA receptors on both vestibular hair cells and afferent neurons. The NMDAR receptor (NMDAR) subunits NMDAR1, NMDAR2A, NMDAR2B, NMDAR2C, and NMDAR2D are reportedly expressed in rat vestibular afferent neurons [6]. Electrophysiological studies have suggested that the application of NMDA antagonists [2-amino-5-phosphonopentoanoic acid (AP5) and 7-chloro-kynurenic acid (7ClKyn)] decreased spontaneous spike discharge in vestibular afferents [9]. In addition, an electrophysiological study using whole-cell patch clamp methods in the brainstem reported NMDA receptors contribute to afferent synaptic transmission in the medial vestibular nucleus (MVN) of the rat [10]. These studies suggest that NMDA receptors contribute to afferent neurotransmission in both the peripheral and central vestibular system.
Evidence for KA glutamate receptors in the vestibular system is far less compelling, and glutamate affinity at ionotropic KA receptors seems to be low. There are five KA receptor subunits (GluR5-7 and KA1-2); however, GluR5, GluR6, KA1, and KA2 were only immunohistochemically expressed in mammalian vestibular ganglia [6]. Several pharmacological studies have suggested that KA receptors like other glutamate receptors act during afferent neurotransmission in mammalian vestibular neurons. Trimeprazine, a potent antagonist of KA receptor, blocked kainate-induced excitatory responses in the rat vestibular afferent neurons [11]. AMPA/KA receptor antagonists, CNQX and NBQX, were delivered to the interstitial fluids of the inner ear through perilymphatic perfusion and the effect on vestibular compound action potentials using linear vestibular sensory evoked potentials (VsEPs) showed VsEP response amplitudes were significantly reduced [12]. Evidence for metabotropic glutamate receptors in the vestibular pathways is far less compelling, with a limited number of studies. Numerous studies have shown that the afferents innervating hair cells are triggered by responses to the activation of glutamate receptors, and glutamate is a major afferent neurotransmitter at both peripheral and central afferent synapses.

ACh receptors

The primary neurotransmitter of vestibular efferent synapses is acetylcholine [13,14]. In mammals including humans, the activity of choline acetyltransferase (ChAT), which synthesizes ACh, and acetylcholinesterase (AChE), which inactivates ACh, was found in numerous bouton terminals at the basal surface of the vestibular hair cells [13,15]. Two major classes of ACh receptors found in the vestibular neuroepithelium are nicotinic ACh receptor (nAChR) and muscarinic ACh receptor (mAChR). Over the last decade, Holt and his colleagues have focused on addressing the function of the ACh receptor (mAChR). Over the last decade, Holt and his colleagues have focused on addressing the function of the ACh receptor (mAChR). Over the last decade, Holt and his colleagues have focused on addressing the function of the ACh receptor (mAChR), and mACh receptors are metabotropic receptors (i.e., G-protein-coupled receptors) and its receptor subunits (m1-5) are expressed in mammalian vestibular end organs and Scarpa’s ganglion [13,18]. Because of the G-protein-coupled receptor signaling mechanism, mAChR-mediated responses should follow relatively slower kinetics than nAChRs. Despite the slow kinetics, mACh receptors have been the target of vestibular suppressants (e.g., scopolamine). Whole-cell patch clamp recordings of rat vestibular afferent neurons showed that the mAChR agonist, oxotremorine-M, significantly reduced outward polarizing K+ current called “M-current,” causing depolarization and excitation of the neurons [19]. Its action was blocked by atropine, an mAChR antagonist, thus suggesting the presence of mAChRs on vestibular afferent neurons. Recently using in vivo recordings, pharmacological reduction of M-current was shown to significantly alter peripheral vestibular afferent responses suggesting that efferent control of mAChRs may provide a means to modulate primary afferent response characteristics [20].

In the vestibular nuclei, specific nAChR and mAChR subunits were not clearly identified. Even in the vestibular efferent neurons of brainstem, ChAT (responsible for the synthesis of ACh) is found only in some of the vestibular efferent neurons [13] suggesting that some of these neurons may not be mediated by nAChRs and mAChRs. Intracellular recordings of rat MVN have shown that nACh and mACh receptor agonists produced membrane depolarization [21]. Extracellular recordings in all four major vestibular nuclei (i.e., medial, lateral, inferior, and superior) of the rat vestibular nuclear complex have indicated that nACh and mACh receptor agonists (carbachol and muscarine) increased spontaneous firing rates and established that the effect of ACh agonists was highest in the MVN [22]. These studies indicate that both nACh and mACh receptors are present and influence the excitability of the mammalian vestibular nucleus neurons.

