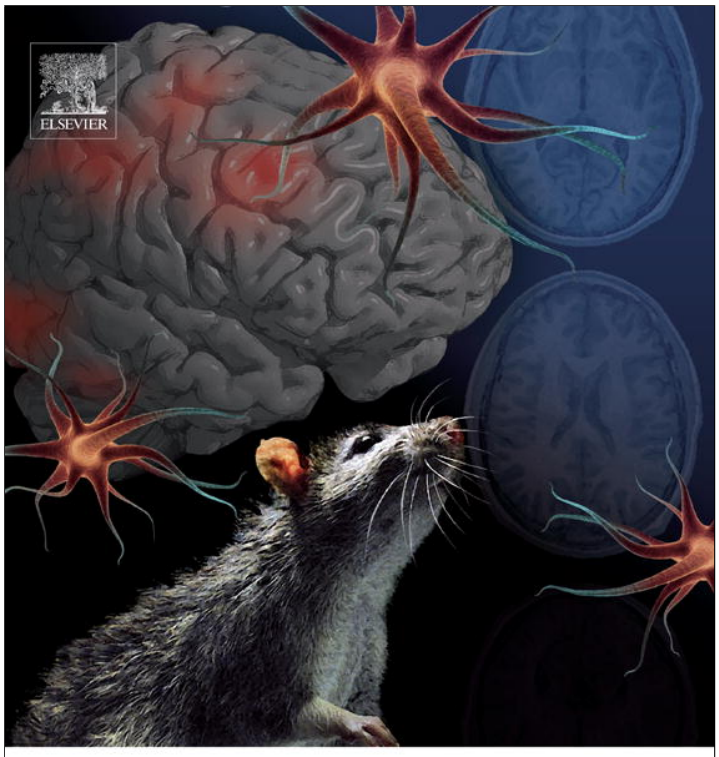

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Short communication

Awakening properties of newly discovered highly selective H_3 receptor antagonists in rats

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ABSTRACT

The objective of the present study was to compare the awakening effects of two newly discovered H_3 receptor antagonists (i.e. SAR110894 and SAR110068) with those of reference H_3 receptor ligands (i.e. ciproxifan, ABT-0239 and GSK189254) and classical psychostimulants (i.e. amphetamine and modafinil) by using EEG recording in rats during their light phase. Results showed that SAR110068 (10 and 30 mg/kg, p.o.) increased wakefulness and decreased slow wave sleep to a similar degree than ciproxifan (10 mg/kg, i.p.), ABT-0239 (10 mg/kg, p.o.) and GSK189254 (10 mg/kg, p.o.), while SAR110894 (3–30 mg/kg, p.o.) did not modify significantly any of the sleep/wakefulness parameters. Time-course analysis revealed that the awakening effects of GSK189254 lasted for about 1 h, while ciproxifan, ABT-0239 and SAR110068 produced such effects for 3–4 h. The magnitude of the awakening effects of the psychostimulants, amphetamine (3 mg/kg, i.p.) and modafinil (300 mg/kg, i.p.), was dramatically higher than with the H_3 compounds, and they lasted for 5 and 6 h, respectively. However, unlike the H_3 receptor antagonists, both psychostimulants produced a strong increase in theta (θ) rhythm, which is indicative of CNS side effects, such as hyperactivity or abnormal excitation. In conclusion, this study provides further evidence to support the potential use of H_3 receptor antagonists in the treatment of vigilance and sleep-wake disorders such as narcolepsy.

1. Introduction

The histaminergic system plays a major role in the maintenance of waking. Because H_3 receptors (H_3-Rs)control the release, synthesis, and turnover of histamine, and the neuronal activity of histaminergic cells, it was suggested that this action on sleep-wakefulness involves the H_3-R subtype, which may thus constitute a therapeutic target for the treatment of sleep-wake disorders, an idea which led to the identification of selective H_3-R antagonists with a rich structural diversity [1]. Much research has focused on the identification of these latter agents to improve somnolence and vigilance deficiency of diverse pathophysiological origins. Among the most investigated compounds are pitolisant, PF-03654746, GSK189254, JNJ-17216498 and ABT-288 (for recent reviews, see [2–5]). These drugs have been shown to promote cortical activation and waking in rodents, and for some of them (i.e. pitolisant and GSK189254) to suppress narcoleptic episodes in orexin knockout mice [6]. Interestingly, unlike classical psychostimulants, such as modafinil or amphetamine, H_3-R antagonists produce their waking effects in the absence of behavioral excitation and sleep rebound [7]. These promising preclinical data are substantiated by a phase II proof-of-concept study in narcoleptic patients, which showed that pitolisant ameliorated excessive daytime sleepiness [8].

