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The antinociceptive effect of zolpidem and zopiclone in mice

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Abstract

Zolpidem and zopiclone are two of a newer hypno-sedative class of drugs, the "Z compounds". Their use for the treatment of short-term insomnia has been expanding constantly during the last two decades. The "Z compounds" are considered to cause less significant rebound insomnia or tolerance than the conventional hypnotic benzodiazepines. Their possible antinociceptive effect and interaction with the opioid system has not been studied yet. Our results demonstrate a significant difference between the antinociceptive properties of zopiclone and zolpidem when injected s.c. in the hotplate analgesic assay in mice. Zopiclone induced a weak, dose-dependent antinociceptive effect, antagonized only by the α_2-adrenergic receptor antagonist yohimbine. Zolpidem induced a weak, biphasic dose-dependent antinociceptive effect, antagonized primarily by the non-selective opioid antagonist naloxone and by yohimbine. The weak antinociceptive effect of both drugs, evident only at very high doses (far beyond those used clinically to induce sleep), implies no clinical use for zopiclone or zolpidem in the management of pain. However, the possible interaction of zolpidem with the opioid system should be further investigated (in behavioral models, which do not overlap with the acute-pain antinociception model we used), both for possible side effects in special populations (i.e. elderly) and for possible drug–drug interactions, in order to minimize possible hazards and maximize clinical beneficial effects of its use for sleep.
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1. Introduction

Hypno-sedative benzodiazepines such as triazolam and brotizolam substituted the unsafe (first generation) barbiturates, as the treatment of choice for short-term insomnia for many years (Ashton, 1994). But due to their association with adverse effects such as rebound insomnia, withdrawal and dependency (Stewart and Westra, 2002), a newer (third generation) class of drugs has been developed: the non-benzodiazepine "Z compounds". Zolpidem and zopiclone are two of this newer hypno-sedative class of drugs, and their use for the treatment of short-term insomnia has been expanding constantly during the last two decades. These drugs are considered to cause less significant rebound insomnia or tolerance, while being as efficacious as the conventional hypnotic benzodiazepines (Boixet et al., 1996; Busto et al., 2001; Neubauer, 2003) (for a review see Mendelson et al., 2004).

Although the non-BDZ hypnotics zolpidem and zopiclone are chemically unrelated to the BDZ, they share with them, to a varying degree, sedative, hypnotic, anticonvulsant, myorelaxant and amnesic effects. These effects are linked to a specific agonistic activity on a central receptor that belongs to the gamma-aminobutyric acid (GABA) BDZ macromolecular receptor complex, but may be associated with action at different sites on the receptor which modulate the opening of the chloride channel (Davies et al., 2000; Dooley et al., 2000). The three subtypes of benzodiazepine receptors are the ω1, ω2 and ω3 subtypes, and they are found in various combinations in different tissues of the body (Langer and Arbilla, 1988; Langer et al., 1990; Sanger et al., 1994).

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Autoradiographic studies have indicated that traditional benzodiazepines bind non-selectively to the three subtypes, whereas zolpidem (a short-acting imidazopyridine) (Unden et al., 1996; Holm and Goa, 2000) binds with relative (but not complete) selectivity to the ω1 subtype in the brain (Sanger et al., 1994; Davies et al., 2000; Dooley and Plosker, 2000; Langtry and Benfield, 1990), while zopiclone (belonging to the cyclopyrrolone class) (Goa and Heel, 1986; Wadworth and McTavish, 1993; Hajak, 1999) binding is not a subunit specific in the brain (Langer and Arbilla, 1988; Concas et al., 1994; Allain and Monti, 1996). The diversity between the binding affinities of zolpidem and zopiclone has been demonstrated both in vitro (Im et al., 1993) and in vivo (Lillsunde and Seppälä, 1990). However, the clinical importance of this relative binding selectivity is not clearly established.

Zopiclone was introduced into clinical practice in 1985, zolpidem in 1988. Since then, the efficacy and safety profiles of both drugs have been studied in a substantial number of clinical studies and several large post-marketing surveillances. Based on the available epidemiological and clinical data, reviews conclude generally that the risk of dependence with the "Z compounds" is low or minimal (Hajak, 1999; Lader, 1997; Rush, 1998; Darcourt et al., 1999; Sanger et al., 2000), however, at least some warnings have been released about the drugs' misuse (Clee et al., 1996; Rooney and O'Conner, 1999; Hajak et al., 2003). This may add to the importance of a thorough evaluation of the possible interaction of the "Z compounds" with the opioid system, which has not been studied yet.