GABA receptors

The role of GABA in the vestibular system has been widely debated, but a clear consensus has not been reached. GABA receptors are divided into three types [23]: 1) GABA_A receptor is an ionotropic receptor controlling a ligand-gated Cl⁻ control the membrane permeability to cations especially Ca²⁺ ions [17] and when activated lead to membrane depolarization and excitation of vestibular afferents. However, α9α10 nACh receptors when activated increase Ca²⁺ entry into the cell, which in turn activates Ca²⁺-dependent K⁺ (SK) channels. This produces membrane hyperpolarization, inhibition of neurotransmitter release and a reduction in the excitatory drive on primary afferents [14].
Histamine and its four receptors (H1, H2, H3, and H4) have been identified in the vestibular sensory pathway: H1, H2, and H3 receptors in the vestibular hair cells [29]; H3 and H4 receptors in the vestibular afferents [30,31]. All histamine receptors are metabotropic, with four different G-protein coupled receptors acting through a second messenger intracellularly. Evidence for histamine receptors in the vestibular system suggests that they may perform an important role in the control of vestibular function.

Even though H1-3 receptors are expressed and their activation induces an influx of Ca\(^{2+}\) in vestibular hair cells, intracellular recordings of guinea pig vestibular hair cells have shown that H3 receptors may mediate a notably larger increase in Ca\(^{2+}\) permeability (larger influx of Ca\(^{2+}\)) compared to H1 and H2 receptors [29]. Recently, H4 antagonist JNJ7777120 has been studied in Scarpa’s ganglion of the rat and electrophysiological recordings showed reversible inhibitory effects elicited by the H4 receptor antagonist without subsequent excitatory action [31]. However, this effect may not be shared by central vestibular nucleus neurons. The findings suggest that H4 receptors mediate an excitatory action in vestibular primary afferent neurons. Histamine also modulates the neural activities of the second order neurons in the vestibular nuclei and its various effects on the vestibular nuclei have been reported in several electrophysiological studies. Dimaprit, a selective H2 receptor agonist, produced an excitatory action on rat MVN neurons, and its effect was blocked by ranitidine, a selective H2 receptor antagonist, blocked its effect [32]. Beiahistine (strong H3 receptor antagonist and weak H1 receptor agonist), produced a weak excitatory action, but significantly reduced the excitatory effect elicited by histamine on the MVN neurons [32,33]. Thus, the effectiveness of histamine receptor antagonists on motion sickness, vertigo and dizziness can be explained by their action in reducing the excitatory actions in the mammalian vestibular nuclei and/or in the vestibular periphery.

Opioid peptide receptors

The opioid receptors preferentially activated by the enkephalins largely comprise three receptor subtypes (μ-, κ-, and δ-receptors; G-protein coupled receptors) based on their pharmacological characteristics [34]. In addition to three major receptor subtypes, the opioid-like orphan (ORL1) receptor is another member of the opioid receptor family and is specifically activated by nociceptin. Enkephalins and opioid receptors were found in the vestibular sensory pathway: μ- and k-opioid receptors in the vestibular hair cells and afferent neurons; δ-opioid and ORL1 receptors in the MVN neurons [4,13,35]. Opioid peptides may be candidates for modulating synaptic transmission in the vestibular afferent neurons. Whole-cell patch clamp recordings of amphibian vestibular hair cells showed that vestibular afferents were excited by μ-receptor

Histamine receptors

Histamine and its four receptors (H1, H2, H3, and H4) have been identified in the vestibular sensory pathway: H1, H2, and H3 receptors in the vestibular hair cells [29]; H3 and H4
agonists at the postsynaptic level (postsynaptic activation of afferent neurons) and inhibited by k-receptor agonists at the presynaptic level (inhibition of hair cells), reducing Ca\(^{2+}\) currents in the hair cells [36]. This study suggests that the vestibular afferents are regulated by the complex of opioid receptors. Electrophysiological data from mammalian MVN neurons indicated that the 6-opioid receptor agonists inhibited rotation- and glutamate-induced firing rates [37] and ORL1 receptor agonists also inhibited the spontaneous discharge rates [35]. These results suggest that enkephalins modulate afferent transmission at both the peripheral and the central vestibular levels.

