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The role of the angiotensin AT2 receptor on the diurnal variations of nociception and motor coordination in rats

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ABSTRACT

Phasic pain demonstrates significant diurnal variation in rats. Angiotensin II modulates pain transmission and the diurnal variation in nociception in several rodent pain models. The participation of AT2 receptors in the diurnal regulation of nociception is not yet elucidated. In the present study we investigated the effects of selective peptide AT2 agonist CGP 42112A and the nonpeptide AT2 receptor antagonist PD 123319 on the nociception, motor coordination and arterial blood pressure. Male Wistar 12 weeks old rats were used. CGP 42112A was injected at single doses of 1 and 5 μg/rat intracerebroventricularly (ICV) and infused chronically ICV at a dose of 12 μg/rat/day during 14 days by osmotic minipumps. PD123319 was injected at single doses of 1 and 5 μg/rat, ICV and chronically subcutaneously at a dose of 10 mg/kg/day/14 days. Nociception was assessed by an analgesimeter, arterial blood pressure (ABP) was measured by tail cuff method, and motor coordination by Rota-rod method. Single doses of CGP 42112A (1 and 5 μg/rat) provoked a short lasting antinociception. Unlike acute injection, chronic CGP 42112A infusion increased nociception at the beginning and the end of light phase thus attenuating the diurnal variations observed in the controls. Moreover, it produced an increase of ABP and improved motor coordination. Both acute (1 μg/rat) and chronic PD 123319 treatment resulted in a decrease of pain threshold and chronic treatment attenuated its diurnal fluctuation. Our data support a role for Ang II type 2 receptors in the control of diurnal variations of nociception in rats.

1. Introduction

Diurnal rhythms in the physiological functions and behavior are a fundamental property of living organisms. Circadian rhythms are regulated through neuronal mechanisms coordinated by suprachiasmatic nucleus (SCN), which plays a role of main pacemaker [26]. SCN generates endogenous circadian rhythms and synchronizes these rhythms with the light/dark cycle. Numerous classical neurotransmitters and regulatory peptides are implicated in the synchronization of the diurnal rhythms [36]. Brain structures such as epiphysis and paraventricular nucleus, functionally related to SCN, contain components of the renin–angiotensin system (RAS) [3,18]. Angiotensin II (Ang II) is one of the major physiologically active peptides of the renin–angiotensin system. It has substantial role in the regulation of blood pressure, heart rate, and hormone release, and also modulates behavior [43,44]. Two distinct Ang II receptor subtypes, AT1 and AT2, were cloned [12]. Both after systemic administration of Ang II in rats [5], or in TGR (mREN-2) 27 transgenic rats [19], a significant inversion in circadian rhythms of arterial blood pressure (ABP) is observed. Ang II participates not only in the circadian regulation of ABP but also in diurnal variations of the behavior. Mistlberger et al. [25] reported that in AT1A receptor knockout mice an increase in both motor activity and drinking behavior during the light phase was observed, compared to the wild type mice. Multiple data reveal the functional role of Ang II receptor activation in the nociception [13,14,17,34,40] and particularly the activation of AT2 receptors [13,30].

The establishment of circadian pattern of pain sensitivity is important not only of theoretical point of view but also for the diagnostics and the evaluation of familiar and newly synthesized analgesics. Diurnal variations in nociception, neuronal pain transmission, and motor responses to noxious stimuli already were reported in rodents [10,22,32,33,35,39,42].

Our previous studies showed that Ang II administered acutely into the lateral brain ventricle induced an antinociception mainly during the dark phase in Wistar rats [28]. The chronic treatment with Ang II AT1 antagonist losartan produced an inverted diurnal pattern of nociception in spontaneously hypertensive rats, with a

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highest threshold in dark phase, in contrast to normal pattern for Wistar rats [29]. There are not available data about the participation of Ang II AT2 receptors in the regulation of the diurnal variations of nociception.

The aim of the present study was to assess the effect of a highly selective peptide AT2 receptor agonist CGP 42112A and of a selective nonpeptide AT2 receptor antagonist PD 123319 on the diurnal patterns of nociception and motor coordination and on the arterial blood pressure in normotensive Wistar rats. Motor coordination was tested in order to characterize the state of withdrawal reflex and to evaluate its influence on the responses to noxious stimuli [11].