The objective of the present study was to compare the awakening effects of two newly discovered H_3-R antagonists (i.e. SAR110894 and SAR110068) with those of reference H_3-R ligands (i.e. ciproxifan, ABT-0239 and GSK189254) and classical psychostimulants (i.e. amphetamine and modafinil) by using EEG recording in rats during their light phase. Both SAR110894 and SAR110068 are potent and highly selective H_3-R antagonists (Table 1) [9–11].

2. Methods

2.1. Animals and surgery

Male Sprague-Dawley rats (Iffa Credo, L'Arbresle; Charles River, Saint-Aubin-lès-Elbeuf, France), weighing between 300 and 350 g at the time of testing, were used. They were implanted under anesthetized with Zoletil®50, mounted in the stereotaxic apparatus and secured using blunt rodent ear bars. A scalp incision was made after local anesthesia with lidocaine 2% and the skin was retracted. The skull surface was cleaned to implant small stainless steel screw electrodes (0.9 mm in diameter). Three cortical electrodes were screwed into the bone over the sensori-motor, the visual cortice and over the cerebellum. They were attached to a connector (Winchester®, 5-led) and fixed with dental cement to the cranium. Animals were allowed to recover from surgery in their individual cage for three weeks prior

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Table 1
In vitro binding profile of the H_3-R antagonists tested in this study at human H_1-, H_2-, H_3- and rodent H_3-Rs. Individual Ki curve were calculated by using the formula: (Ki = IC_{50}/(1 + [radioligand concentration]/Kd)) and Ki values were the arithmetic mean and standard error of the mean. Affinities for recombinant H_1- and H_2-Rs were obtained from CEREP.

Receptor (cells, structure, ligand)	Hr-H_1 (HEK-293) [^{3}H]Pyr. Ki (nM)	Hr-H_2 (CHO) [^{126}I]-APT.	Hr-H_3 (CHO) [^{3}H]NAMH.	Mouse-H_3 (cortex) [^{3}H]NAMH.	Rat-H_3 (cortex) [^{3}H]NAMH.	Hr-H_4 (CHO) [^{3}H]His
SAR110894	>10,000[a]	>10,000[a]	0.06[a]	0.48[a]	0.4[a]	>10,000[a]
SAR110068	>10,000[b]	>10,000[b]	1[b]	1[b]	10[d]	>10,000[b]
Ciproxifan	>10,000[a]	>10,000[d]	191.0[c]	1.23[c]	0.79[c]	>10,000[a]
ABT-0239	>10,000[a]	>1600[a]	14.1[a]	25[a]	11.0[c]	>10,000[a]
GSK189254	>1000[c]	>1000[c]	0.26[c]	3.1[c]	1.29[c]	>1000[d]

[a] Adapted from Griebel et al. [11].
[b] Adapted from Beeské et al. [9].
[c] Adapted from Medhurst et al. [21].
[d] Adapted from Esbenshade et al. [23].

recordings, housed individually in plexiglas cylinders with free access to food and water and kept under a 12/12 h light/dark cycle (lights on 7.00 a.m. to 7.00 p.m.) and a constant temperature of 21 °C. All experimental procedures described herein were approved by the Animal care and Use Committee of Sanofi or the Institutional Animal Care. Our animal facilities and animal care and use programs are in accordance with French legislation which implemented the European directive 86/609/EEC.

