

New insights into vestibular neuropharmacology: From bench to bedside

Christian Chabbert

INSERM U1051 Montpellier and UMR 7260 CNRS Aix-Marseille University, Marseille, France

E-mail: christian.chabbert@univ-amu.fr

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Abstract. Recent epidemiological investigations have highlighted the high prevalence of vestibular dysfunctions in the adult population and its association with aging. Despite a large and unmet medical need, the pharmaceutical options of targeted and efficient drugs to reduce the symptoms associated with vestibular deficits remains largely insufficient.

This special issue of the Journal of Vestibular Research is devoted to the session: *New insights on vestibular neuropharmacology: From bench to bedside*, that was organized at the 2012 Midwinter Meeting of the Association of Research in Otolaryngology.

This special issue intends 1. to emphasize the current state of the medical need for potent pharmacological treatments of vestibular deficits while highlighting questions regarding the molecular targets, the therapeutic window and the role of pharmacological treatment versus physiotherapy; 2. to give an overview of the fundamental mechanisms of vestibular system function and the mechanism of action of the drugs currently used in the treatment of vestibular disorders and 3. to present recent discoveries in basic research, that may lead to future drug identification to efficiently alleviate the vertigo crisis and protect the vestibule. This theme should target a broad audience ranging from ENT clinicians to scientists, including pharmacologists and pharmacists.

1. Vestibular function remains among the least understood sensory functions

Vestibular function involves highly tuned motor actions allowing us to offset perturbations induced by displacement or acceleration detected by the three-dimensional angular and linear accelerometers nestled into our temporal bones. Although essential for the interaction with our environment, the complete role of this *sixth sense* remains largely unknown: First, its physiological role is so subtle and constant that it is difficult to perceive. Second, vestibular function integrates multisensory inputs that combine vestibular, visual and proprioceptive inputs, into complex neuronal networks. The specific interplay between these functions in the regulation of posture, gaze fixation during displacement or in the setting of subjective visual vertical is only partly understood. Also, regulatory or adaptive mechanisms such as vestibular compensation or the intrinsic capacities of peripheral vestibular synapses to repair, although known for decades,

still lack complete understanding [1–4]. Finally, recent studies have revealed an even more complex and broader role for the vestibular organs in regulating homeostatic and circadian functions such as body temperature, heart rhythm and bone metabolism [5,6]. From a clinical perspective, management of vertigo symptoms may involve neurology, otolaryngology and in some cases, ophthalmology, internal medicine or psychiatry, resulting in few clinicians having a complete knowledge of both the central and peripheral components of the pathology. Therefore, vertigo patients often do not know whom to consult first [7].

2. Physiology and pathophysiology of the vestibular function

To permanently ensure proper reaction to any displacement or acceleration, vestibular sensory information conveyed to the brain stem and combined with information from other sensory organs will follow

several reflex arcs [8]. The vestibulo-oculomotor reflex acting directly on the muscles controlling the eye position will ensure gaze fixation on the sidewalk while walking or on the stairs while we descend. Any impairment of the vestibular endorgans function impacting this reflex arc will induce the phenomenon of *oscillopsia*, often described as the visual sensation perceived during a car drive in an uneven path. The vestibulo-cerebellar and vestibulo-cortical reflexes contribute as well, in setting the subjective vertical that serves as internal reference in each of our movements and in our orientation in space. Alteration of these reflexes will provoke spatial disorientation and promote reactive actions such as head tilt to counterbalance the altered verticality. The vestibulo-spinal reflex allows the maintenance of posture at rest and during movement. Any insult to or dysfunction of the vestibular organs impacting on this specific pathway will cause static and dynamic imbalances resulting in difficulty in moving or simply standing and result in an increased susceptibility to falling (Fig. 1).

It is therefore easy to envision the functional, psychological and social impact that may result from a vestibular impairment. The psychological trauma associated with an acute vertigo crisis together with the phobia of its recurrence, along with the physical disability that accompanies vestibular deficits may lead to socio-professional consequences, accompanied by cognitive impairments that may eventually result in psychological and social isolation [9].

3. The incidence of vestibular pathologies is extremely high

Over the last decade, consultations related to vertigo have exponentially increased [10]. This probably relies on the age-related functional decline in a growing elderly population. Transient or lasting vertiginous sensations, the loss of control of certain movements and resulting disability are increasingly considered as a real pathology with reason to consult a doctor, rather than a simple consequence of aging. A recent epidemiological study from the American *National Health and Nutrition Examination Survey* reports that more than 1/3 of American adults over 40 years old exhibit vestibular dysfunctions [11].