2. Materials and methods

2.1. Animals and drug treatment

Adult male Wistar rats obtained from Breeding House of Bulgarian Academy of Sciences were used. All rats were 12 weeks old at the beginning of the experiment. The animals were housed individually in metabolism cages in a separate room under standardized laboratory conditions: temperature 22 ± 1 °C, humidity 60 ± 10% and an artificial 12 h/12 h light (08:00–20:00 h)/dark (20:00–08:00 h) cycle with light intensity of about 250 lx at the front of the cages. Standard rodent diet and tap water were provided ad libitum except during the measurements. Rats were allowed 2 weeks of habituation to the laboratory conditions and experimenter before the start of the experiments. N_α-Nicotinoyl-Tyr-(N_α-Cbz-Arg)-Lys-His-Pro-Ile (CGP 42112A, Sigma–Aldrich), an AT2 receptor agonist, was dissolved in sterile isotonic saline and administered as a single injection at doses of 1 (n = 10) and 5 μg/rat (n = 8), intracerebroventricularly (ICV) and chronically as an infusion at a dose of 12 μg/rat/day ICV (n = 10) for 14 days by brain kits and osmotic minipumps (Alzet, model 2002), which deliver at 0.5 μL/h. The selective nonpeptide AT2 receptor antagonist S-(+)-1-[(4-(dimethylamino)-3-methylphenyl)methyl]-5-(diphenylacetyl)-4,5,6,7-tetrahydro-1H-imidazo[4,5-c]pyridine-6-carboxylic acid di(trifluoroacetate) salt hydrate (PD123319, Sigma–Aldrich) was dissolved in sterile isotonic saline and was administered as a single injection i.c.v. at doses of 1 μg/rat (n = 8) and 5 μg/rat (n = 7) and chronically as an infusion at a dose of 10 mg/kg/day (n = 10) for 14 days subcutaneously through osmotic minipumps (Alzet, model 2002). The pumps were inserted s.c. under pentobarbital anesthesia (Nembutal, Abbott, 40 mg/kg, i.p.) between the scapulae in a small pocket formed using a haemostat, in accordance with manufacturer's instructions. Brain infusion kit 2 (Alzet) for chronic peptide infusion or guide cannulae for acute injection of CGP 42112A were implanted in the lateral brain ventricle with coordinates 1 mm lateral and 3 mm posterior to Bregma and 4 mm deep from skull surface [27] and fixed on the skull through screws and dental cement. Control groups were injected with sterile saline (n = 8) or implanted with saline filled pumps (n = 7). No differences were found between controls, which give us a reason to unify them. All pumps were removed under pentobarbital anesthesia upon completion of their delivery rate (15th day after the implantation). All experiments were approved by government authorities fully in accordance with EC Directive 86/609/EEC for animal experiments.

2.2. Experimental design

The animals were weighted every day during habituation period and during the infusion. Blood pressure and nociception after acute drug injection were measured between 09:00 and 11:00 am. The test time points were chosen depending on the light/dark regimen. In groups with a single dose administration the nociception was measured at 5th, 15th and 30th minute after the drug injection. For each chronically treated experimental group tests were carried out on the 12–13th days of drug or saline treatment with first time point 1 h after light onset (09:00 h) and subsequent tests in 3 h interval for nociception and 6 h for motor coordination. During the dark period the trials were conducted in dim red light (25 W red bulb). All experiments were carried out in the autumn (October–November).

2.3. Measurement of arterial blood pressure

Systolic arterial blood pressure (sABP) was measured non-invasively in conscious unrestrained rats by the tail cuff method [8] (Ugo Basile blood pressure recorder 5800). The animals were adapted to measurement procedures including pre-warming in a thermostatic chamber (29–30 °C) and accustomed to tail-cuff and pulse transducer. The ABP value for each rat was obtained as a mean from three consecutive measurements.

2.4. Paw-pressure test for nociception

The paw pressure withdrawal reflex was determined with an analgesimeter (Ugo Basile). The mechanical pressure (in grams) required eliciting nociceptive responses such as withdrawal or struggle was established as mechanical pain threshold. The mechanical nociceptive threshold testing was optimized by single training of the animals 1 day before the experiments [2].

2.5. Rota-rod test

Motor coordination was measured by a "Rota-rod" test according to the procedure described elsewhere [37]. The apparatus consisted of a horizontal rod (6 cm in diameter, 11 cm long) bordered with discs (40 cm diameter). It was programmed to rotate at a constant rate of 8 rpm. The animals were placed on the rotating rod with head directed against the direction of the rotation so that the animals had to progress forward to maintain equilibrium. Animals were trained 1 h before the start of the testing. The length of time the animal remained on the rotating cylinder was recorded in seconds, up to 180 s.