The aim of the present study was to evaluate whether zopiclone and/or zolpidem exert any antinociceptive properties, and if so, if this effect is mediated through opioid, adrenergic or serotonergic mechanisms.

2. Materials and methods

2.1. Animals

The experimental protocol was approved by the local ethics committee of the Sackler Faculty of Medicine (no. M-03-010) and complied with the guidelines for animal experimentation of the National Institutes of Health [DHEW Publication (NIH) 85-23, revised, 1995]. Male ICR mice from Tel-Aviv University colony (Tel-Aviv, Israel), weight 25–35 g (age 5–6 weeks) were used. The mice were maintained on a 12 h light:12 h dark cycle with Purina rodent chow and water available ad libitum. Animals were housed five per cage in a room maintained at 22±0.5 °C until testing. All the injections were made s.c. or i.p. Mice were used only once.

2.2. Agents

Several agents were generously donated as follows: zolpidem and zopiclone by Unipharm (Tel-Aviv, Israel), morphine by TEVA (Jerusalem, Israel), naloxonazine and naloxone benzoyl-hydrazone (NalBzoH) by Dr. G.W. Pasternak from Memorial Sloan-Kettering Cancer Center, New York, USA, U50,488-H {trans-3,4-dchloro-*N*-methyl-*N*-[2-(1-pyrrolindinyl)-cyclohexyl]-benzeneacetamide} by Upjohn Pharmaceutics (West Sussex, England), SNC80 was obtained by Dr. Kenner C. Rice from NIH (Bethesda, MD, USA), β-funaltrexamine (β-FNA), naltrindole HCl, naloxone HCl and Nor-binaltorphamine (Nor-BNI) were obtained from the Research Technology Branch of NIDA. Ethrane (Enflurane) was purchased from Abbott (Campoverde, Italy). Yohimbine HCl, metergoline (N-CBZ-[8b)-1,6 dimethylergolin-8 yl] methylamine), serotonin (5-hydrotryptamine creatinine sulphate (5-HT)) and clonidine HCl were purchased from Sigma (Israel). All other compounds were purchased from commercial sources. Yohimbine HCl was dissolved in distilled water. All other drugs were dissolved in saline; 5-HT contained 0.2 mg/ml ascorbic acid in addition to saline.

2.3. Antinociception assessment

Mice were tested with the hotplate analgesic meter Model 35D (IITC Inc., Woodland Hills, CA), as previously described (Schreiber et al., 2002a). The device basically consists of a metal plate (40×35 cm) heated to a constant temperature, on which a plastic cylinder was placed. The analgesic meter was set to a plate temperature of 55.5±0.5 °C.

The latencies between the second the animal was placed on the hotplate surface until it expressed pain reaction (licked its back paw or jerked it strongly or jumped out) were recorded. Baseline latencies were determined before experimental treatment for each mouse as the mean of two trials. Post-treatment latencies were determined 30 min after the drug injection. To minimize tissue damage a cut-off time 30 s was adopted. The antinociceptive effects were defined by calculating the differences between the baseline latencies and the experimental latencies for each mouse. Each mouse, which its antinociceptive latency was doubled, was considered analgesic. This quantitative measurement allowed us to receive a total group effect calculated in percentage.

2.4. Procedure

The study was conducted in three experiments.

2.4.1. Experiment 1

Groups of mice ($n \geq 15$) were injected subcutaneously with increasing doses of zolpidem or zopiclone (from 5 mg/kg to 120 mg/kg) to determine the effect of the drug in eliciting antinociception. The doses of the drugs are far beyond the "therapeutic range" used in clinical indications in humans, and were chosen based on previous experience with zopiclone (Weizman et al., 2001) and

regarding the quasi-equipotent of psychotropic drugs in acute pain animal models (Pick, 1996; Schreiber et al., 2002b).