**Dopamine receptors**

Dopamine receptors have been divided into two families: a D1-like family of dopamine receptors including D1 and D5 as well as a D2-like family including D2, D3, and D4 (all G-protein coupled receptors) [38]. Several findings support a possible involvement of dopamine as a modulator of excitatory neurotransmission at postsynaptic afferent terminals [38,39]. In the mammalian vestibular neuroepithelium, immunohistochemical evidence has indicated that dopamine D1 and D2 receptors are expressed in both type I and type II vestibular hair cell membranes [40]. Pharmacological studies using extracellular recordings showed that frog vestibular afferents were excited by EAA agonists and the excitation was suppressed by co-administration of D1 or D2 agonists [39]. This result suggests that the responses of D1 and D2 receptors act not only to modulate glutamate receptors postsynaptically, but also may have a protective function in the vestibular dendrites. In the vestibular nuclei, guinea-pig MVN neurons were depolarized only by D2 agonists; D1 receptors were not involved, suggesting the presence of D2 receptors in the mammalian MVN [41]. In clinical applications, dopaminergic receptor antagonists such as prochlorperazine, promethazine, and domperidone [27] might exert a modulatory action on vestibular afferent neurons.

**CGRP receptors**

Immunohistochemical studies found that ChAT and CGRP probably co-exist in vestibular efferent neurons [13,42]. Electrophysiological data confirmed the function of CGRP receptor and showed that CGRP released from efferent neurons increased vestibular afferent activities [3]. Sewell and Starr [43] argued that CGRP released from efferent neurons produces an increase in spontaneous discharge rate and this increases the probability of excitatory postsynaptic potentials. Recently, mice with loss of \(\alpha\)CGRP gene \((-/-)\) showed a significant reduction in Vestibular Ocular Reflex (VOR) gain, suggesting CGRP dependent effects in peripheral and/or central vestibular pathways [42]. Taken together, the results of these studies regarding CGRP suggest that efferent fibers making contact with both calyx afferents and type II hair cells contain CGRP and CGRP may exert modulatory effects on ACh receptors to increase the excitability of peripheral vestibular afferents.

**Immunocytochemistry studies** have reported the presence of substance P in mammalian vestibular hair cells and Scarpa’s ganglion [3,4,44] and investigated the coexistence of substance P and CGRP in the rat vestibular end organs using immunocytochemistry. Usami, et al. [44] revealed three different types of immunoreactivities localized within as well as beneath the sensory epithelia in rats. Since most immunoreactivity data clearly indicate that CGRP is associated with efferent fibers, the finding of substance P also supports the coexistence of the two and suggests a possible role for substance P in modulating the peripheral vestibular system.

**Conclusion**

The current review of the literature reveals that basic research on the pharmacological targets of drugs and medications has provided many answers to questions about the biochemical, molecular and functional nature of neural signaling in the vestibular sensory pathways. If we are to understand the action of drugs and medications, we must first understand the target receptors through which drugs and medications act to produce clinical outcomes. A considerable amount of effort has been carried out to identify neurotransmitters and modulators in the vestibular system using in vitro animal preparations. Medications work by mimicking, suppressing or otherwise altering these normal signaling processes. One may speculate and infer that the lessons learned from study of target processes and mechanisms, although often discovered in vitro, also apply to drug actions in the intact animal. However, in many cases particularly in the case of new and promising medications, drug actions in the intact animal are not fully understood. Therefore, developing reliable direct in vivo assessment tools for the study of vestibular sensory pathways will be important to accurately quantify drug effects on vestibular function. Clinically, in vivo research on vestibular pharmacological targets may aid the development of more accurate and effective intervention strategies for the treatment of dizziness and vertigo.

**Acknowledgments**

We thank Drs. Sherri Jones and J. Chris Holt for their comments on an earlier version of this work.
Conflicts of interest

The authors have no financial conflicts of interest.