This prevalence increases with age, as vestibular dysfunction affects 65% of people over 60 and 85% over 80 years. Moreover, the risk of falls is significantly increased in the population with vestibular dys-

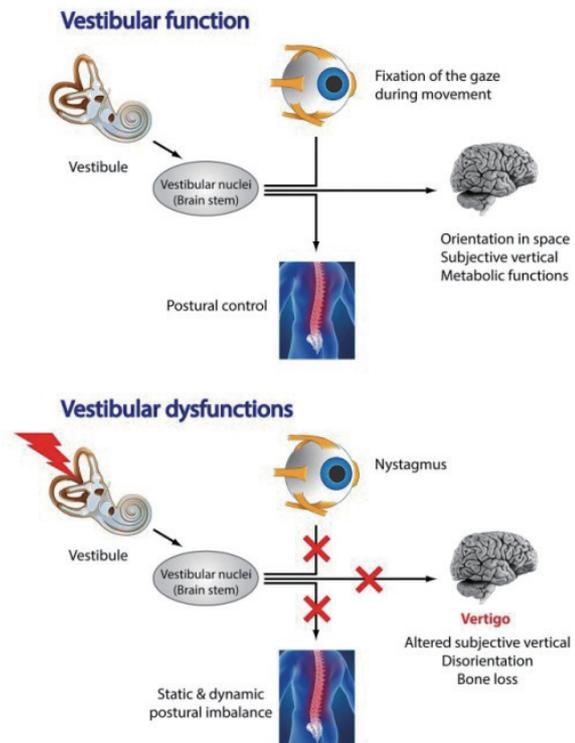


Fig. 1. Neurophysiological pathways involved in the vestibular function and dysfunctions. Schematic representation of the vestibulo-oculomotor (upper arrows), vestibulo-cerebellar/cortical (middle arrows and vestibulo-spinal reflexes arcs (lower arrows). (Colours are visible in the online version of the article; <http://dx.doi.org/10.3233/VES-130495>)

functions (Fig. 2). In this journal issue, Dr Y Agrawal from the John Hopkins Hospital in Baltimore details the prevalence of vestibular dysfunction among US adults and the increasing prevalence associated with aging. Dr Agrawal also details the sociodemographic characteristics of vestibular deficits and their association with the risk of falling.

4. Vestibular pathologies represent an unmet medical need and untapped market

Considering the size of the market, the lack of impactful therapeutic solutions for the vestibular pathologies raises interesting questions. Current treatments of vestibular disorders aim to alleviate the acute vestibular symptoms, protect from aggravation of inner ear damages, enhance central compensation and promote vestibular rehabilitation [12]. Repositioning maneuvers are the main therapy for Benign Paroxysmal Positional Vertigo. Physiotherapy is also widely used to

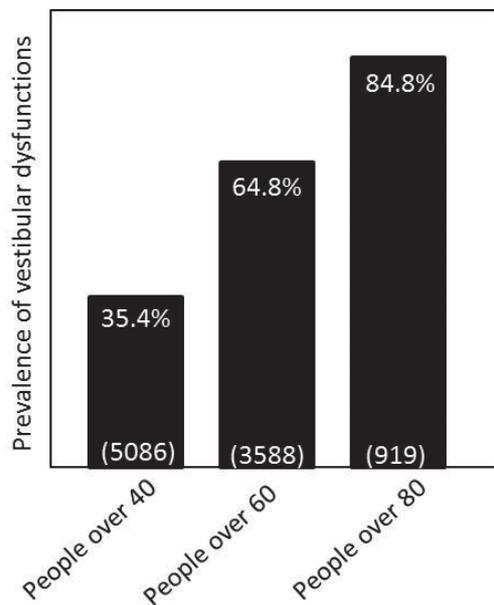


Fig. 2. Prevalence of vestibular dysfunction in the United States. (Number of observation) Adapted from Agrawal et al. [11].

promote functional recovery during the rehabilitation of vestibular neuritis patients. Since the demonstration by Barany in the first part of the 20th century that pharmacological approaches may significantly alleviate inner ear symptoms [13], neuropharmacology is considered a potent option in the management of the vestibular pathologies. However, current antivertigo treatments suffer from significant side effects and lack of efficacy. Furthermore, the molecular basis of their actions mostly remains unknown. For these reasons, in most countries, marketed antivertigo drugs are no longer reimbursed. Moreover, apart from corticosteroids with questionable effect [14], no therapy to protect or repair the inner ear is currently available.