2.4.2. Experiment 2

The sensitivity of zolpidem and zopiclone to specific opioid, adrenoreceptor and serotonin receptor antagonists was examined. First we determined the effect of the non-selective opioid antagonist naloxone by using low and high doses (1 and 10 mg/kg s.c.) on both drugs. Since only zoplidem antinociception was inhibited by naloxone, we continued examining the effect of the specific opioid antagonists only with it. Mice ($n \geq 10$ for each group) administrered with zolpidem were treated with one of the following drugs: β-FNA (μ1 and μ2 antagonist; 40 mg/kg s.c.) or naloxonazine (μ1 antagonist; 35 mg/kg s.c.), 24 h before zolpidem challenge. Naltrindole (δ antagonist) 20 mg/kg s.c., Nor-BNI (κ antagonist) 10 mg/kg s.c. or saline were injected at the same time with zolpidem. For comparison, β-FNA and naloxonazine were tested against morphine, Nor-BNI against U50, 488H and naltrindole against SNC-80, in separate groups of mice (data not shown). All the drugs and doses used in the present work were chosen according with our previous works. Subsequently, we examined the effects of metergoline (a serotonergic antagonist; 2 mg/kg i.p.) and yohimbine (an adrenergic antagonist; 4 mg/kg i.p). The drugs were co-injected with zolpidem or zopiclone.

2.4.3. Experiment 3

The sensitivity of zolpidem and zopiclone to specific opioids, adrenergic and serotonin receptor agonists was examined, as follows: (a) Groups of mice ($n \geq 15$) were given increasing doses of morphine (μ-receptor agonist), or with U50,488H (κ1 agonist), or with SNC-80 (δ agonist), or with NalBzoH (κ3 agonist) with an behaviorally inert doses (inactive dose—7.5 mg/kg zolpidem or 5 mg/kg zopiclone). (b) Clonidine (an adrenoreceptor agonist) was injected s.c. alone or with an inactive dose of zolpidem or zopiclone. (c) Serotonin (serotonergic receptor agonist) was injected s.c. alone or with an inactive dose of zolpidem or zopiclone. The inactive dose of each drug was determined empirically.

2.5. Statistic analysis

For dose–response curves a modification of the Tallarida and Murray method was used in order to determine ED_{50} values and 95% confidence limits (Tallarida and Murray, 1987). This program maximizes the log-likelihood function to fit a parallel set of Gaussian normal sigmoid curves to the dose-response data. ED_{50} values were deemed significantly different if there was no overlap of 95% confidence limits. Single dose antagonist studies (direct comparison of quantal results) were analyzed using the Fisher exact test.

3. Results

3.1. Zopiclone and zolpidem antinociception

The evaluation of zopiclone and zolpidem in the hotplate analgesic assay in mice was performed. Groups of mice ($n \geq 15$) were injected with various doses of zopiclone and zolpidem. No visible sedative effects were observed following the injections of the drugs and normal motor behavior was observed in the staircase maze as described previously by ours (Weizman et al., 2001). Zopiclone induced a weak analgesic effect following an s.c. injection in a dose-dependent manner with ED_{50} 86.6 mg/kg (35.6, 217.1, 95% CL; Fig. 1). Zolpidem yielded a biphasic dose-response curve: At doses from 15 to 80 mg/kg, zolpidem administered s.c. induced an antinociceptive effect in the hotplate test in a dose dependent manner (Fig. 1). The antinociceptive effect observed with 15 mg/kg was 10% while its effect observed with 80 mg/kg zolpidem elevated to 80%. As the zolpidem dose increased beyond 90 mg/kg, hotplate latencies declined.

3.2. Sensitivity of zopiclone and zolpidem antinociceptive effect to selective antagonists

3.2.1. Zopiclone

The antinociceptive effect of zopiclone (120 mg/kg s.c.), which produced an 80% antinociception, was abolished completely by yohimbine, a α_2-adrenergic antagonist

