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Lateralization of the effects of the benzodiazepine drug oxazepam on medial olivocochlear system activity in humans

N. Morand-Villeneuve [a], E. Veuillet [a,*], X. Perrot [a], P. Lemoine [b], M.C. Gagnieu [c], P. Sebert [d], J.D. Durrant [a,e], L. Collet [a]

[a] *Laboratoire "Neurosciences et Systèmes Sensoriels", CNRS UMR 5020, Université Claude Bernard Lyon I, 50 av. Tony Garnier, 3 Place d'Arsonval, Pavillon U, Hôpital Edouard Herriot, 69366 Lyon, Cedex 07, France*
[b] *Unité clinique de Psychiatrie Biologique, Le Vinatier, Bron, France*
[c] *Laboratoire de Pharmacologie, Hôpital Edouard Herriot, Lyon, France*
[d] *Pharmacie du CHS le Vinatier, Bron, France*
[e] *Departments of Communication Science and Disorders and Otolaryngology, University of Pittsburgh, Pittsburgh, PA, USA*

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Abstract

Benzodiazepines (Bzd) are known to interact with GABAergic inhibitory neurotransmission. Previous research on their effect on human auditory efferent pathways – through evoked otoacoustic emissions suppression by contralateral acoustic stimulation (CAS) – indicated a decrease in medial olivocochlear (MOC) efferent system inhibitory activity, after oral intake of oxazepam – representative of the Bzd drug class. To date, this pharmacological effect was only assessed in the right ear. Since a leftward asymmetry of Bzd receptors localization in human auditory cortex has been described recently, we explored in this study the hypothesis of an asymmetrical action of Bzd on MOC efferent functioning. The results revealed a significant difference of Bzd effect probing the right ear versus the left ear, with CAS-induced suppression being less effective in the right than left ear after oxazepam intake. This finding raises the question of possible neurochemical left–right asymmetry in the descending auditory pathways. The potential localization of this asymmetry is discussed.

Keywords: Benzodiazepines; Descending auditory pathways; Medial olivocochlear efferent bundle; Left–right asymmetry; Evoked otoacoustic emissions

1. Introduction

Descending, or centrifugal, projections are an important component of most sensory systems. In the auditory system, some descending projections are described as projecting to all levels of the auditory pathways (Huffman and Henson, 1990; Rouiller, 1997; Spangler and Warr, 1991). Schematically, the auditory cortex sends projects to the medial geniculate body and the inferior colliculus (IC). The IC projects to two auditory brain stem areas, the superior olivary complex (SOC) and the cochlear nucleus (CN). Finally, at the last stage, neurons originating in the SOC innervate the cochlea. These auditory olivocochlear efferent pathways play a significant role on the hearing function and are now largely studied. There are two major groups of fibers projecting peripherally to the cochlea: the medial olivocochlear

Abbreviations: Bzd, benzodiazepines; CAS, contralateral acoustic stimulation; CN, cochlear nucleus; EA, equivalent attenuation; IC, inferior colliculus; LOC, lateral olivocochlear nucleus; MOC, medial olivocochlear; OHCs, outer hair cells; SOC, superior olivary complex; TEOAE, transient evoked emissions

* Corresponding author. Tel.: +33 1 4 72 11 05 02; fax: + 33 1 04 72 11 05 04.
E-mail address: evelyne.veuillet@chu-lyon.fr (E. Veuillet).

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(MOC) bundle, which originates in the medial part of the SOC and the lateral olivocochlear (LOC) bundle, which originates more laterally. The fibers of the MOC system make synapses directly at the base of the outer hair cells (OHCs) in the cochlea, while LOC fibers project onto afferent dendrites innervating the inner hair cells (Guinan et al., 1983; Rasmussen, 1946; Warr, 1992).

In humans, the efferent pathways can be probed non-invasively through measures of otoacoustic emissions including transient evoked otoacoustic emissions (TEOAE) which are sounds emitted by the cochlea (Kemp, 1978) and thought to reflect active micromechanical properties of OHCs (Brownell, 1990). Given the direct projection of MOC fibers onto the OHCs (Rasmussen, 1946), the MOC system can be assessed by measuring TEOAE suppression caused by contralateral acoustic stimulation (CAS) (Buño, 1978; Collet et al., 1990; Veuillet et al., 1991).

