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Physiological assesment of vestibular function and toxicity in humans and animals

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ABSTRACT

Physiological methods that can be similarly recorded in humans and animals have a major role in sensory toxicology, as they provide a bridge between human sensory perception data and the molecular and cellular data obtained in animal studies. Vestibular toxicity research lags well behind other sensory systems in many aspects, including the availability of methods for functional assessment in animals that could be robustly translated to human significance. Here we review the methods available for the assessment of vestibular function in both humans and laboratory animals, with an emphasis on their similarity or divergence, to highlight their potential utility for the predictive assessment of vestibular toxicity.

1. Introduction

The vestibular system in the inner ear detects linear and angular accelerations of the head, including gravity and those generated by active and passive body movements and head rotations (Goldberg et al., 2013). Vestibular perception is essentially unconscious in healthy individuals, but its importance is revealed by the dramatic consequences of vestibular dysfunction (Bronstein, 2013). Vestibular loss causes loss of balance and gaze control. Abrupt changes of vestibular function in one labyrinth results in vertigo, dizziness and nausea, and is profoundly disabling. A more frequent condition is a stable but permanent loss of function that has evolved progressively; this results in loss of automatization of balance, loss of image stabilization (decrease of dynamic visual acuity), and loss of automatization of spatial orientation (Bronstein, 2013). Vestibular loss also has large consequences on cognitive, endocrine, and autonomic nervous system functions. Thus, vestibular dysfunction has been demonstrated to result in reduced bone mass, cardiovascular modifications, circadian rhythm alterations, and impaired cognitive performance (Martin et al., 2016; Besnard et al., 2015; Vignaux et al., 2015). Epidemiological data reveal that vestibular dysfunction contributes to the increased risk of falls in the elderly, and these are a large cause of morbidity and mortality (Agrawal et al., 2009; Ward et al., 2013).

Among the chemicals that are known to cause vestibular toxicity, aminoglycoside antibiotics occupy a prominent place. They are the main cause of human vestibular toxicity, and have received considerable research attention. Anti-malarial drugs, loop diuretics, and cisplatin are additional therapeutic agents known to cause vestibular toxicity (Rybak and Whitworth, 2005; Xie et al., 2011; Schacht et al., 2012; Yorgason et al., 2006; Callejo et al., 2017). These compounds are ototoxic, affecting both the auditory and the vestibular systems. Other ototoxic compounds are found in the workplace as solvents and synthetic intermediates. These include toluene, styrene, trichlorethylene, and cis-2-pentenenitrile (Fechter et al., 1998; Hoet and Lison, 2008; Pouyatos et al., 2002; Saldaña-Ruíz et al., 2012a,b; Campo et al., 2013).

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Physiological assessment has an important role in the study of sensory toxicity. Physiological data from animal studies can often be matched to human data obtained with the same or at least roughly equivalent methodologies. This provides a bridge between the human perception deficits and the histological and molecular observations that can only be obtained in animal models. In the case of the vestibular system, the animal to human comparison is favored by its evolutionary conservation across vertebrates (Day and Fitzpatrick, 2005). However, vestibular assessment presents by itself several difficulties that make the task a challenging one. First, vestibular perception is mostly unconscious and this limits the role of the human subject in the assessment. For visual system assessment, you can ask subjects to order objects according to their graded colors, but it is not obvious how to obtain similarly rich information on the subject's vestibular function. Second, it is difficult to obtain recordings of electrical potentials generated by vestibular signaling. The peripheral vestibular system is very small, containing only a few thousand cells (Desai et al., 2005a,b), and therefore generates electrical potentials that are small (Brown et al., 2017). In addition, cortical areas receiving vestibular information are widespread and poorly defined (Brown et al., 2017), contrary to the well-known and clearly defined somatosensory, visual, and auditory primary cortical areas. Third, it is difficult to study the responses of the system to its natural stimuli, because these include head accelerations, which are not easy to deliver to the subjects, neither humans (Ertl et al., 2017) nor laboratory animals (Jones et al., 2011; Beraneck et al., 2012; de Jeu and De Zeeuw, 2012). Nevertheless, several methods are available for the assessment of human vestibular function, and these include recently developed approaches that are transforming the field of vestibular diagnosis in clinical settings (Walther, 2017). Methods to assess vestibular function in animals are also available, including some that are exclusive to laboratory species and others that are equivalent to the ones used in patients.

One important aspect to consider is that many of these methods are indirect, that is, do not measure vestibular function directly, but a motor response that is controlled by vestibular input; typically, these responses will also be influenced by proprioceptive and/or visual input (Serra et al., 2013; Allum and Carpenter, 2013), making it necessary that the vestibular contribution is identified and differentiated from the contribution by other systems. In clinical practice, the functional endpoint (e.g., equilibrium) is usually evaluated for its own clinical relevance and is not followed by an intention to discriminate the underlying functional deficits (Horak et al., 2009).