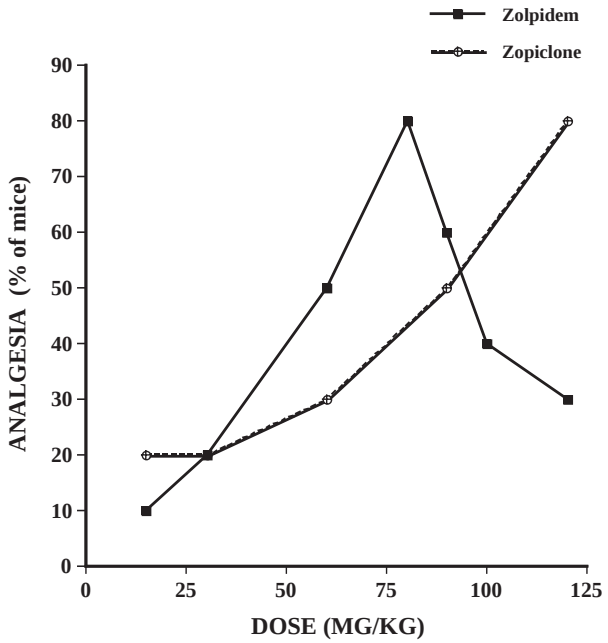

Fig. 1. Dose–response curve for zopiclone and zolpidem analgesia. Groups of mice ($n \geq 15$) were injected with various doses of zopiclone and zolpidem and were tested in the hot plate 30 min later. The results expressed as % analgesia of mice for each dose.

($p<0.05$; Fig. 2). No antagonism to zopiclone antinociception was found by the non-specific opioid antagonist naloxone (1 and 10 mg/ kg) and by metergoline, a non-selective 5-HT receptor antagonist.

3.2.2. Zolpidem

High doses of zolpidem (80 mg/kg), which produced 80% antinociception, were injected with the non-specific opioid antagonist naloxone (1 and 10 mg/ kg). This analgesic effect was antagonized to 20% and 30%, respectively ($p<0.05$; Fig. 3) imply an opioid mechanism of action involved in zolpidem-induced antinociception.

All the selective opioid antagonists (for μ-, δ- and κ_1-opioid receptor subtypes) and Yohimbine; α_2-adrenergic antagonist reversed zolpidem antinociception ($p<0.05$; Fig. 3). Metergoline, a non-selective 5-HT receptor antagonist had no effect on zolpidem antinociceptive. The activity of each of the antagonists was confirmed with its prototypic agonists (data not shown). None of the antagonists mediated antinociception by themselves, nor did they change the baseline latencies of the pretreated animals.

3.3. Sensitivity of zopiclone and zolpidem antinociceptive effect to selective agonists

3.3.1. Zopiclone

Groups of mice ($n\geq15$) were injected with a behavioral inert dose of zopiclone (5 mg/kg s.c.) in addition to specific opioid, adrenergic and serotonin receptor agonists. An increasing dose of morphine, or one of the following drugs, U50,488H, SNC-80, NalBzoH, clonidine or serotonin were co-injected with zopiclone injection. No significant differences were found between the dose-dependent curves with and without zopiclone.

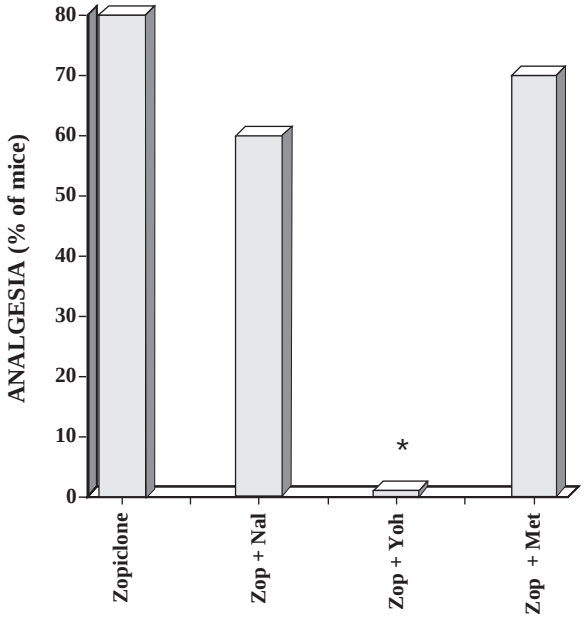

Fig. 2. Interactions of zopiclone with opioid, adrenergic and serotonin receptor agonists. Groups of mice ($n\geq15$) were treated with a high dose of zopiclone (120 mg/kg), alone or were challenged in addition with naloxone (1 or 10 mg/kg s.c.) or with metergoline (2 mg/kg i.p.) or yohimbine (4 mg/kg i.p). The asterisk indicates a significant decrease in analgesic response compared to zopiclone alone ($p<0.05$).

