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Sleep Medicine 7S1 (2006) S3–S9

SLEEP MEDICINE

www.elsevier.com/locate/sleep

Original article

Further potential of the GABA receptor in the treatment of insomnia

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Available online 15 May 2006

Abstract

The benzodiazepine binding site on the $GABA_A$ receptor is the target for the majority of hypnotics, including the nonbenzodiazepine 'Z drugs' (zaleplon, zolpidem, zopiclone and eszopiclone). Concerns still exist over long-term benzodiazepine use, and efforts are, therefore, being made to search for new hypnotic agents and alternative receptor target sites, with novel mechanisms of action. Clinically useful compounds, including GABA mimetics and GABA-uptake inhibitors, have been found by developing structurally rigid analogs of GABA. The GABA-site agonist 4,5,6,7-tetra hydroisoxazolo[5,4-c]pyridin-3-ol (THIP) shows high potency for extrasynaptic $GABA_A$ receptor subtypes, which are not primary targets for classical benzodiazepines or the Z drugs. Hence, THIP targets a novel set of $GABA_A$ receptors. The antiepileptic drug, tiagabine, is a specific blocker of the GAT-1 GABA-transporter, increasing GABA levels following synaptic GABA release. It is proposed that this promotes extrasynaptic $GABA_A$ receptor activity. In contrast, two other GABA analogs, pregabalin and gabapentin, are not GABA mimetics but appear to act at calcium channels responsible for neurotransmitter release, rather than at the GABA receptors. All of these GABA analogs modify sleep behaviors and so are potentially effective hypnotic drugs that provide an alternative to the benzodiazepine binding site of the $GABA_A$ receptor.

Keywords: GABA; Hypnotic; THIP; Tiagabine; Pregabalin

1. Introduction

The amino acid, gamma-aminobutyric acid (GABA), was first identified in the mammalian brain more than 50 years ago [1]. It is the major inhibitory neurotransmitter in the brain, localizing to approximately 30% of central nervous system (CNS) synapses. GABAergic transmission plays a key role in sleep regulation and is also associated with anxiety, depression, pain and epilepsy. Of the three main GABA receptors ($GABA_A$, $GABA_B$ and $GABA_C$), $GABA_A$ receptors have traditionally been the most important with regard to sleep medicine and the treatment of insomnia. The benzodiazepine binding site on the $GABA_A$ receptor is the target for most hypnotics, including the nonbenzodiazepine 'Z drugs' (zaleplon, zolpidem, zopiclone and eszopiclone) [2].

Recent advances in our understanding of the $GABA_A$ receptor reveal that it belongs to a family of closely related receptors, the members of which exhibit different pharmacological specificities and efficacies for benzodiazepine-site modulators [1,2]. Sites other than the benzodiazepine binding site on the $GABA_A$ receptor are suitable targets for hypnotic action and not all $GABA_A$ receptor subtypes bind benzodiazepines. Furthermore, increases in $GABA_A$ receptor activity can also be achieved by blocking the uptake of synaptically released GABA via one or more of its transporters. The discovery of extrasynaptic $GABA_A$ receptor binding has added an additional level of complexity to the GABAergic system.

In this article, we will consider several approaches to modulating GABA activity, with the aim of treating insomnia. These include the development of structurally rigid analogs of GABA to modulate $GABA_A$ receptor activity, including GABA mimetics and drugs that act at sites other than the $GABA_A$ receptor or on GABA transporters. All of these GABA analogs modify sleep behaviors and so reveal potential as effective hypnotic drugs, using receptor sites other than the benzodiazepine binding site on the $GABA_A$ receptor. This article will focus primarily on the GABA mimetics, 4,5,6,7-tetrahydroisoxazolo(5,4-c)pyridin-3-ol (THIP) and tiagabine, and the nonmimetic GABA analogs, gabapentin and pregabalin.

