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Barrel Rotation Induced by Central Arginine^8-Vasopressin Treatment: Involvement of Neurohypophyseal Peptide Receptors

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DIAMANT, M., A. M. BAARS, G. L. KOVÁCS AND D. DE WIED. *Barrel rotation induced by central arginine^8-vasopressin treatment: Involvement of neurohypophyseal peptide receptors.* PHARMACOL BIOCHEM BEHAV 47(1) 27–32, 1994.—Two series of experiments were done to investigate the mechanism underlying arginine^8-vasopressin (AVP)-induced barrel rotation in rats. In the first series, the effect of intracerebroventricular (ICV) administration of various neurohypophyseal hormone antagonists on AVP-induced barrel rotation was studied. The more vasopressin was given, the more the rats exhibited barrel rotation. ICV pretreatment with a V_1 vasopressin receptor antagonist, d(CH_2)$_5$[Tyr(Me)^2]AVP, prevented barrel rotation, while similar treatment with a V_2-antagonist, d(CH_2)$_5$[dIle^{2}Ile^4]AVP, did not affect vasopressin-induced barrel rotation. However, Des-Gly,NH_2d(CH_2)$_5$[Tyr)Me^2)Thr^{4}Orn^8]-vasotocin, a specific oxytocin antagonist, potentiated the effect of AVP on barrel rotation.

The second experiment was performed in rats equipped with a telemetry system to measure heart rate (HR), core temperature (CT), and gross locomotor activity. Also, in this experiment the incidence of AVP-induced barrel rotation was dose-dependent, as was the number of rats that died. Barrel rotation was accompanied by a significant decrease in CT and HR, while rats that did not develop hypothermia did not show barrel rotation. These results suggest that a V_1 receptor is involved in barrel rotation. Since AVP-induced hypothermia is also mediated by a V_1 receptor, it is postulated that hypothermia is a prerequisite for barrel rotation to occur. Further experiments are needed to substantiate this hypothesis.

Arginine^8-vasopressin Vasopressin receptor antagonists Barrel rotation Receptors Core temperature Heart rate

AN unusual motor disturbance occurs in conscious rats following intracerebroventricular (ICV) administration of arginine^8-vasopressin (AVP) (1,25,29,35,36). This behavioral syndrome, often fatal, includes ataxia, body swaying, a sudden asymmetric increase in tone of stretch muscles, spastic limb abductions, opisthotonos, and, most characteristically, rotations along the long axis of the body (25,35). A dose of 8–10 ng of AVP, injected into the lateral cerebral ventricle (ICV), appears to be the threshold for the induction of barrel rotation, and the dose-response relationship was described as extremely flat (2), or as an "all or none" phenomenon which does not follow dose-response relationships (35).

The underlying neuronal mechanisms of barrel rotation are largely unknown. Abood et al. (1) observed altered hippocampal EEG activity after ICV AVP treatment and found that the most commonly used antiepileptic drug (phenytoin) reduced the incidence of AVP-induced barrel rotation. Other antiepileptic compounds, such as diazepam, valproic acid, or phenobarbital, also reduced the proportion of rats with barrel rotation and prolonged the latency of the onset of this motor disturbance. Chlorpromazine, a compound with considerable muscle relaxant effects, was also found to antagonize barrel rotation induced by AVP treatment. In keeping with the theory of a proconvulsive action of AVP is the suggestion (19,20) that vasopressin mediates febrile convulsions and that rats can be sensitized to vasopressin-induced barrel rotation (8). Moreover, AVP has been shown to potentiate pilocarpine-induced epilepsy (10). In contrast, Burke and Fahn (7) found that barrel rotation (induced by somatostatin) was not associated with paroxysmal epileptiform activity. Wurpel et al. (36) noted that many rats, just prior to barrel rotations, displayed nystagmus and assumed a posture resembling that of hemilabyrinthectomized rats. These authors therefore concluded that abnormality of the vestibular-visual system may also contribute to the occurrence of AVP-induced barrel rotation.