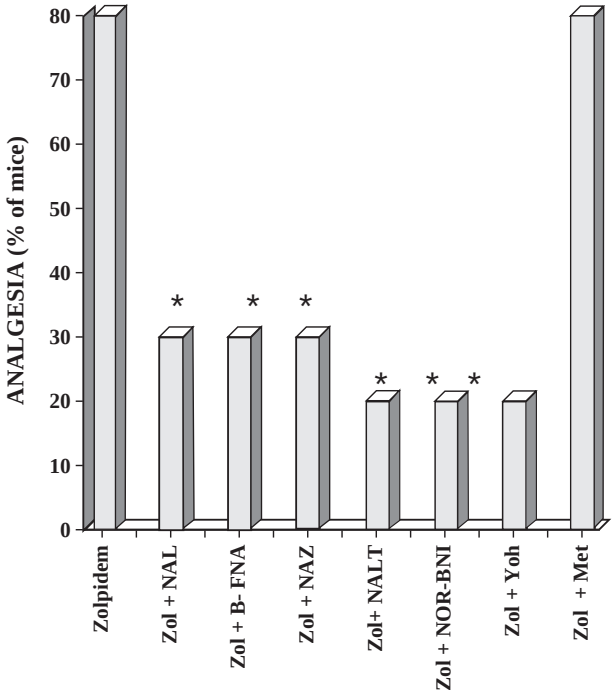

Fig. 3. Interactions of zolpidem with opioid, adrenergic and serotonin receptor agonists. Groups of mice ($n\geq15$) were treated with a high dose of zolpidem (80 mg/kg), alone or were challenged in addition with naloxone (1 or 10 mg/kg s.c.), or β-funaltrexamine (β-FNA,40 mg/kg s.c.), or naloxonazine (35 mg/kg s.c.) or naltrindole (20 mg/kg s.c.) or Nor-binaltorphamine (Nor-BNI,10 mg/kg s.c.) or metergoline (2 mg/kg i.p.) or yohimbine (4 mg/kg i.p). The asterisk indicates a significant decrease in analgesic response compared to zolpidem alone ($p<0.05$).

3.3.2. Zolpidem

Behavioral inert doses (7.5 mg/kg) of zolpidem were given with increasing doses of specific opioid, adrenergic and serotonin receptor agonists. No significant differences in dose response were found between the dose-dependent curves with and without zolpidem.

4. Discussion

Our results demonstrate an interesting difference between the antinociceptive properties of the two non-benzodiazepine, hypnotic "Z compounds" zopiclone and zolpidem when injected s.c. in the hotplate analgesic assay in mice. While both drugs induced only a weak antinociceptive effect, the antinociception of zopiclone was dose-dependent and antagonized by the α_2-adrenergic receptor antagonist yohimbine alone. Zolpidem induced in the same analgesia assay a biphasic (inverted V shape) dose-dependent

antinociceptive effect, and it was antagonized primarily by the non-selective opioid antagonist naloxone and by the selective μ_1- and μ_2-opioid receptor antagonist β-FNA, the selective μ_1-opioid receptor antagonist naloxonazine, the selective δ-opioid receptor antagonist naltrindole, the k_1-opioid receptor antagonist Nor-BNI. In addition, zolpidem's antinociception was antagonized by the α_2-adrenergic receptor antagonist yohimbine. The significance of these findings is that while zopiclone-induced antinociceptive effect is mediated through noradrenergic mechanisms only (without any detectable involvement of either opioid or serotonergic mechanisms), zolpidem-induced antinociception is mediated through both noradrenergic and (vast) (either direct or indirect) opioid mechanisms, with no involvement of serotonergic mechanisms.

When trying to compare our findings with data regarding the antinociceptive properties of some hypnosedative benzodiazepines, we found no published data regarding possible antinociceptive properties of triazolam and brotizolam, while flunitrazepam has been found to antagonize oipiod-induced analgesia in the tail-flick test (Rosland and Hole, 1990). As for other benzodiazepines, some (i.e. diazepam, midazolam) have been found to induce a dose-dependent attenuation of the antinociception of opiates in different tests of nociception (Rosland and Hole, 1990; Nemmani and Mogil, 2003), others yet (i.e. alprazolam) have been found to induce opioid-mediated antinociceptive effects (Pick, 1997) evident only in some strains of mice (Pick, 1996). Our findings regarding zopiclone's interaction with the opioid system disconcord with a previous study in which zopiclone was found to potentiate the antinociceptive effect of morphine in rats (Zambotti et al., 1987), however, the studies were performed with different rodents, using different analgesia assays (tail-flick vs. hotplate), and different modes of administration (intraperitoneal vs. s.c.).