2.2. Electroencephalogram recording procedure

Rats were habituated in their home cage to the recording cable and room for one day prior to each EEG recording session. On the recording day, they were connected to the cable at 9:45 a.m. Recording sessions took place in the home cage between 10.00 a.m. and 04.00 p.m. and lasted 6 h. Sleep recording sessions were carried out 15 min after drug (D) or vehicle (V) injection over a 6 h period during 3 consecutive days: control day (D1), drug day (D2), control recovery day (D3). Drugs were administered p.o. (SAR110894, SAR110068, ABT-0239 and GSK189254) or i.p. (amphetamine, ciproxifan and modafinil) 15 min before recording, on D2 at 5 ml/kg (Fig. 1).

2.3. Signal processing and sleep parameters

Implanted rats were connected to an EEG recording system (2 Grass, 12 tracks, 79D model) by a flexible cable with a rotating collector (APCL 12 channels, Air precision), which allowed rats to move freely. EEG signals were filtered at 1 and 100 Hz (6 dB/octave). They were then acquired and digitized at 256 Hz using the software Coherence 32 (Deltamed). Activities in the sensorimotor and visual cortices were recorded over the 6-hr recording period by comparison with the reference electrode placed over the cerebellar cortex. Three sleep/wakefulness states of vigilance were considered: (1) Wakefulness characterized by low voltage EEG signal and fast frequency (theta (θ) rhythm: within the 6–9 Hz range) on both cortical derivations; (2) slow wave sleep (SWS) characterized by high voltage with slow wave (delta (δ) rhythm: within the 1–4 Hz range) with bursts of sleep spindles (sigma (σ) rhythm: within the 10–15 Hz range) on the sensorimotor derivation; (3) rapid eye movement sleep (REMS) by hypersynchronisation of the θ rhythm (within the 4–9 Hz range) in the visual area. Analysis of the EEG signal was performed automatically by a computerized system discriminating between the various phases and visual control was also performed. The parameters examined were (1) total wakefulness-time, (2) total SWS-time, (3) total REMS-time, number and mean duration (4; 5) wakefulness and (6; 7) sleep episodes (SWS + REMS) over the 6 h recording sessions.

2.4. Drugs

The drugs tested included ciproxifan, SAR110894 (no information of the structure or patent can be disclosed), SAR110068 (tetrahydro-pyran-4-carboxylic acid [2-methyl-4-(2-methyl-[1,3′]bipyrrolidinyl-1′-yl)-phenyl]-amide), methylphenidate, amphetamine, ABT039, GSK189254 and modafinil (all synthesized by Sanofi medicinal chemistry). The drugs were prepared daily using saline (0.9% NaCl) for intraperitoneal (i.p.) administrations, or distilled water containing methylcellulose (0.6%) with a drop of Tween 80 for oral (p.o.) administration, unless specified otherwise. Volume of administration was 5 ml/kg in rats.

3. Results

The statistical analyzes are summarized in Table 2 and the data are presented in Table 3. SAR110894 did not significantly modify any of the sleep/wakefulness parameters over the entire dose-range tested (i.e. 3–30 mg/kg). SAR110068 increased wakefulness, while decreasing SWS at 10 and 30 mg/kg, an effect which reached statistical significance the first 3 h and 6 h post-dosing at 10 mg/kg, and the first 2 h at 30 mg/kg. SAR110068 did not modify significantly REM sleep. Ciproxifan promoted significantly wakefulness, while decreasing SWS at 10 mg/kg. Time-course analysis of this effect indicated that the drug modified significantly these sleep/wakefulness parameters for 3 h. ANOVA indicated that ciproxifan modified significantly REM sleep, but again post hoc analysis did not confirm such an effect. ABT-0239 increased significantly wakefulness and decreased SWS at 10 mg/kg for 4 h. Two-way ANOVA on REM sleep just failed to reach statistical significance ($P = 0.06$), but it is noteworthy that ABT-0239 tended to decrease this parameter (Table 3). GSK189254 increased wakefulness and decreased SWS, but only the effect on the former parameter reached statistical significance. The drug had no significant effect on REM sleep. Modafinil significantly increased wakefulness and decreased SWS over the entire dose-range (i.e.