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doi:10.1016/j.sleep.2006.03.001

2. The GABA receptors

There are three main types of GABA receptor ($GABA_A$, $GABA_B$ and $GABA_C$), which can be distinguished by structure, mechanism of action and pharmacological profile (Fig. 1) [1,3,4]. $GABA_A$ and $GABA_C$ receptors are structurally related, and although these ligand-gated ion channels can be distinguished pharmacologically, some authors regard them as being part of the same receptor family [1,3,4]. $GABA_B$ receptors are structurally dissimilar to $GABA_A$ and $GABA_C$ receptors. They are coupled to second messenger systems by G proteins and modulate calcium and potassium channels [1]. $GABA_A$ receptors are activated by GABA, which normally results in neuronal hyperpolarization, leading to reduced action-potential firing and a reduction in neuronal activity [1,5]. $GABA_A$ receptors are heterogeneous, comprising a large family of receptors that are comprised of multiple homologous subunits arranged in a pentamer. Each subunit is encoded by a separate gene. There are at least 16 $GABA_A$ receptor subunit genes, classified into seven isoforms according to sequence relatedness (α, β, γ, δ, ε, θ, π) [1–3,5]. The most common forms are composed of the α, β and γ subunits, but the γ subunit may be substituted by a δ subunit [2,3,5]. $GABA_A$ receptors are the targets for the most widely prescribed sleep medicines, including benzodiazepines, barbiturates and neurosteroids, with a number of separate modulator binding sites and broad receptor heterogeneity [1]. The best studied of these sites is the benzodiazepine modulatory binding site [2,6].

3. Benzodiazepine-site hypnotics

The benzodiazepine binding site is located at the interface of an α subunit and $\gamma 2$ subunit. Modulation of $GABA_A$ receptor activity by benzodiazepines produces sedative, hypnotic, anxiolytic and anticonvulsant activities [2]. The major subunit structure for mediation of sedation is the $\alpha 1$, $\beta 2$, $\gamma 2$ subtype, which has high affinity for benzodiazepines and the Z drugs [7].

Short half-life benzodiazepines (e.g. triazolam) have been particularly useful in treating insomnia, but concerns about the potential for tolerance of the drug to build up and the possibility of developing dependence on classical benzodiazepines has led to them being prescribed much less than previously [2,6]. The sedative Z drugs have activity at the same modulatory site as benzodiazepines, yet they seem to have greater selectivity than benzodiazepines for $GABA_A$ receptors of certain subunit composition, and shorter elimination half-lives (especially for zaleplon and zolpidem), thus making them potentially more effective with fewer side effects [5,8].

4. New GABAergic targets for treating sleep disorders

Targets for new drugs can be divided into agents that directly affect GABAergic neurotransmission and other proteins that bind GABA (GABA receptors, transporters [uptake of GABA from the synapse], and synthetic and catabolic enzymes involved in GABAergic neurotransmission).

The rapid component of GABAergic neurotransmission occurs when $GABA_A$ receptor molecules on the postsynaptic neurons are activated by brief nonequilibrium exposure to GABA (Fig. 2) [1]. In addition, extra-synaptic $GABA_A$ receptor molecules mediate tonic currents as a result of persistent activation by submicromolar concentrations of ambient GABA (Fig. 2). Tonic inhibition helps to regulate neuronal excitability by contributing to the setting of the threshold for action-potential generation and the

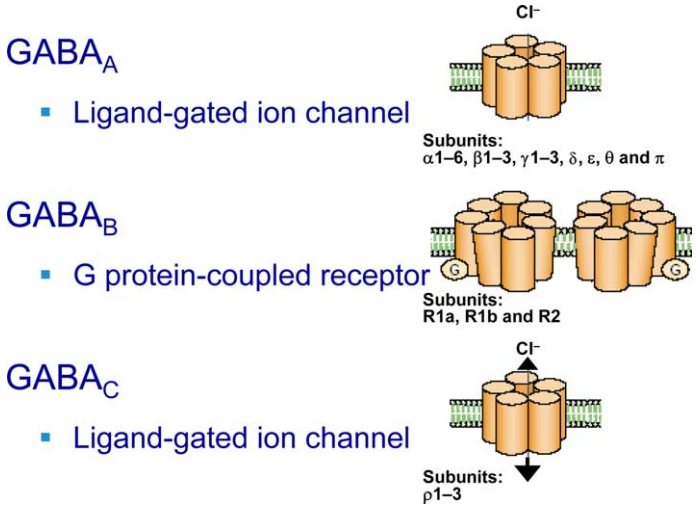

Fig. 1. Structure of GABA receptors. Adapted with permission [1].