Neuropharmacology 88 (2015) 155–163

Contents lists available at ScienceDirect

Neuropharmacology

journal homepage: www.elsevier.com/locate/neuropharm

Differences between magnetoencephalographic (MEG) spectral profiles of drugs acting on GABA at synaptic and extrasynaptic sites: A study in healthy volunteers

David Nutt [a, *], Sue Wilson [a], Anne Lingford-Hughes [a], Jim Myers [a], Andreas Papadopoulos [b], Suresh Muthukumaraswamy [c]

[a] Division of Brain Sciences, Centre for Neuropsychopharmacology, Imperial College London, UK
[b] Psychopharmacology Unit, School of Social and Community Medicine, University of Bristol, UK
[c] CUBRIC, School of Psychology, Cardiff University, UK

ARTICLE INFO

Article history:
Available online 4 September 2014

Keywords:
GABA
Magnetoencephalography
Human
Zolpidem
Gaboxadol
Tiagabine

ABSTRACT

A range of medications target different aspects of the GABA system; understanding their effects is important to inform further drug development. Effects on the waking EEG comparing these mechanisms have not been reported; in this study we compare the effects on resting MEG spectra of the benzodiazepine receptor agonist zolpidem, the delta sub-unit selective agonist gaboxadol (also known as THIP) and the GABA reuptake inhibitor tiagabine. These were two randomised, single-blind, placebo-controlled, crossover studies in healthy volunteers, one using zolpidem 10 mg, gaboxadol 15 mg and placebo, and the other tiagabine 15 mg and placebo. Whole head MEG recordings and individual MEG spectra were divided into frequency bands. Baseline spectra were subtracted from each post-intervention spectra and then differences between intervention and placebo compared. After zolpidem there were significant increases in beta frequencies and reduction in alpha frequency power; after gaboxadol and tiagabine there were significant increases in power at all frequencies up to beta. Enhancement of tonic inhibition via extrasynaptic receptors by gaboxadol gives rise to a very different MEG signature from the synaptic action of zolpidem. Tiagabine theoretically can affect both types of receptor; from these MEG results it is likely that the latter is the more prominent effect here.

This article is part of the Special Issue entitled 'GABAergic Signaling in Health and Disease'.

1. Introduction and rationale

The GABA system is the key inhibitory system in the brain and many neuropsychiatric disorders result from its dysregulation including insomnia, epilepsy, anxiety disorders, some aspects of substance abuse and possibly psychosis. There are a range of medications that target different aspects of this system and understanding their effects is important to inform further drug development. One approach has been to examine the effects of medication on EEG-measured sleep architecture in humans. These studies have shown marked differences between the drugs which promote GABA function by effects on extrasynaptic receptors [e.g. gaboxadol], or by inhibition of reuptake [e.g. tiagabine], compared with the positive allosteric modulators (PAMs) such as the benzodiazepines. Therefore it would be interesting to look at the effects of these different classes of drugs on the waking state to compare brain mechanisms.

In this paper we report on the use of human MEG to examine the actions of 3 drugs acting on this system – specifically the intrasynaptic benzodiazepine alpha-1 selective receptor site PAM zolpidem, the extra-synaptic alpha-4 delta receptor PAM gaboxadol and a presumed synaptic GAT1 GABA reuptake blocker tiagabine, all of which have been used for the treatment of human brain disorders.

GABA-A benzodiazepine receptor PAMs such as benzodiazepines and zolpidem enhance synaptic phasic inhibitory currents. Their effects on EEG have been studied extensively in man. During waking, and persisting into sleep, they give rise to a dose-dependent and plasma-concentration-dependent appearance of a regular, smoothly formed beta rhythm over the whole of the

* Corresponding author. Centre for Neuropsychopharmacology, Division of Brain Sciences, Imperial College, Hammersmith campus, Burlington Danes Building, Du Cane Road, London W12 0NN, UK. Tel.: +44 207 594 7047.
E-mail address: d.nutt@imperial.ac.uk (D. Nutt).

http://dx.doi.org/10.1016/j.neuropharm.2014.08.017

cortical region, beginning at the frontal area (Greenblatt et al., 2006; Malizia et al., 1996). This rhythmic beta activity has no correlation with state of awareness but is correlated with brain benzodiazepine receptor occupation (Malizia et al., 1996). It is seen in the EEG healthy participants receiving acute doses of these drugs for research studies, but also in patients who are taking the drugs long-term and are tolerant to their sedative effects. Barbiturates also produce this beta activity, and both they and benzodiazepines have been used clinically for many years to identify areas of damaged cortex in epilepsy and other disorders: the so-called 'beta gap' where damaged tissue does not produce this drug-induced rhythm (Claus et al., 2012, 2009; Pampiglione, 1952). A MEG study of diazepam described increased power and decreased frequency of beta oscillations over rolandic areas and attributed this to an increase in IPSCs onto inhibitory neurons rather than an increase in IPSCs onto excitatory pyramidal cells (Jensen et al., 2005). These drugs also reduce alpha-frequency activity over the whole cortical area (Connemann et al., 2005) during wakefulness. During sleep, there are the usual EEG signs of reduced awareness with increases in slower activity as in normal drowsiness and sleep, but these PAM drugs increase the amount of spindle activity, and in higher doses reduce delta activity (Brunner et al., 1991; Hindmarch et al., 2005; Karacan et al., 1981).