AVP has been shown to attenuate endotoxin-induced hyperthermia [for reviews see (14,33)]. Few studies have investigated the direct effect of centrally administered AVP on rest-

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ing body temperature (16,19,30). Using high doses of AVP, several authors have observed a marked decrease in body temperature. Whether AVP-induced hypothermia and AVP-induced barrel rotation follow a similar time course is unknown.

Peripheral hormonal as well as central neuronal actions of AVP are thought to be mediated via specific receptors [for review see (6)]. In the brain, the existence of V_{1a}-type (pressor) and oxytocinergic receptors have been identified by various groups of authors (21,31,32). There is no firm evidence for the existence of V_{1b} or V_2 receptors in the central nervous system. Functional data, however, suggest that V_2-type vasopressinergic receptors might also be of importance in mediating some central nervous effects of AVP (9,10,13).

The present experiments were undertaken to analyze the effect of graded doses of centrally administered AVP on barrel rotation in rats treated with various neurohypophyseal peptide receptor antagonists. The last part of the experimental work focuses on the autonomic changes—in particular, heart rate and temperature alterations—associated with AVP-induced barrel rotation.

METHODS

Experiment 1: The Effect of Graded Doses of AVP on Barrel Rotation

The experiments were performed on male rats of the Wistar strain (Harlan Cpb, Zeist, The Netherlands) weighing 160 ± 10 g. Rats were anaesthetized with fentanyl (Hypnorm®, Janssen Pharmaceutica, Beerse, Belgium, 0.02 mg/kg body weight), and a polyethylene cannula was inserted into the right lateral cerebral ventricle according to a previously described technique (11). Appearance of cerebrospinal fluid in the cannula indicated the correct position in the ventricle. Experiments were performed five days after surgery. The animals were kept in individual cages. Various doses of AVP were given as a sole treatment or in combination with the peptide receptor antagonists, and the incidence of barrel rotations was recorded by an observer. Peptide antagonists $d(CH_2)_5$[Tyr-(Me)^2]AVP (abbreviated as V_1) for the V_1 receptors, $d(CH_2)_5$-[dIle^{2}Ile^4]AVP (abbreviated as V_2) for the V_2 receptors, and Des-Gly,$NH_2d(CH_2)_5$[Tyr)Me^2)Thr^{4}Orn^8]-vasotocin for the oxytocin receptors (referred to as AOXT in this article), were kindly donated by Dr. Maurice Manning (Toledo, OH). The antagonists were injected ICV at a dose of 100 ng, dissolved in 0.2 μl pyrogenic free 0.9% saline. AVP (Organon, Oss, The Netherlands) was given 30 min after the antagonist, also in a volume of 0.2 μl.

Experiment 2: Time Courses of Changes in Heart Rate, Core Temperature, and Gross Activity

Animals. Male albino rats of an inbred Wistar strain (Cpb: WU) were used, initially weighing 200–220 g. Following surgery, the animals were housed individually and kept under controlled conditions for temperature (22 ± 2°C) and light (lights on between 0600 and 2000). Food and tap water were available ad lib. Throughout the experimental period the rats remained in the translucent Plexiglas home cages. The animals underwent a daily handling routine for weighing and habituation purposes, starting the day after surgery.

Data-collecting devices. The Cardio Tel™ Telemetry System (Mini-mitter Co., Sunriver, OR) was used to measure three parameters (i.e., heart rate [HR], core temperature [CT], and gross locomotor activity). This system consists of a small implantable wireless transmitter (model CTT85-SA) with two voltage-sensing leads originating at the top of it, and a receiver. The transmitters were calibrated in a constant water bath at temperatures of 35 and 39°C, respectively, prior to implantation. Sampling and processing of data was performed by the Dataquest III data acquisition system (Mini-mitter Co.), which was run on an IBM XT computer. This system has been described previously (15). In the present study, each rat in its home cage was placed directly on the receiver. A 30-s sampling period was used to collect data of five to six animals at a time.