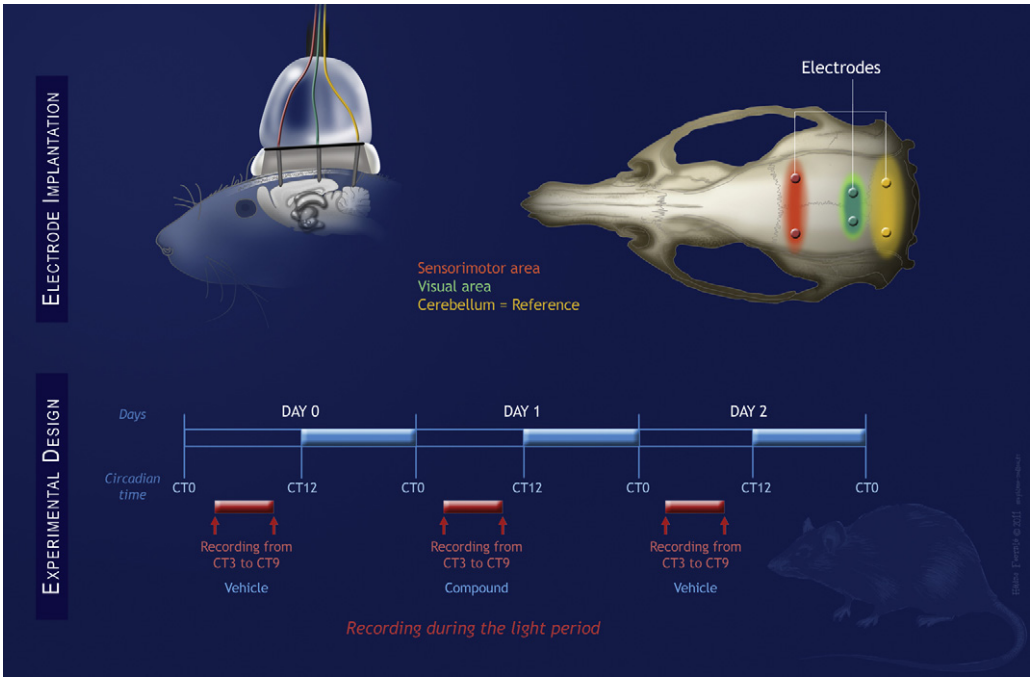

Fig. 1. Electrode placement and experimental design.

100 to 200 mg/kg). While this effect lasted for 1 and 3 h, at 100 and 200 mg/kg, respectively, it lasted over the entire recording period (i.e. 6 h) at 300 mg/kg. Modafinil significantly decreased REM sleep for 3 h at 200 mg/kg. Amphetamine increased wakefulness and decreased SWS, an effect which was significant for 5 h. Two-way ANOVA on REM sleep did not reveal any significant main effect, but the drug tended to decrease this parameter.

A visual observation of the power spectra revealed that amphetamine and modafinil produced a shift of the θ rhythm toward higher frequency (8 Hz) (Table 3 and Fig. 2). This shift is generally associated with an increase in locomotor activity. ABT-0239 produced a shift of the θ rhythm toward lower frequency (5.5 Hz). Such an effect is considered to be indicative of reduced locomotor activity. SAR110894, SAR110068 and GSK189254 did not produce any shift in θ rhythm, suggesting no evidence of motor impairment (not shown).

4. Discussion

The main objective of this study was to compare in rats the sleep/wakefulness profile of the novel H_3-R antagonists, SAR110894 and SAR110068 with that of reference H_3-R antagonists and the wake-promoting agents, modafinil and amphetamine.

SAR110894 and SAR110068 are selective, high-affinity antagonists at the human recombinant (Ki of 0.06 and 1 nM, respectively) and rat native H_3-R (Ki of 0.4 and 10 nM, respectively) (Table 1) [9–11]. Functional measurement of H_3-R occupancy showed that oral administration of SAR110894 from 30 mg/kg and SAR110068 from 1 mg/kg caused an increase in histamine turnover in the prefrontal cortex (+190% and +230%, respectively) (Dr. Lionel Bert, Sanofi, personal communication) [10]. In the current study, SAR110068, but not SAR110894, induced a clear state of increased vigilance in rats with concomitant decreases in SWS. This effect

Table 2
Summary of statistical analyses using two-way ('day' × 'hour') ANOVA with repeated measures on factor 'hour'.