5. Clinical diagnostic and pathogenic hypothesis for vestibular deficits

Although a standardized protocols commonly approved and applied by the international community is currently lacking, the clinical diagnosis of vestibular deficits benefits from semi-quantitative analysis methods that monitor alterations in the different types of vestibular reflexes. With these current clinical approaches, it is usually possible to distinguish a peripheral impairment from a central pathology that may bear similar symptoms, such as the sensation of vertigo or the presence of nystagmus. However, the lack

of diagnostic tools allowing direct analysis of specific markers of the pathology, together with the insufficient resolution of available clinical imaging techniques results in an inadequate etiological classification of most vestibular pathologies. Thus, apart from some cases of trauma of the temporal bone or impairments resulting from the known intake of ototoxic compounds, the etiology of vestibular impairments remains mostly unresolved.

6. Effectors involved in the processing of the vestibular information are potential pharmacological target

Though knowledge of pathological mechanisms is lacking, the scientific legacy of preclinical studies performed over the past decades constitutes a valuable source of information of the anatomical structures and physiological mechanisms that support the processing and transmission of the vestibular sensory information [15]. These elements constitute potential pharmacological targets for controlling the sensory information, as well as protecting or even restoring the vestibular sensory network. In this journal issue Dr E Soto from the Universitat de Pueblo in Mexico gives an overview of the cellular actors involved in the shaping of the vestibular sensory information, together with the mechanism of action of drugs currently used in the treatment of vestibular disorders.

7. What diagnostic or therapeutic actions for vestibular deficits?

Several therapeutic options may be applied in the different situations leading to vestibular disorders. Neuromodulation, through control of the sensory information along the vestibular neuronal pathways intends to attenuate the imbalance of activity between the healthy and impaired peripheral vestibular organs, thereby reducing the amplitude and duration of vestibular symptoms [16]. Protection of vestibular hair cells, primary neurons or their synaptic contacts is also essential to preserve the sensory network under damaging conditions such as local ischemia, ototoxicity or inflammation. Regeneration of sensory cells and primary neurons is currently receiving strong research attention with the aim to define adequate strategies to reconstitute the altered sensory network and restore inner ear function [17]. Finally the pharmacological en-

hancement of central compensation is also a therapeutic approach that may significantly improve the long term outcome following vestibular damage. In each of these fields, recent reports have brought tangible evidence for the potential of targeting appropriate cellular effectors without the need of local drug application to bring significant treatment benefits for vestibular pathologies, with possible further extension to other inner ear pathologies.

Through the development of animal models of human vestibular pathology, it is now possible to investigate the different stages of a vestibular insult, understand their mechanisms and evolution, and evaluate the therapeutic benefits of modulating pharmacological targets. In this special issue of the *Journal of Vestibular Research*, several novel pharmacological approaches that modulate receptors or ionic channels expressed along the vestibular sensory pathway are presented.

Dr. M. Lacour from the Université de Provence in Marseille describes the role of betahistine, a histamine type 3 receptor antagonist in modulating central compensation in a cat model of unilateral vestibular areflexia. Along with an overview of the preclinical data on betahistine, Dr Lacour details recent observations of the therapeutic effect in Menière's patients after vestibular neurectomy [18].

Dr. E. Wersinger from Sensorion presents evidence for selective antagonism of type 4 histamine receptors as a dose and class-dependent option for excitability modulation of mammal vestibular primary neurons. Systemic administration of type 4 histamine receptor antagonists in rats with ototoxically- or excitotoxically-induced vestibular insults significantly reduces the altered behavior associated with vestibular deficits. This effect is deemed to result from the reduction of the imbalance of activity between the healthy and the injured vestibular organs [16]. Dr. C. Holt from the University of Rochester describes in present issue the mixed role of the cholinergic efferents in modulating both sensory cells and vestibular afferents through distinct receptor subtypes. He also discusses how these different types of receptors may offer opportunities for controlling vestibular sensory information through the use of selective modulators. Finally, Dr J Dyhrfeld-Johnsen from Sensorion provides the first evidence for significant functional and cellular-level protective action of ondansetron in a rat model of excitotoxically-induced vestibular deficits. These observations may explain recently reported therapeutic benefits of this antiemetic drug in reducing both the vestibular deficit symptoms, day to first walk and duration of hospitalization in patients with vestibular neuritis [19].

8. How far are we from bedside?

Although these encouraging results demonstrate that it may be possible to effectively protect or modulate vestibular function through targeted pharmacological approaches, several considerations must be addressed prior to advancing to human therapy. One challenge is the administration of active compounds to allow controlled, reproducible and safe delivery into the inner ear. Also, current animal models of vestibular disorders must be optimized to mimic human pathogenesis and symptomology as closely as possible while allowing the identification of highly selective drugs to minimize side effects. Eventually, the interference of pharmacological approaches with endogenous repair processes and vestibular compensation must be addressed in order to ensure the overall favorable long-term outcome for patients.

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Conflict of interest

Dr. C. Chabbert is a consultant at Sensorion-Pharmaceuticals.

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