Animals were equipped with a polyethylene cannula in the lateral cerebral ventricle to allow ICV treatments (see above). Two days after ICV cannulation, the IP implantation of the transmitter was performed under ether anaesthesia according to a previously described method (15).

Experimental protocol. Baseline autonomic monitoring started five days after transmitter implantation when rats had regained their preoperative weights. All behavioral and telemetered recordings were carried out between 0900 and 1600. On the first habituation day (day 0), all rats were monitored for 30 to 60 min in their home cages to obtain baseline HR, CT, and gross activity values. On the second habituation day (day 1), baseline recordings according to the same protocol were made. This time, however, each rat was exposed to sham ICV injection after the measurements. Hereupon rats were randomly assigned to recording groups consisting of five to six animals. On the actual test days the following routine was performed. After 60 to 90 min of habituation to the experimental room, data acquisition channels were turned on to allow baseline recordings for 15–30 min, prior to ICV injections. Subsequently, rats received AVP or saline ICV. In the meantime, sampling of autonomic data was continued. Immediately after ICV injections, behavioral scoring was started by an observer. Both autonomic and behavioral monitoring lasted up to 60 min after ICV treatments. All experiments were done at an ambient temperature of 21 ± 1.5°C. AVP was injected at a dose range in a volume of 0.1–100 ng per rat in a volume of 2 μl.

Statistics and data analysis. Upon conclusion of the experiments, the localization of the cannula was controlled by injection of methylene-blue into the lateral ventricle of decapitated rats. Only data obtained from rats with a correctly placed cannula were included in the analysis.

Experiment 1. Following ICV injection of AVP, some rats showed typical symptoms of barrel rotation. The proportion of rats showing AVP-induced barrel rotation was recorded, and Fisher's exact probability test was used for statistical analysis.

Experiment 2. Analysis of variance (ANOVA), followed by post hoc comparison tests, was used for statistics. Significance was accepted at p values less than 0.05.

RESULTS

Experiment 1

The dose-related effect of AVP on the incidence of barrel rotation is illustrated in Fig. 1. ICV injection of AVP resulted in a dose-dependent increase in barrel rotation. Following the injection of 1 ng AVP no barrel rotation was observed, while 52% of rats displayed barrel rotation following a dose of 300 ng AVP ($p < 0.01$). From the rats receiving an intermediate dose (ranging from 10 to 100 ng), 20–23% showed barrel rotation ($p < 0.05$). In this group, the average mortality in rats

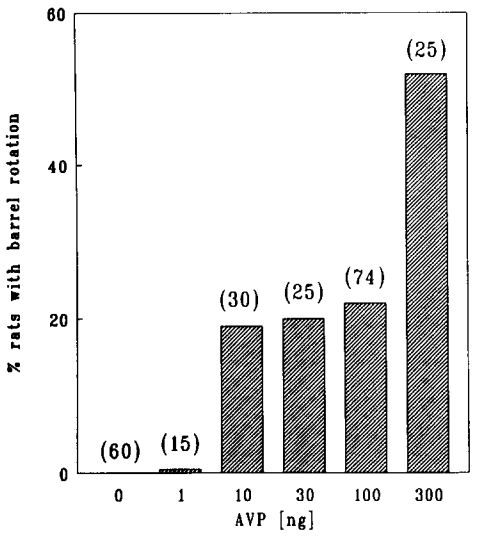

FIG. 1. The effect of AVP on the incidence of barrel rotations (the number of rats in each group are indicated in parentheses). At all but the 1-ng dose, ICV-injected AVP resulted in a significant increase in the occurrence of barrel rotation ($p < 0.05$).

showing barrel rotation was 5%, whereas mortality in rats with barrel rotation after the 300-ng dose of AVP was as high as 46.2% (data not shown). Of note, there were no initial differences in HR, CT, or in any other measure between rats that died from barrel rotation and those that survived this event (data not shown).