REFERENCES

1) Watkins JC, Evans RH. Excitatory amino acid transmitters. Ann Rev Pharmacol Toxicol 1981;21:165-204.
2) Hilding D, Wersäll J. Cholinesterase and its relation to the nerve endings in the inner ear. Acta Otolaryngol 1962;55:205-17.
3) Guth PS, Perin P, Norris CH, Valli P. The vestibular hair cells: post-transductional signal processing. Prog Neurobiol 1998;54:193-247.
4) Soto E, Vega R, Seseña E. Neuropharmacological basis of vestibular system disorder treatment. J Vestib Res 2013;23:119-37.
5) Highstein SM, Holstein GR. The anatomy of the vestibular nuclei. Prog Brain Res 2006;151:157-203.
6) Niedzielski AS, Wenthold RJ. Expression of AMPA, kainate, and NMDA receptor subunits in cochlear and vestibular ganglia. J Neurosci 1995;15(3 Pt 2):2388-53.
7) Rabajac D, Devau G, Raymond J. AMPA receptors in cultured vestibular ganglion: detection and activation. Eur J Neurosci 1997;9:221-8.
8) Popper P, Rodrigo JP, Alvarez JC, Lopez I, Honrubia V. Expression of the AMPA-selective receptor subunits in the vestibular nuclei of the chinchilla. Mol Brain Res 1997;44:21-30.
9) Soto E, Flores A, Eróstegui C, Vega R. Evidence for NMDA receptor in the afferent synaptic transmission of the vestibular system. Brain Res 1994;633:289-96.
10) Sakai N, Ujihara H, Ishihara K, Sasa M, Tanaka C. Electrophysiological and pharmacological characteristics of ionotropic glutamate receptors in medial vestibular nucleus neurons: a whole cell patch clamp study in acutely dissociated neurons. Jpn J Pharmacol 1996;72:335-46.
11) Dayanithi G, Desmadryl G, Travo C, Chabbert C, Sans A. Trimerazine modulates AMPA/kainate receptors in rat vestibular ganglion neurons. Eur J Pharmacol 2007;574:8-14.
12) Irons-Brown SR, Jones TA. Effects of selected pharmacological agents on avian auditory and vestibular compound action potentials. Hear Res 2004;195:54-66.
13) Holt JC, Lysakowski A, Goldberg JM. The efferent vestibular system. In: Ryugo DK, Fay RR, Popper AN, editors. Auditory and vestibular agents on avian auditory and vestibular compound action potentials. Hear Res 2004;195:54-66.
14) Holt JC, Kewin K, Jordan PM, Cameron P, Klaczynski M, McIntosh JM, et al. Pharmacologically distinct nicotinic acetylcholine receptors drive efferent-mediated excitation in calyx-bearing vestibular afferents. J Neurosci 2015;35:3625-43.
15) Ishiyama A, Lopez I, Wackym PA. Choline acetyltransferase immune-reactivity in the human vestibular end organs. Cell Biol Int 1994;18:797-84.
16) Jordan PM, Parks XX, Contini D, Holt JC. A review of synaptic mechanisms of vestibular efferent signaling in turtles: extrapolation to efferent actions in mammals. J Vestib Res 2013;23:161-75.
17) Weisstaub N, Vetter DE, Elgoyhen AB, Katz E. The alpha4alpha7 nicotinic acetylcholine receptor is permeable to and is modulated by divalent cations. Hear Res 2002;167:122-35.
18) Wackym PA, Chen CT, Ishiyama A, Pettis RM, López IA, Hoffman L. Muscarinic acetylcholine receptor subtype mRNAs in the human and rat vestibular periphery. Cell Biol Int 1996;20:187-92.
19) Pérez C, Limón A, Vega R, Soto E. The muscarinic inhibition of the potassium M-current modulates the action-potential discharge in the vestibular-primary-afferent neurons of the rat. Neuroscience 2009;158:1662-74.
20) Lee C, Holt JC, Jones TA. The effect of M-current modulation on mammalian vestibular responses to transient head motion. J Neurophysiol 2017 Aug 30 [Epub ahead of print]. https://doi.org/10.1152/jn.00384.2017.
21) Phelan KD, Gallagher JP. Direct muscarinic and nicotinic receptor-mediated excitation of rat medial vestibular nucleus neurons in vitro. Synapse 1992;10:349-58.
22) Sun Y, Waller HJ, Godfrey DA, Rubin AM. Spontaneous activity in rat vestibular nucleus in brain slices and effects of acetylcholine agonists and antagonists. Brain Res 2002;934:58-68.