Gaboxadol also known as THIP (4,5,6,7-tetrahydroisoxazolopyridin-3-ol) is the first extra-synaptic GABA-A agonist to have been used in humans (Faulhaber et al., 1997). It enhances tonic GABA-A-mediated current (Drasbek et al., 2007) and has sleep promoting properties (Lancel et al., 2001) but can cause undesirable mental effects at higher doses. There are no published studies of the effect of gaboxadol on EEG or subjective ratings during wakefulness in man. In mice, both waking and sleeping EEG show a dramatic increase in slower EEG frequencies (<6 Hz) after gaboxadol, and this effect is not seen in mice deficient in the GABA-A delta-subunit gene (Winsky-Sommerer et al., 2007). Human sleep studies have described gaboxadol's effects in detail, with reports of marked increases in power in frequencies below 10 Hz delta and high theta activity and reduction of sleep spindles (Dijk et al., 2010; Walsh et al., 2007). There are no reported studies of MEG and gaboxadol.

Tiagabine is a GAT1 reuptake blocker originally developed as a treatment for epilepsy, whose effects are largely thought to be on intra-synaptic GABA (Madsen et al., 2009). The extent of GABA spillover into peri- and extra-synaptic space after GAT1 blockade is not well understood, but may contribute to tiagabine's effects. Extra-synaptic and pre-synaptic GABA mechanisms such as tonic inhibition and feedback autoinhibition may be activated by reuptake blockade (Axmacher and Draguhn, 2004). The effect of tiagabine on waking EEG in man has not been reported, although there are MEG studies of stimulus-related responses after tiagabine (Muthukumaraswamy et al., 2012, 2013b). In the rat in the awake state there was a small increase in beta band power in one study (Cleton et al., 1999) and no significant change in any spectral band in another (Lancel et al., 1998). Its effect on the human EEG has been studied during sleep (Mathias et al., 2001; Walsh et al., 2006); in

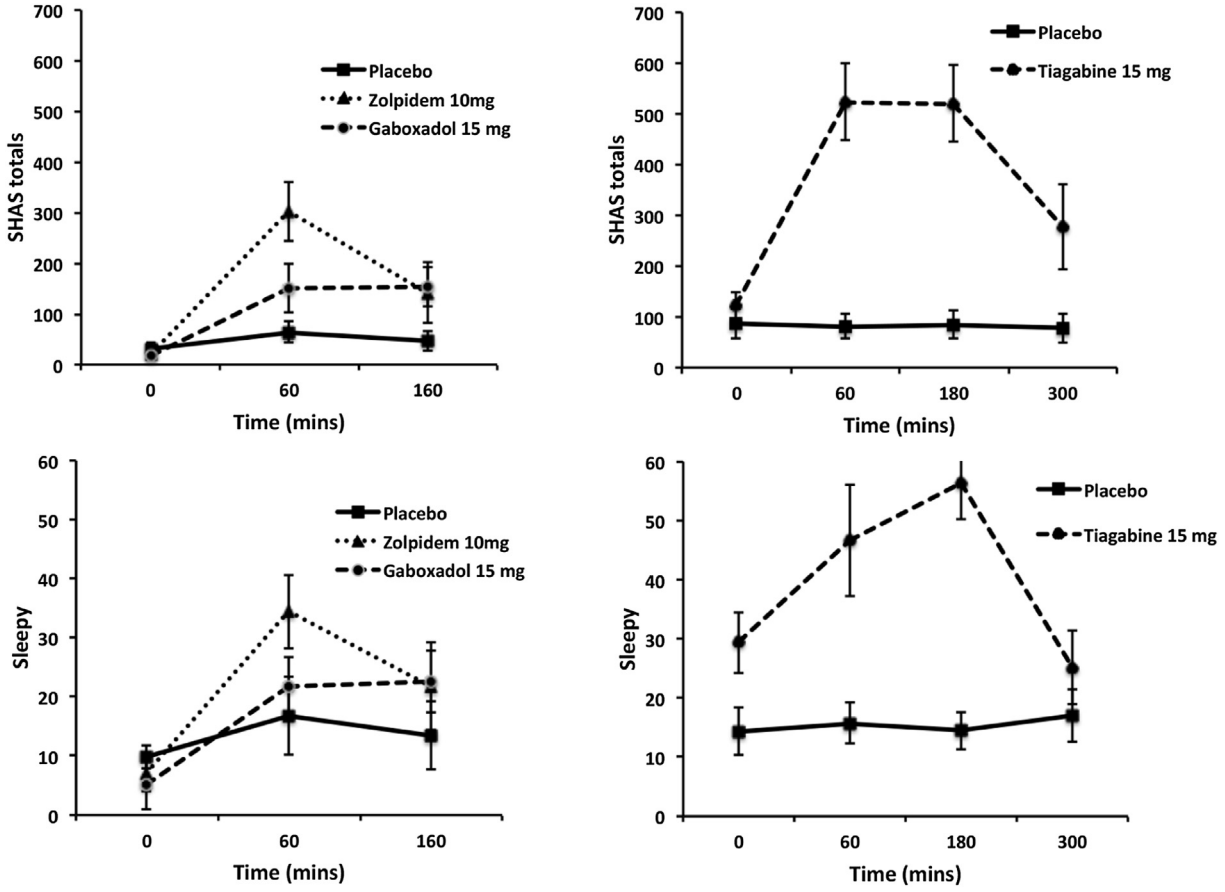

Fig. 1. Summary of total scores (upper panels) for participants on the subjective high assessment scale for gaboxadol/zolpidem (left) and tiagabine (right) with a single sub-scale item (sleepy) displayed on the lower charts. The SHAS consists of 13 items scored 0–100. These items are "uncomfortable", "high", "clumsy", "muddled", "slurred speech", "dizzy", "nauseated", "drunk", "sleepy", "distorted sense of time", "effects of alcohol", "difficulty concentrating" and "feeling of floating".