The interaction of neurohypophyseal neuropeptide receptor antagonists with AVP is illustrated in Fig. 2. When given as a sole treatment, the peptide antagonists (100 ng ICV) failed to induce barrel rotations (data not shown). When pretreated with 100 ng of the V1 antagonist, the effect of 300 ng AVP on barrel rotation was almost completely blocked ($p < 0.01$). The V2 antagonist (100 ng) was not effective. The oxytocin antagonist (AOXT) facilitated barrel rotation ($p < 0.05$). The incidence after pretreatment with AOXT was 93.3% (Fig. 2).

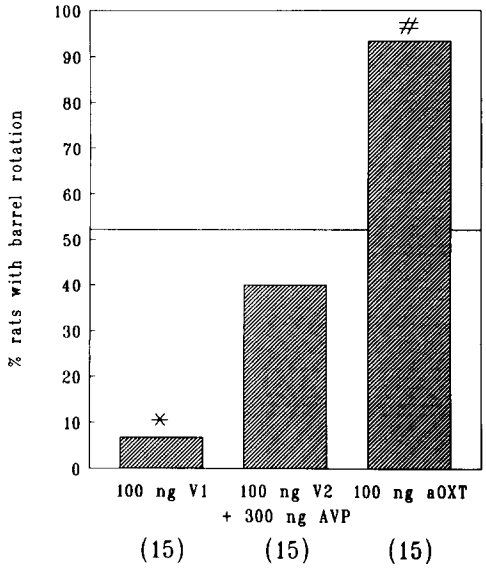

FIG. 2. The interaction of neurohypophyseal peptide receptor antagonists and AVP on the incidence of barrel rotations. The horizontal line indicates the incidence of barrel rotations in rats treated with 300 ng AVP only ($n = 25$). *$p < 0.01$ vs. AVP; #$p < 0.05$ vs. AVP (for statistics and details see text).

Experiment 2

Similar to the results from the first experiment, the frequency of barrel rotation was found to be dose-dependent: In the 100-ng group, 6/9 (66%), in the 30-ng group, 3/9 (33%), and in the 10-ng group, 1/10 (10%), rats developed barrel rotation. Four out of 10 rats (40%) with barrel rotation died within 30 min after ICV injection. Mortality was also found related to the dose: None of the three lower doses (0.1, 1.0, and 3.0 ng, respectively) produced barrel rotation. Figure 3 illustrates the simultaneous changes in HR and CT, associated with gross activity in a rat that developed barrel rotation 3 min after ICV treatment with 100 ng AVP. The sharp increase in HR, coinciding with the vigorous long-axis rotation, was followed by bradycardia. A significant marked decline in CT was observed, while HR was still significantly increased. Based on previous studies on AVP-induced barrel rotation, which have found barrel rotation to be an all-or-none response with a flat dose–response relationship, we have analyzed HR and CT data of all rats that exhibited the syndrome, irrespective of the dose given (BR rats). Rats that did not develop barrel rotation after AVP injection were used as controls (non-BR rats). Both groups were matched for the injected doses of AVP. Figures 4A and 4B show the mean thermic and cardiac responses, respectively, in both groups after AVP administration. In BR rats, a significant short-term tachycardia response was observed, starting immediately after ICV treatment with AVP (Figs. 3 and 4). Calculation over the first 30 min after AVP treatment revealed an increase in HR in non-BR rats, whereas a tendency towards bradycardia was found in BR rats (Fig. 4). In addition, a sharp decline in CT (of later onset, however) was observed in BR rats after AVP treatment, but not in non-BR rats: In the latter group, some rats showed a mild, temporary decrease, while others exhibited a slight increase in CT. This differential response may explain the large standard error of the mean ΔCT in this group (Fig. 4). As a rule, the severe hypothermia lasted up to 30 min ($p < 0.005$), with a maximum decrease at 13 to 18 min, whereas HR returned to baseline values within 10 min after ICV treatment (Fig. 4). In some BR rats, the extreme hypothermia outlasted the entire recording period (Fig. 4; $p < 0.02$).