23) Molinoff PB. Neurotransmission and the central nervous system. In: Brunton LL, Chabner BA, Knollman B, editors. Goodman & Gilman’s the pharmacological basis of therapeutics, 12th ed. New York: McGraw-Hill Companies;2010. p.378-9.
24) Meza G. Modalities of GABA and glutamate neurotransmission in the vertebrate inner ear vestibule. Neurochem Res 2008;33:1634-42.
25) Matsubara A, Usami S, Fujita S, Shinkawa H. Expression of substance P, CGRP, and GABA in the vestibular periphery, with special reference to species differences. Acta Otolaryngol Suppl 1995;519:248-52.
26) Cortes C, Galindo F, Galicia S, Cebada J, Flores A. Excitatory actions of GABA in developing chick vestibular afferents: effects on resting electrical activity. Synapse 2013;67:374-81.
27) Hain TC, Uddin M. Pharmacological treatment of vertigo. CNS Drugs 2003;17:85-100.
28) Lee C. Effects of pharmacological agents on mammalian vestibular function [dissertation]. Lincoln(NE): University of Nebraska-Lincoln,2016.
29) Tomoda K, Nagata M, Harada N, Iwai H, Yamashita T. Effect of histamine on intracellular Ca2+ concentration in guinea pig isolated vestibular hair cells. Acta Otolaryngol Suppl 1997;528:37-40.
30) Trittin S, Bottu L, Zamponi V, Zucca G, Valli P, Masetto S. Calyx and dimorphic neurons of mouse Scarpa’s ganglion express histamine H3 receptors. BMC Neurosci 2009;10:70.
31) Desmadryl G, Gaboyard-Niay S, Brugeaud A, Travo C, Broussey A, Saleur A, et al. Histamine H4 receptor antagonists as potent modulators of mammalian vestibular primary neuron excitability. Br J Pharmacol 2012;167:905-16.
32) Wang JJ, Dutia MB. Effects of histamine and betahistamine on rat medial vestibular nucleus neurons: possible mechanism of action of anti-histaminergic drugs in vertigo and motion sickness. Exp Brain Res 1995;105:18-24.
33) Dutia MB. Betahistine, vestibular function and compensation: in vitro studies of vestibular function and plasticity. Acta Otolaryngol Suppl 2000;544:11-4.
34) Dhawan BN, Cesselin F, Rahubhir R, Reisine T, Bradley PB, Portgheese PS, et al. International Union of Pharmacology. XII. Classification of opioid receptors. Pharmacol Rev 1996;48:567-92.
35) Sulaiman MR, Niklasson M, Tham R, Dutia MB. Modulation of vestibular function by nociceptin/orphanin FQ: an in vivo and in vitro study. Brain Res 1999;828:74-82.
36) Vega R, Soto E. Opioid receptors mediate a postsynaptic facilitation and a presynaptic inhibition at the afferent synapse of axolotl vestibular hair cells. Neuroscience 2003;118:75-85.
37) Kawabata A, Sasa M, Ujihara H, Takaori S. Inhibition by enkephalin of medial vestibular nucleus neurons responding to horizontal pendular rotation. Life Sci 1990;47:355-63.
38) Beaulieu JM, Gainetdinov RR. The physiology, signaling, and pharmacology of dopamine receptors. Pharmacol Rev 2011;63:182-217.
39) Andrianov GN, Ryzhova IV, Tobias TV. Dopaminergic modulation of afferent synaptic transmission in the semicircular canals of frogs. Neurosignals 2009;17:222-8.
40) Drescher MJ, Cho WJ, Folbe AJ, Selvakumar D, Kewson DT, Abu-Hashan MD, et al. An adenylyl cyclase signaling pathway predicts direct dopaminergic input to vestibular hair cells. Neuroscience 2010;171:1054-74.
41) Vibert N, Serafin M, Crambes O, Vidal PP, Mühlthaler M. Dopaminergic agonists have both presynaptic and postsynaptic effects on the guinea-pig’s medial vestibular nucleus neurons. Eur J Neurosci 1995;7:555-62.
42) Luebke AE, Holt JC, Jordan PM, Wong YS, Caldwell JS, Cullen KE. Loss of α-calcitonin gene-related peptide (αCGRP) reduces the efficacy of the Vestibulo-Ocular Reflex (VOR). J Neurosci 2014;34:10453-8.

43) Sewell WF, Starr PA. Effects of calcitonin gene-related peptide and efferent nerve stimulation on afferent transmission in the lateral line organ. J Neurophysiol 1991;65:1158-69.

44) Usami S, Hozawa J, Ylikoski J. Coexistence of substance P and calcitonin gene-related peptide-like immunoreactivities in the rat vestibular endorgans. Acta Otolaryngol Suppl 1991:481:166-9.