Compound	Dose (mg/kg)	Values for 'day' × 'hour' interaction			Effect of factor 'day' for each level of factor 'hour'
		Wakefulness	SWS sleep	REM sleep	
SAR110894 (p.o.)	3	$F(10,60) = 1.46$, ns	$F = 1.13$, ns	$F = 1.05$, ns	None
	10	$F(10,60) = 1.87$, ns	$F = 1.57$, ns	$F = 2.35$, $P < 0.05$	None
	30	$F(10,75) = 1.55$, ns	$F = 1.36$, ns	$F = 1.26$, ns	None
SAR110068 (p.o.)	1	$F(10,60) = 1.64$, ns	$F = 1.53$, ns	$F = 0.77$, ns	None
	3	$F(10,60) = 1.15$, ns	$F = 1.18$, ns	$F = 0.57$, ns	None
	10	$F(10,60) = 3.25$, $P < 0.01$	$F = 3.83$, $P < 0.001$	$F = 0.91$, ns	1,2,3,6
	30	$F(10,150) = 4.17$, $P < 0.001$	$F = 4.14$, $P < 0.001$	$F = 1.62$, ns	1,2
Ciproxifan (i.p.)	10	$F(10,60) = 4.45$, $P < 0.001$	$F = 3.84$, $P < 0.001$	$F = 2.69$, $P < 0.01$	1,2,3
ABT-0239 (p.o.)	10	$F(10,75) = 12.38$, $P < 0.001$	$F = 17.20$, $P < 0.001$	$F = 1.86$, ns	1,2,3,4
GSK189254 (p.o.)	10	$F(10,75) = 1.96$, $P < 0.05$	$F = 1.83$, ns	$F = 1.54$, ns	1,6
Modafinil (i.p.)	100	$F(10,60) = 2.59$, $P < 0.05$	$F = 2.33$, $P < 0.05$	$F = 1.25$, ns	1
	200	$F(10,75) = 2.42$, $P < 0.05$	$F = 2.25$, $P < 0.05$	$F = 2.23$, $P < 0.05$	1,2,3
	300	$F(10,75) = 2.90$, $P < 0.01$	$F = 3.14$, $P < 0.01$	$F = 0.89$, ns	1,2,3,4,5,6
Amphetamine (i.p)	3	$F(10,60) = 4.96$, $P < 0.001$	$F = 6.58$, $P < 0.001$	$F = 1.46$, ns	1,2,3,4,5

ns = non significant.

Table 3
Summary of effect of H_3-R antagonists and stimulant drugs on sleep/wakefulness parameters.

Compound	Dose mg/kg	Difference (in %) Day 2 vs Day 1 over a 6 h recording period			Theta (θ) rhythm
		Wakefulness	SWS sleep	REM sleep	
SAR110894 (p.o.)	3	−5	+3	−7	Unchanged
	10	+21	−10	−4	Unchanged
	30	+32	−17	−17	Unchanged
SAR110068 (p.o.)	1	+25	−10	−14	Unchanged
	3	+52**	−18**	−11	Unchanged
	10	+68***	−31***	−34	Unchanged
	30	+63***	−21***	−4	Unchanged
Ciproxifan (i.p.)	10	+85***	−36***	−11	Unchanged
ABT-0239 (p.o.)	10	+84***	−47***	−70**	Strong decrease
GSK189254 (p.o.)	10	+60***	−30***	+11	Unchanged
Modafinil (i.p.)	100	+35	−23*	−19	Unchanged
	200	+60*	−33*	−27	Increase
	300	+265***	−89**	−96**	Strong increase
Amphetamine (i.p)	3	+148***	−75***	−98**	Strong increase

* $P<0.05$.
** $P<0.01$.
*** $P<0.001$ (Two-tailed Dunnett's test).

occurred immediately in the 1 h post-injection, continued into subsequent intervals (i.e. 2- and 3-h) and reappeared during the last recording hour (i.e. 6 h) at the dose of 10 mg/kg. It is important to note that the overall increase in wakefulness by SAR110068 was due to more frequent and shorter duration wake episodes throughout the recording period, rather than due to a prolonged sleep latency or a few long-lasting episodes of wake (not shown).