DISCUSSION

When injected into the lateral cerebral ventricle ICV, AVP modulates autonomic nervous activity and cardiovascular responses, as well as affects thermoregulation and behavior (3, 11,14,16,32). The present results confirm those of previous studies (1,24,34,35), showing that central administration of high doses of AVP results in the occurrence of a typical motor disturbance termed "barrel rotation." This paroxysmal abnormal motor activity includes immobility, ataxia, body swaying, opisthotonos, and, most characteristically, short-lasting convulsive-like rotation of the animal about its longitudinal axis. Presently, a receptor-mediated mechanism underlying AVP-

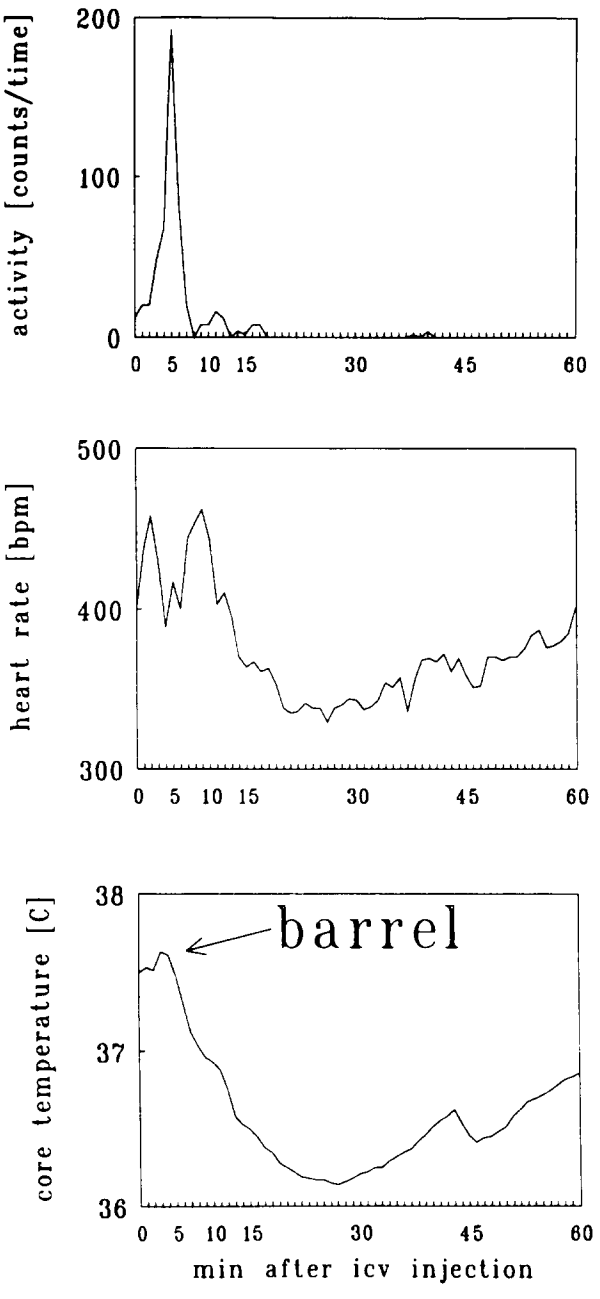

FIG. 3. Time courses of changes in gross activity, heart rate, and core temperature in a rat during and after AVP-induced barrel rotation. AVP (100 ng ICV) was injected at time zero.

induced barrel rotation was demonstrated by treating rats with various AVP receptor antagonists prior to ICV injection of the peptide. In addition, in search of a possible relation among AVP-induced barrel rotation and other central effects of the peptide a link was observed between AVP-elicited hypothermia and barrel rotation.

In contrast to previous reports, which regarded barrel rotation as an "all-or-none" response (35,36), in both of our experiments the incidence of barrel rotation showed dose-dependency. In 8–10% of rats in the first experiment and in 40% of rats in the second experiment, barrel rotation was fatal (i.e., rats died under the symptoms of respiratory failure). With regard to mortality related to barrel rotation, others report variable data ranging from no mortality at a dose of 1 μg AVP (29,30) up to a 30% mortality following administration of nanogram amounts of the peptide (24). Therefore, in contrast to our findings, those authors conclude that mortality after barrel rotation in response to central AVP injection may not be dose-dependent.