2.6. Statistical analysis

All data are expressed as mean ± SEM. Statistics were performed by two-way ANOVA using time and drug (chronic treatment) or dose (acute injection) as factors and one-way ANOVA within group with Bonferroni post test. P values of less than 0.05 were considered as statistically significant.

3. Results

3.1. Effects of acute and chronic infusion of AT2 receptor agonist CGP 42112A into the lateral brain ventricle on the nociception

CGP 42112A showed a significant "Dose" effect ($F(2, 133) = 22.214$, $p < 0.001$) when given as a single injection i.c.v. The results from the intervals of 5, 15 and 30 min after injection of peptide, showed a time-dependence ($F(3, 133) = 3.552$, $p = 0.017$). At a dose of 1 μg/rat CGP 42112A provoked a short lasted antinociception 15 min after the injection ($p = 0.042$), whereas at a dose of 5 μg/rat the antinociception extended from 5th to 30th minute ($p < 0.001$) (Fig. 1).

Chronic i.c.v. infusion of CGP 42112A at a dose of 12 μg/rat/day during 14 days produced a significant "Drug" effect ($F(1, 149) = 6.175$, $p = 0.014$), "Time" effect ($F(8, 149) = 2.413$, $p = 0.023$), as well as an interaction between above mentioned factors ($F(8,$

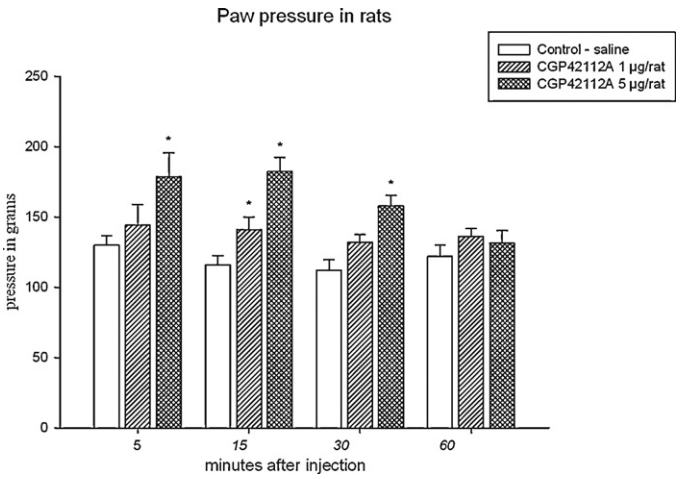

Fig. 1. Time-dependent effects of CGP 42112A administered ICV at single doses of 1 and 5 µg/rat on nociception in paw pressure test. Data showed mean ± SEM. $^{*}p < 0.05$ vs. control (saline treated) group.

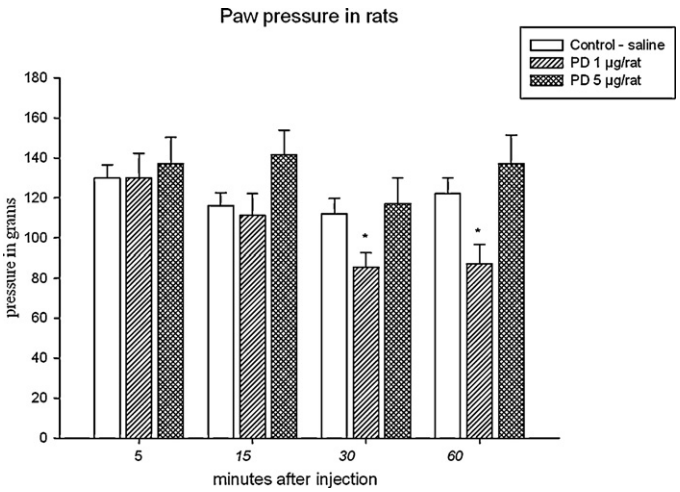

Fig. 3. Time-dependent effects of PD 123319 administered ICV at single doses of 1 and 5 µg/rat on nociception in paw pressure test in rats. Data showed mean ± SEM. $^{*}p < 0.05$ vs. control (saline treated) group.