The aim of this article is to compare the methods used in human clinical practice for the evaluation of vestibular function with the methods available for the evaluation of vestibular function in laboratory animals, with emphasis on their use or suitability to assess vestibular toxicity. Table 1 contains a list of methods used in human and animal studies, which includes references of example studies using them for toxicity evaluation. The final goal is to appraise the translational value of the animal models, and their intrinsic value for objective and quantitative assessment.

2. Vestibular function

As stated previously, the vestibular system detects angular and linear accelerations. To this end, the transducer sensory cells, named hair cells (HCs), are organized in five sensory epithelia in each ear (Fig. 1). Each side of the head contains three cristas in orthogonally oriented semi-circular canals, and two otolith organs, the utricle and saccule. The canals sense angular accelerations whereas the utricle and saccule sense linear accelerations including head tilt (Goldberg et al., 2013). Within the gravitational field of the earth, most head movements combine both rotational and translational components, and the labyrinth in each side of the head will experience different forces depending on the position of

Table 1
Methods for vestibular function assessment, and literature examples of their use to evaluate toxicity.

A. Human		B. Laboratory animals	
A.1. Observational and semi-quantitative		B.1. Observational and semi-quantitative	
Spontaneous nystagmus	(13, 26)	Abnormal spontaneous motor behavior (waltzing syndrome)	
Eye response to head impulse		Circling	(1) (a)
Caloric nystagmus	(2, 10, 11, 15, 37)	Abnormal head movements (head bobbing)	(1) (a)
Dynamic visual acuity test	(11)	Backward walking	(1) (a)
Unterberger-Fukuda stepping test	(26)	Ataxia	(7)
Romberg test	(11, 26)	Swimming deficits	(16, 35)
Babinski-Weil test	(26)	Head tilt	(9)
Bárány's pointing test		Abnormal anti-gravity reflexes	
Postural sway		Air-righting reflex	(a)
Pointing deviation		Contact-inhibition of the righting reflex	(a)
Subjective vertical		Tail-lift reflex	(a)
		Vestibular dysfunction test battery	(4, 5, 6, 7, 16, 24, 25, 27, 30)
A.2. Quantitative		B.2. Quantitative	
VOR assessment		Video-oculography	
Electro-nystagmography/-oculography	(2, 3, 10, 12, 19, 23, 34, 37)	Spontaneous nystagmus	(8)
Scleral search coil technique		Post-rotatory nystagmus	(14, 18)
General video-oculography	(3)	Direct VOR assessment	(32)
video Head Impulse Test (vHIT)	(33)	VOR assessment by other techniques	(28, 31)
Ocular Vestibular-Evoked Myogenic Potential (oVEMP)		Ocular Vestibular-Evoked Myogenic Potential (oVEMP)	(17, 36)
Cervical Vestibular-Evoked Myogenic Potential (cVEMP)		Cervical Vestibular-Evoked Myogenic Potential (cVEMP)	(17, 36)
Static posturography		Vestibular evoked potentials	(21, 22, 29)
Dynamic posturography	(3)	Motor activity	(4, 7)
		Inertial measurement of head kinematics	(20)

References: (1) Alleva and Balazs, 1978; (2) Barza et al., 1980; (3) Black et al., 2004; (4) Boadas-Vaello et al., 2005; (5) Boadas-Vaello et al., 2007; (6) Boadas-Vaello et al., 2009; (7) Boadas-Vaello et al., 2017; (8) Dyhrfjeld-Johnsen et al., 2013; (9) Horiike et al., 2004; (10) Hoshino et al., 2008; (11)Hydén et al., 1983; (12) Kitsigianis et al., 1988; (13) Kusakari et al., 1981; (14) Larsby et al., 1986); (15) Lerner et al., 1977; (16) Llorens et al., 1993; (17) Lo et al., 2015; (18) Meza et al., 1992; (19)Nordström et al., 1990; (20) Pasquet et al., 2016; (21) Perez et al., 2000; (22) Perez et al., 2013; (23) Pollastrini et al., 1994; (24) Saldaña-Ruíz et al., 2012a,b; (25) Saldaña-Ruíz et al., 2013; (26) Scheenstra et al., 2009; (27) Sedó-Cabezón et al., 2015; (28) Sergi et al., 2003; (29) Sichel et al., 2000; (30) Soler-Martín et al., 2007; (31) Song et al., 1997; (32) Takimoto et al., 2016; (33) Tarnutzer et al., 2016; (34) Tjernström, 1980; (35) Wu et al., 2017; (36) Yang et al., 2010b; (37) Young et al., 2001. (a): Behavior included in the Vestibular dysfunction test battery.

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