Although Meisenberg and Simmons (29,30) did not find a hypothermia to coincide with the occurrence of barrel rotation, our results suggest that these effects may be related. Rats that did not develop hypothermia after AVP injection did not show barrel rotation, whereas barrel rotation was invariably associated with a severe lowering of core temperature. Kasting et al. (19) treated rats with AVP on subsequent days and found a marked sensitization to the seizure-inducing, but not to the hypothermic, effect of AVP. However, those authors did not observe barrel rotation after the first injection, while we have used the rats only once.

Barrel rotation has been regarded as an epileptic phenomenon, as its occurrence was inhibited by antiepileptic drugs (2,35). However, in a second set of experiments those authors did not find EEG abnormalities commonly associated with epileptic disorders (36). The V1 receptor antagonist completely prevented the effects of a high dose of AVP (300 ng) on barrel rotation, suggesting the involvement of V1 vasopressinergic receptors in mediating the action of AVP on barrel rotation. These receptors are also involved in the antipyretic effects of AVP observed after ICV (23) or intraseptal (34) injection. Interestingly, while treatment of rats with the V2 receptor antagonist did not affect barrel rotation, suggesting no involvement of this receptor subtype in AVP-induced barrel rotation, ICV injection of the same amount of the V2 receptor antagonist was found to attenuate the antipyretic effect of centrally administered AVP (22). In contrast, ICV administration of AOXT antagonist significantly potentiated the effect of AVP on barrel rotation. In this respect, it may be of interest to note the findings by Abood et al. (1) showing that oxytocin reverses the effect of AVP on barrel rotation in rats. In keeping with the well-known opposite central nervous effects of AVP and OXT (5,14,24), the OXT receptor antagonist may potentiate AVP-induced barrel rotation by blocking OXT receptors. However, central injection of OXT does not produce an opposite effect on core temperature (23).

AVP has been found to affect both the sympathetic and the parasympathetic branch of the autonomic nervous system [(3); reviewed in 14)]. The peptide seems to modulate cardiac responses through a direct activation of parasympathetic pathways to the heart and baroreceptor function (18). These effects may be responsible for the enforcement of vagal activation observed in a number of behavioral paradigms in freely moving rats (3). The initial bradycardic response which is found in rats exposed to emotional stress is absent in rats of the Brattleboro strain with a hereditary diabetes insipidus (3). The resting tachycardia in these rats was ascribed to a relative increase in sympathetic tone which was reversed by treatment with AVP (18). These findings are in agreement with our previous study, showing that ICV-injected AVP induces bradycardia and that the V1 receptor antagonist, given as a sole treatment to freely moving rats in their home cages, results in an increase in heart rate, core temperature, and behavioral activation, effects opposite to those produced by AVP under the same circumstances (16). The tendency to bradycardia, as found in rats with AVP-induced barrel rotation, may be the