149) = 2.215, $p = 0.036$) with lower pain threshold at 09:00 h ($p < 0.001$) and 18:00 h ($p = 0.005$). One-way repeated measures ANOVA showed a significant diurnal variations of nociception in saline treated control group – $F(8, 100) = 3.891$, $p < 0.001$, whereas in CGP 42112A-treated group there were not significant diurnal differences (Fig. 2).

3.2. Effects of acute and chronic infusion of AT2 receptor antagonist PD 123319 on the nociception

PD 123319 administered acutely i.c.v. showed a significant "Dose" effect of ($F(2, 108) = 7.585$, $p < 0.001$) which effect was time-dependent ($F(3, 108) = 4.271$, $p = 0.007$). PD 123319 at a dose of 1 µg/rat produced a pronociception at 30th ($p = 0.029$) and 60th ($p = 0.022$) minute after injection and injected at a dose of 5 µg/rat it had no effect (Fig. 3).

Chronic subcutaneously infusion of PD 123319 at a dose of 10 mg/kg/day during 14 days led to a significant changes in the diurnal variation of nociception (Drug – $F(1, 156) = 17.043$, $p < 0.001$; interaction Time × Drug – $F(8, 156) = 3.136$, $p = 0.003$). It decreased the pain threshold at the beginning of the light phase ($p = 0.001$) (Fig. 4).

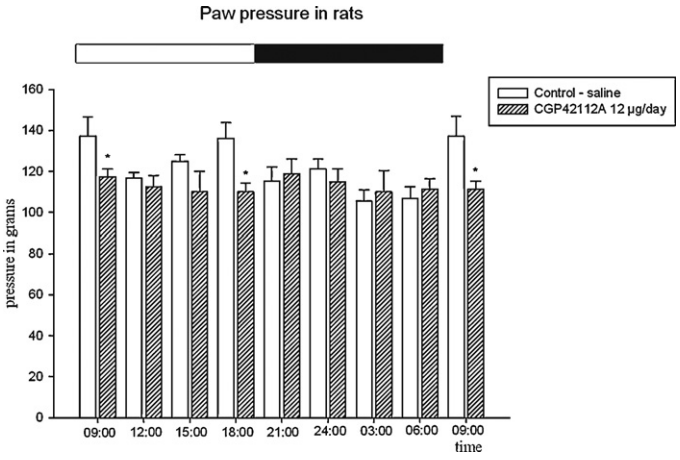

Fig. 2. Effects of CGP 42112A administered chronically ICV at a dose of 12 µg/rat/day during 14 days on the diurnal variations of nociception in paw pressure test. Data showed mean ± SEM. $^{*}p < 0.05$ vs. control (saline treated) group. Horizontal bars showed duration of the light (empty bar) and dark (filled bar) phase of the 24-h cycle.

Chronic i.c.v. treatment with CGP 42112A at a dose of 12 µg/rat/day, 14 days produced a small but significant ($p < 0.05$) increase in ABP in contrast to chronic treatment with PD 123319 which did not change the mean values of ABP (Fig. 5).

Motor coordination did not show significant diurnal fluctuations in the controls. Chronic CGP 42112A treatment improved the motor coordination (Drug effect $F(3, 76 = 41.222$, $p < 0.001$) at the end of light (15:00 h – $p = 0.004$) and during the dark phase (21:00 and 03:00 h – $p < 0.001$), while PD 123319 was without effect (Fig. 6).

4. Discussion

In the present study CGP 42112A administered acutely into the lateral cerebral ventricle induced an antinociception in paw pressure test in rats, whereas the nonpeptide AT2 receptor antagonist PD 123319 provoked a pronociception. The role of AT2 receptors in Ang II-induced antinociception is demonstrated by

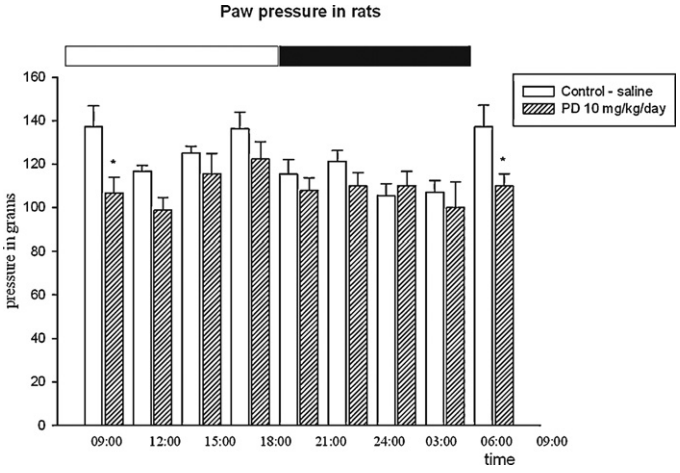

Fig. 4. Effects of PD 123319 administered chronically subcutaneously at a dose of 10 mg/kg/day during 14 days on the diurnal variations of nociception in paw pressure test in rats. Data showed mean ± SEM. $^{*}p < 0.05$ vs. control (saline treated) group. Horizontal bars showed duration of the light (empty bar) and dark (filled bar) phase of the 24-h cycle.

