

Hypnotic-Sedating Drugs in the Treatment of Insomnia: Objective or Subjective Improvement?

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Introduction

Chronic insomnia affects a significant proportion of adult population. More precisely, around 10% of the population admits their insomnia as chronic [1]. In a recent study by the National Sleep Foundation [2], 48% of Americans referred insomnia symptoms every night, with women presenting this in a higher proportion. Insomnia is responsible for a lowering of the quality of life compared to that appearing in other chronic diseases such as diabetes, arthritis or cardiopathies [3] which usually implies treatment with hypnotic-sedative drugs in most cases [4].

Sleep Regulation Mechanisms

Sleep regulation is controlled by two independent mechanisms: the homeostatic [5] and the circadian [6]; sleep predisposition is determined both by these two mechanisms joint action and by the subject's external condition. The homeostatic mechanism regulates the physiological need for sleep, which gradually increases with vigil, sleep deprivation and, consequently, with the accumulated sleep debit. We know the importance of the ventroposterolateral nucleus of the hypothalamus (VPLO) and its GABAergic efferent inhibitory projection towards the monoaminergic centers of arousal, found in the posterior hypothalamus and the medulla oblongata (tuberomammillary nucleus, locus coeruleus and dorsal raphe [7]), as the basic control system of the sleep homeostatic mechanism. The significant reduction of up to 50% in the number of neurons present in the VPLO in long-living individuals, would partly explain the difficulty that this population shows to start and maintain sleep [8]. The circadian mechanism depends on an endogenous clock localized in the suprachiasmatic nucleus (SCN) of the anterior hypothalamus, and it is capable of precisely regulating the daily transitions between sleep and vigil. Melatonin is the hormone that regulates this circadian clock with an increase in secretion towards the latter hours of the evening, as a means of promoting physiologic sleep [9]. Despite the independence of these two mechanisms, current knowledge of sleep structure and its underlying neurobiologic process suggest an integration of both, at least partially, interrelating VPLO and SCN directly and indirectly [10].

Hypnotic-sedating Drugs Effects

Of these knowledge derives the need to study the effects exercised by hypnotics on the neural pathways of sleep, further than the known effects on GABAergic receptors. The hypnotic-sedating group of drugs has historically been the one mainly used to treat insomnia, always searching a quantitative improvement of sleep. However, current trends

when prescribing drugs to treat insomnia look mainly to improve the quality of sleep.

Benzodiazepines

The effect of hypnotic-sedating has been extensively studied since, when at the end of the 50s of the last century, benzodiazepines and their agonist effect on the GABA-A receptor were discovered. More specifically, the α -1 subtype of the GABA-A receptor represents 60% of all subtypes, being the most abundant in the cerebral cortex. It is on this that benzodiazepines exert their sedating, amnesic and anticonvulsant effects [11]. The hypnotic effect, the reduction in slow waves in the NREM phases, the reduction in sleep fragmentation and the decrease in duration of REM cycles-events occurring after the administration of diazepam- have been proven to be due to the action of the drug on GABA-A receptor subtypes different from α -1 [12]. This suggests a predominant role of subcortical neuronal synapses. Benzodiazepines, in general, reduce the percentage of N1 and N3 phases of REM sleep (although the number of sleep cycles increase) and they increase the N2 phase of sleep. They also increment the time of latency between the spindles and the REM phase.

We can thus conclude that they increase the total NREM sleep time at the expense of phase 2, decreasing the total time of N3 and REM. Hence benzodiazepines promote a sleep which is more superficial than the one in biological conditions. Notwithstanding this, patients that are treated with the hypnotic-sedating drugs present with a subjective feeling of rest and repairing sleep the following day.

Z-group drugs

By contrast, the so-called non-benzodiazepinic hypnotics, the drugs of the Z-group (zolpidem, zaleplone and zopiclone), show a higher specificity for the GABA-A α -1 receptor subtype compared to the group of classic benzodiazepines [13]. The advantage of the Z-group drugs with respect to benzodiazepines is that they show less adverse effects, mainly the behavioral problems and the next-day somnolence. The washout period is also shorter, although the hypnotic effect is shorter as well.

Conclusion

Established the action of hypnotic-sedating on the GABA-A receptors, we believe this cannot be the only mechanism responsible for the subjective feeling of improvement of sleep, and there must be other mechanisms in relation to efficacy and tolerability/safety to the drugs. Probably these mechanisms are related not only to composition and heterogeneity of the distinct subtypes of GABA-A receptors, but also to their regional and cellular distribution, as well as to the

subcortical interactions that must regulate, at the least, the hypothalamic control of sleep-vigil cycles.

Moreover, the improvement in organization of sleep manifested by a decrease in its fragmentation and a fewer number of micro-awakenings in the patients treated with benzodiazepines or hypnotic non-benzodiazepinic group-Z drugs, seems to contribute to this subjective improvement despite a superficialization of the total time of sleep. Studies on the different subtypes of GABA-A receptors apart from the majoritarian α -1 in relation to the hypothalamic-subcortical interaction occurring globally during insomnia, might open new paths of research for the development of more selective drugs which will induce a more efficient, deep and repairing sleep, with less adverse effects.

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