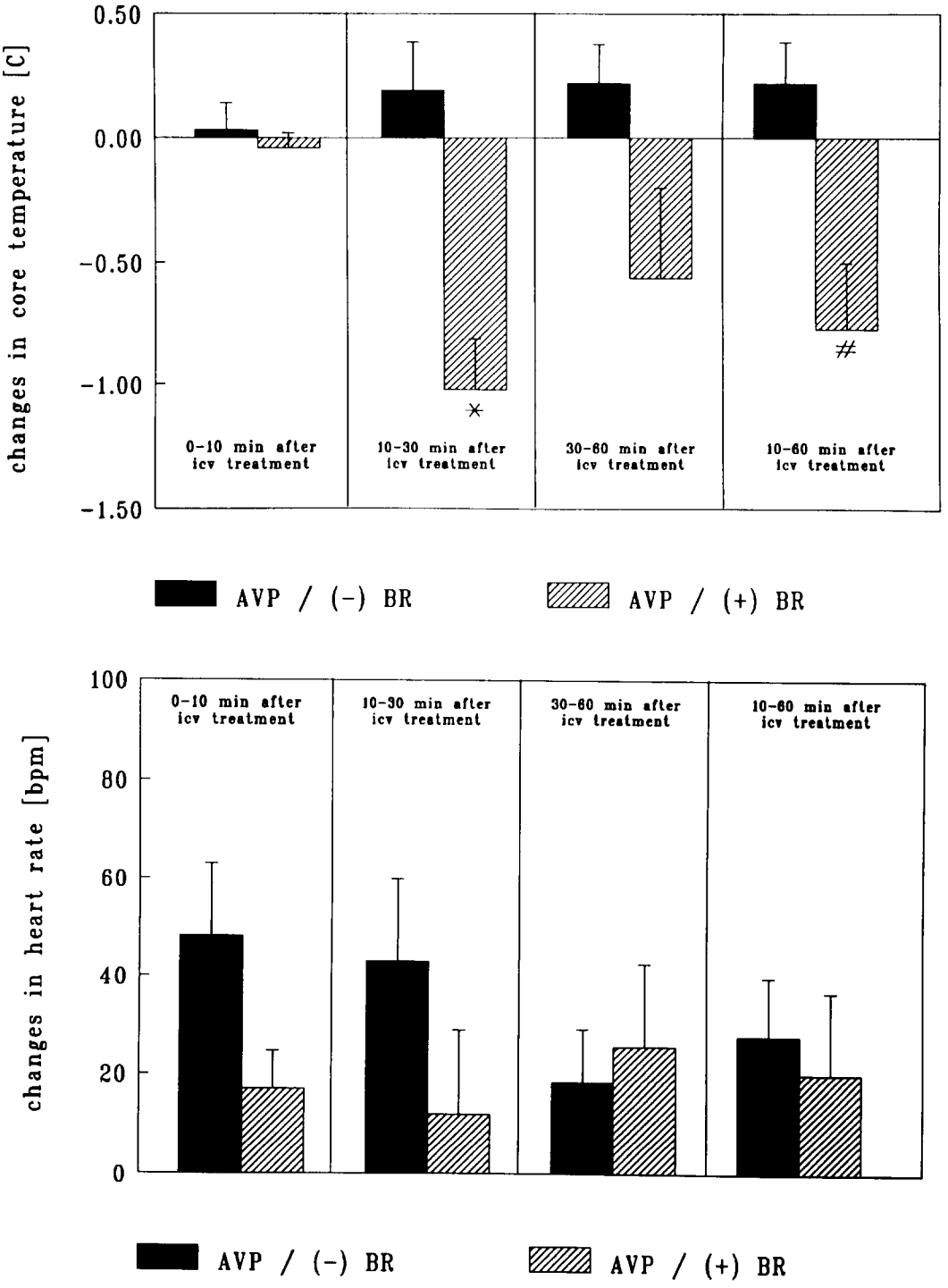

FIG. 4. (top) Hypothermia and barrel rotation (BR) after ICV injection of AVP in rats. Both groups are matched for AVP-doses (n = 6, each group, consisting of 1 rat given 10 ng, 2 rats given 30 ng, and 3 rats given 100 ng AVP ICV). *$p < 0.005$ vs. (−) BR; #$p < 0.02$ vs. (−) BR. (bottom) Heart rate and barrel rotation (BR). For details see (top) and text.

result of parasympathetic activation. Since temperature regulation is under the control of the autonomic nervous system, it may well be that severe hypothermia is directly or indirectly the result of increased parasympathetic activity.

To summarize, our results suggest that the V1 receptor is involved in AVP-induced barrel rotation. In addition, since the effect of ICV-injected AVP on core temperature is also mediated by a V1 receptor, we suggest that the observed occurrence of hypothermia may be a prerequisite for the appearance of barrel rotation in rats.

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