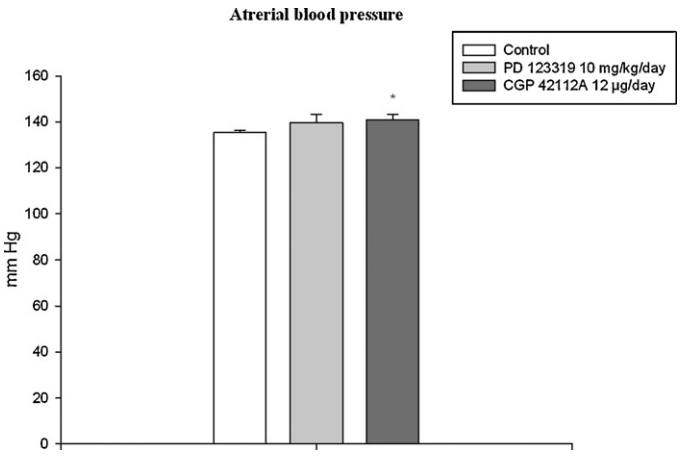

Fig. 5. Effects of AT2 receptor ligands CGP 42112A (12 μg/rat/day, ICV) and PD 123319 (10 mg/kg/day, SC) administered during 14 days on the arterial blood pressure measured by tail-cuff method in rats. Data showed mean ± SEM. $^{*}p < 0.05$ vs. control (saline treated) group.

our earlier data showing that a selective AT2 receptor antagonist PD 123319 produces a pronociception and abolishes the Ang II-induced antinociception [13]. This is supported by the finding that AT2 receptor knock-out mice possess lower nociceptive threshold [38] and also that AT2 receptors in periaqueductal gray matter participate in Ang II-induced antinociception in rats [30]. In the latter study, however, CGP 42112A was considered to be an AT2 receptor antagonist, which had not its own effects on the nociception however successfully abolished Ang II and Ang III-induced antinociception [31]. This peptide is a highly selective AT2 receptor ligand, which is able to displace Ang II analogs by this receptor type in particular brain structures such as trigeminal nucleus, the ventroposteromedial thalamic nuclei, olfactory bulbs and piriform cortex [15,16]. Moreover, CGP 42112A acts as a full agonist to inhibit the guanylate cyclase activity in PC12W cells [7] or to decrease blood pressure in presence and/or absence of AT1 receptor antagonist through nitric oxide related mechanism [9]. Recently reported data confirmed that the peptide is a neuroprotective agonist of AT2 receptors, the effect that was antagonized by PD123319 [24]. Merabet et al. [23] allowed that CGP 42112A might have an agonistic effect depending on the dose used. All these data was additionally complicated by the fact that AT1 and AT2 receptors led to opposed effects of the Ang II-mediated functions such as

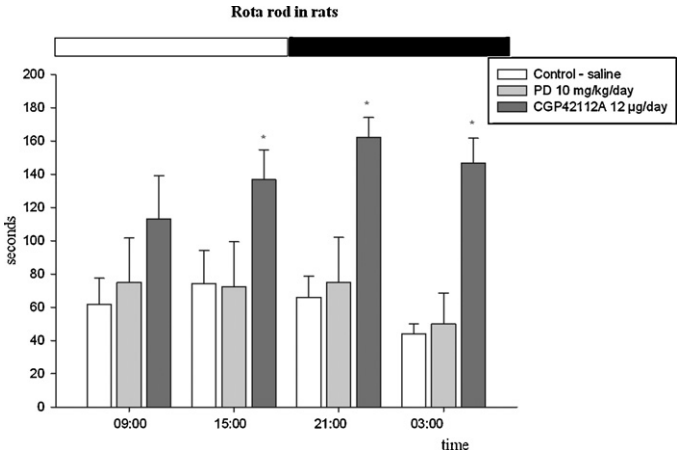

Fig. 6. Effects of AT2 receptor ligands CGP 42112A (12 μg/rat/day, ICV) and PD 123319 (10 mg/kg/day, SC) administered during 14 days on the diurnal variations of motor coordination evaluated by Rota-rod test in rats. Data showed mean ± SEM. $^{*}p < 0.05$ vs. control (saline treated) group. Horizontal bars showed duration of the light (empty bar) and dark (filled bar) phase of the 24-h cycle.