Anatomical considerations above suggest that the MOC bundle could be under cortical influence. Direct monosynaptic projections from the auditory cortex to the auditory nuclei of the brainstem were described in animals, mainly in rats (Doucet et al., 2002; Feliciano et al., 1995). Bypassing the IC, they form synapses in the cochlear nucleus and superior olivary nuclei (Feliciano et al., 1995; Mulders and Robertson, 2000; Weedman and Ryugo, 1996a,b). Another descending projection from the auditory cortex also innervates the inferior colliculus (Andersen et al., 1980; Faye-Lund, 1985; Herbert et al., 1991; Winer et al., 1998) which, in turn, projects to the nucleus of the superior olive, the periolivary nuclei, and the cochlear nucleus (Caicedo and Herbert, 1993; Saldaña, 1993).

Functionally speaking, electrophysiological data in animals have confirmed corticofugal influences on subcortical auditory nuclei and peripheral auditory system (Popelar et al., 2002; Suga and Ma, 2003; Suga et al., 2000, 2002; Torterolo et al., 1998; Yu et al., 2004; Zhang et al., 1997). Through MOC bundle and modulation of active cochlear micromechanics, these feedback loops enable auditory cortex to adjust afferent auditory signal, down to peripheral auditory receptor (Mulders and Robertson, 2000; Popelar et al., 2002; Xiao and Suga, 2002a,b).

Moreover, there are several reports in the literature on the possible cortical influence on the MOC complex in humans, related to physiological cerebral asymmetry (Khalfa et al., 1998) or highlighted by testing MOC function during the performance of cognitive tasks. Thus, modulation of MOC system activity was observed during visual and auditory attention tasks (Maison et al., 2001; Méric and Collet, 1992, 1993; Puel et al., 1988). Furthermore, in a recent study, the MOC system function was tested before and after temporal lobectomy in drug-resistant epileptic patients (Khalfa et al., 2001). The MOC system was found to be less effective in the ear contralateral to the superior temporal gyrus resection, including Heschl's gyrus. These results strongly suggest that the MOC system is modulated by the auditory cortex.

In a recent study, we demonstrated in humans that the effectiveness of the MOC system in right ear is modified by the administration of benzodiazepines (Bzd) (Morand et al., 1998). Given that this class of pharmacological substances are known to facilitate GABAergic neurotransmission (Barbaccia et al., 1988; Choi et al., 1977; Macdonald and Barker, 1978), the decrease of contralateral suppression that we observed could be a reflection of GABAergic projections to the MOC efferent system. Furthermore, we demonstrated in a previous study a leftward asymmetry of Bzd receptors in primary auditory cortex, through a semi-quantitative measurement of flumazenil binding (Morand et al., 2001). Consequently, to assess peripheral auditory activity modulation by the auditory cortex, the purpose of this study was to test the hypothesis that Bzd influence the MOC efferent system asymmetrically, by observing contralateral suppression of TEOAEs during the administration of Bzd and scrutinizing the effect according to ear of stimulation (probe versus contralateral suppression).

2. Methods

2.1. Subjects

The present study employed 12 healthy men ranging from 20 to 25 y (mean = 22 y). All subjects were volunteers, and this study was carried out with the written consent and with the approval of the institutional research board for the use of human subjects. All subjects had negative otologic histories, normal hearing sensitivity (i.e., hearing threshold levels <20 dB between 250 and 8000 Hz, tested at octave frequencies), normal tympanometric recordings, and present TEOAEs (levels better than 5 dB SPL at 80 ±3 dB peSPL clicks) bilaterally. They were all right-handed according to conventional tests of handedness (Oldfield, 1971). A questionnaire and a medical examination permitted us to select subjects without prior use of Bzd, confirmed by an urine analysis on the day of the experiment. These subjects also were not under any form of medical treatment.

2.2. Test of medial olivocochlear system function

TEOAEs were recorded and analyzed according to the methodology of Bray and Kemp (1987) using an Otodynamics® test system (ILO88 v.3.92 system). Briefly, a probe placed in the external ear canal delivered acoustic stimulation via an output transducer (Knowles 1712) and responses were recorded via a miniature microphone (Knowles 1843), both contained in a small ear