The wake-promoting effect of SAR110068 is comparable to that obtained in the current study with first (i.e. ciproxifan) and new (i.e. ABT-0239 and GSK189254) generation H_3-Rs. These findings are in line with previous reports on the awakening effects of

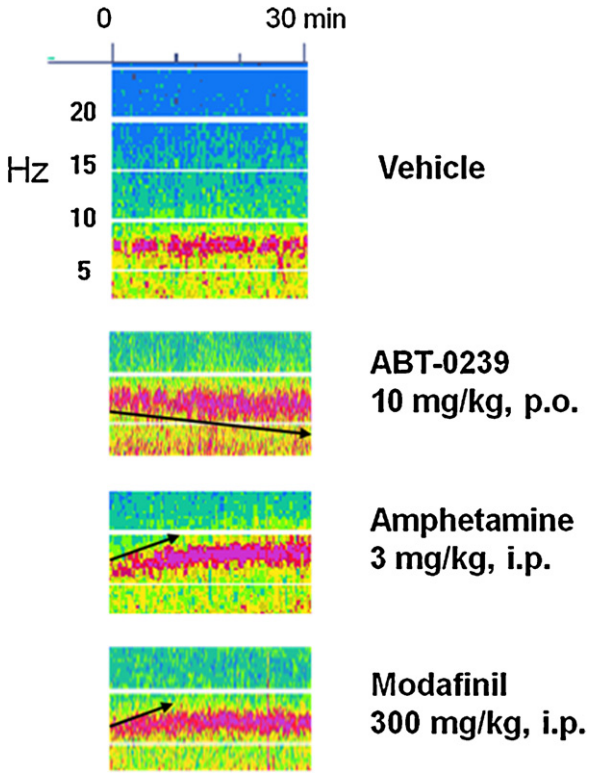

Fig. 2. Analysis of the θ rhythm following the administration of ABT-0239, amphetamine and modafinil in rats.

H_3-R antagonists in rodents [12–14] and in humans [8,15]. However, unlike all other H_3-R antagonists tested in the current study, ABT-0239 produced a strong decrease in the theta (θ) rhythm, which suggests that the awakening effects of the drug may have been contaminated by behavioral suppressant effects.

The lack of significant effect of SAR110894 on wakefulness or sleep cannot be attributed to a weak brain penetration as the compound has demonstrated compelling pro-cognitive effects in rats over the same dose-range as used in the current study [16,17], indicating clearly a central activity. The finding that SAR110894 is endowed with H_3-R inverse agonist properties [10] can also not account for its differential profile on wakefulness as compared to the other H_3-R ligands tested here, as ciproxifan, ABT-0239 and GSK189254, which produced awakening effects in the current and previous studies, have similarly been described as mixed H_3-R inverse agonists/antagonists [18–20]. Alternatively, it has been suggested that higher H_3-R occupancy (estimated >80%) is probably required for wake induction rather than for cognitive improvement [14,21,22]. Although the exact H_3-R occupancy of SAR110894 in rats is not known, it can be speculated that its effect on wakefulness requires significantly higher H_3-R occupancy than when modulating cognition. While the need of higher dosage to induce wakefulness could be a downside for the treatment of somnolence and vigilance deficiency, it could be beneficial in cognitive disorders, such as Alzheimer's disease for example, where wakefulness at night would be highly undesirable. As such, SAR110894 would represent the ideal candidate.

The marked effects of H_3-R antagonist/inverse agonist on sleep-wake cycles in animals support their potential therapeutic role in human sleep-wake disorders. For this purpose, their effects have been compared with those of current wake-promoting substances such as modafinil and the classic psychostimulant amphetamine. Results showed that the magnitude of the awakening effects of amphetamine and modafinil was dramatically higher than with the H_3-R antagonists, and they lasted for the entire recording period of 6 h. However, unlike the H_3-R antagonists, both psychostimulants produced a strong increase in θ rhythm, which is indicative of CNS side effects, such as hyperactivity or abnormal excitation.

In conclusion, the present series of experiments confirmed that selective H_3-R inverse agonists/antagonists have wake-promoting effects, findings which support further the hypothesis that these compounds may have therapeutic utility to improve somnolence and vigilance deficiency of diverse pathophysiological origins.

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