regulation of blood pressure [4] and even AT2 receptor itself acted as an AT1 receptor-specific antagonist in cell cultures mainly by formation of heterodimers with AT1 receptors [1]. Moreover, in the brain most AT1 and AT2 receptors are expressed in different brain nuclei and in neurons mediating different functions [41]. The question whether CGP 42112A is an AT2 agonist or an antagonist still remains open. We may suppose however, that the discrepancy between our results and this of Pelegrini da Silva et al. [30] is closely related to the doses used and the sites of injections in brain areas with different AT2 receptors density.

Above mentioned studies are related to acute effects of AT2 receptor activation. In the present study we showed that chronic i.c.v. treatment with CGP 42112A decreased the pain threshold at the beginning and the end of light phase, abolishing the diurnal variations in nociception. This result suggests some adaptation after chronic Ang II receptor activation. One possible mechanism may be related to desensitization of the AT2 receptors in pain-related structures after long term treatment with an agonist. Such desensitization was established for dipsogenic and natriuretic effect of Ang II after repetitive i.c.v. injections [45]. Recently published data have shown that even morphine that is the gold standard for the treatment of acute pain might induce sensitization of later pain challenges after long term morphine pretreatment [20]. Moreover, chronic brain AT2 receptor activation was able to improve the motor coordination as compared to controls. AT1 and AT2 receptors play different roles in the motor coordination and AT2 selective receptor blocker impairs motor coordination [6]. Improved motor coordination indicates a lack of impairment of withdrawal reflex, and even the latency to paw withdrawal may be reduced. In addition, our data showed an increase in arterial blood pressure after chronic CGP treatment. These results are in contrast with the antihypertensive effect of AT2 receptor activation already reported, but it must be noted that the latter effect was reached only on the background of AT1 receptor blockade and comparatively high dose of AT2 receptor agonist [9].

Acute and chronic subcutaneous treatment with AT2 selective antagonist PD123319 resulted in an increase of nociception and attenuation of diurnal variations in the paw pressure threshold. It is possible that this effect is not only related to the AT2 receptor blockade and also by endogenous Ang II-induced activation of nonoccupied AT1 receptors or other mediatory systems. Chronic systemic infusion of PD123319 decreases angiotensin II AT2 and increases AT1 receptor bindings in brain structures inside the blood–brain barrier [21]. The latter study confirmed not only that PD123319 penetrated the blood–brain barrier but also suggested that chronic blockade of AT2 receptors changed the balance between two Ang II receptor types, decreased tyrosine hydroxylase mRNA and pituitary ACTH and vasopressin content [21].

We have already reported that Ang II takes a part in the regulation of diurnal rhythms of nociception [28] and also that chronic AT1 receptor blockade is able to decrease the diurnal variations of mechanical nociceptive threshold in Wistar rats, the effect being related to an antinociception through the light phase [29]. The present data elucidate further the role of Ang II receptors in the circadian regulation of pain sensitivity. Chronic blockade of AT2 receptors, in contrast with AT1 blockade, increases nociception during the light phase of the day/night cycle.

Taken together the present data suggest that AT2 receptor type participates in the regulation of diurnal rhythm of nociception.

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Glossary

Nociception: It is the afferent activity produced in the peripheral and central nervous systems by stimuli that have the potential to damage tissue. This activity is initiated by nociceptors that can detect mechanical changes above a set threshold. Once stimulated, a nociceptor transmits a signal along the spinal cord, to the brain. Nociception triggers a variety of autonomic responses and may also result in a subjective experience of pain.

Phasic pain: Sudden pain from a newly acquired injury could well overwhelm an animal, preventing it from fighting, running for cover or burrowing to escape a predator during an emergency.

Circadian rhythm: A daily cycle of biological activity based on a 24-h period and influenced by regular variations in the environment, such as the alternation of night and day. It is generated by an internal clock that is synchronized to light–dark cycles and other cues in an organism's environment.