It would be difficult to draw possible clinical conclusions from our findings due to some limitations of our study: Neither zopiclone nor zolpidem manifested a strong enough antinociceptive property to indicate a possible clinical use as analgesic drugs, and the nociception was found only at very high doses, much beyond those used in clinical settings to induce sleep. The complex relations between antinociception, sleep induction, sedative effects, cognitive function and locomotor activity following a drug administration need some elaboration. During general anesthesia ("the utmost analgesia"), auditory, visual and tactile stimuli continue to reach the central nervous system, but further information processing is disturbed, while peripheral nerve conduction and transmission at the neuromuscular junction seems to be scarcely affected (Jessop and Jones, 1992). Even today, more than a century after its introduction, although there seems to be a considerable degree of consent that general anesthesia is characterized by multiple aspects such as unconsciousness, amnesia, depression of motor reflexes and the lack of pain sensation, a commonly accepted definition of general anesthesia is still lacking (Urban and Friederich, 1998). However, the analgesic effect (or antinociceptive effect in animal models) of general anesthesia is not attributed to the presence or absence of locomotor activity, as can be seen in cases of awareness under anesthesia (Lennmarken et al., 2002; Osterman et al., 2001). In the present study we used very high doses of the hypnotic drugs in order to elicit the antinociceptive effect, but noticed no visible sedative effects following the injections of the drugs, while normal motor behavior was observed. This may be attributed to the fact that laboratory models of behavior and antinociception do not necessarily overlap. Since the aim of the present study was to assess the various neurotransmitter systems involved in the antinociception induced by two Z compounds in an acute-pain model of nociception, an elaborated discussion of the differences between behavioral and pain models would be far beyond the scope of this article. For that reason, we evaluated only the possible antinociceptive properties of these two Z compounds, without addressing the well-documented effects of the various members of that group of drugs on locomotor activity, cognitive performance and long-lasting effects on behavior (i.e. driving "the morning after") (Carlson et al., 2001; Verster et al., 2004).

One of the interesting findings of the present work is that although both drugs are part of the "Z compounds" family, each one of them expresses its antinociceptive effect in a different manner and with different types of drug interactions. One of the more intriguing findings is that zolpidem expressed its effect in a biphasic manner, which may indicate that some additional intrinsic systems are involved in its effects, a possibility already hypothesized following some case reports of zolpidem induced psychotic reactions in patients with no history of psychosis (Markowitz and Brewerton, 1996; Ansseau et al., 1992). Clearly, more work must be done in order to discover which systems are actually involved here. Moreover, zolpiden's interaction with the opioid system should be kept in mind, since recent large-scale epidemiological studies have confirmed that insomnia (an inability to initiate or maintain sleep) is the second most prevalent complaint of patients seeing a general physician in routine care condition in the general population (Chevalier et al., 1999; Hajak, 2001; Ohayon and Zulley, 2001; Wittchen et al., 2001), and our findings add the possible abusive potential to the already troublesome cognitive-and motor side-effects of these drugs. Although sleep experts recommend univocally the restriction of the intake of hypnotic drugs to a short-term (Lader and Russel, 1993; Clarenbach et al., 1995; Lader, 1999), leading to the corresponding limitation for use in the labeling of all hypnotic drugs, many patients with insomnia, as well as their treating physicians, favor daily intake of these agents even over prolonged periods of many weeks or months (Boixet et al., 1996; Busto et al., 2001; Mendelson et al., 2004).

In conclusion, the findings of this study show that zopiclone given s.c. is a weak antinociceptor, and this effect is mediated solely through adreno-receptors, while zolpidem given s.c. exerts a weak antinociception effect, mediated through both adreno-receptor and (either direct or indirect) opioid mechanisms. This possible interaction of zolpidem with the opioid system calls for further basic studies and clinical research in order to establish guidelines for the best clinical use of the "Z compounds".

5. Implications statement

The interaction of zopiclone and zolpidem (widely prescribed for insomnia) with opioid, serotonin and noradrenaline receptors was assessed using the hotplate analgesic assay in mice. Data regarding possible such interactions is important to minimize hazards of side effects and potential drug–drug interactions, and to maximize clinical beneficial effects.

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