Circadian Variations in Intracranial Pressure and Translaminar Pressure Difference in Sprague-Dawley Rats

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PURPOSE. To study the circadian (24-hour) change in intracranial pressure (ICP) in conscious, freely moving rats and to project the circadian change in translaminar pressure difference.

METHODS. Telemetric pressure transmitters were implanted to monitor ICP in the lateral ventricle in nine light–dark–entrained Sprague-Dawley rats. ICP and locomotor activity data were collected. The mean results for the 12-hour light period and the 12-hour dark period were compared. The light–dark change in ICP was also determined in six rats under an acute 24-hour constant dark condition. The circadian translaminar pressure difference was projected based on the ICP data and the previously established circadian pattern of intraocular pressure (IOP).

RESULTS. Under the standard light–dark condition, the hourly average ICP was relatively constant (7.47–10.90 mm Hg). The light–dark ICP difference was −0.11 ± 1.45 mm Hg (mean ± SD, P = 0.823), whereas the locomotor activity was significantly higher during the dark period (P < 0.01). Under the acute constant dark condition, the subjective light–dark ICP difference remained small. Compared with a significant light–dark IOP elevation of 5.15 ± 4.47 mm Hg (P = 0.037) in rats housed under the same laboratory conditions, the light–dark ICP variation was considered minimal. The translaminar pressure difference was projected to be 5.26 mm Hg higher in the dark period because of the change in IOP.

CONCLUSIONS. There is no significant circadian ICP variation in Sprague-Dawley rats. The translaminar pressure difference is projected to be higher during the dark period because of the change in IOP.

A major risk factor for glaucoma is elevated intraocular pressure (IOP), which causes progressive optic nerve neuropathy and diminishes the visual field. A critical section of the optic nerve for glaucoma pathogenesis is at the lamina cribrosa. This area is subjected to the influence of two pressures: IOP from the globe and intracranial pressure (ICP) transmitted through the cerebrospinal fluid (CSF) in the retrolaminar subarachnoid space. It has long been speculated that ICP interacts with IOP and plays a role in the pathogenesis of glaucoma.

In normal physiological conditions, the optic disc can move back and forth minute under a low translaminar pressure difference (IOP minus ICP). In glaucomatous eyes with elevated IOP, an abnormally high translaminar pressure difference may press the optic disc backward, leading to ischemia, cytoskeletal disruption, and axonal transport block at the lamina cribrosa. Recent analyses of clinical CSF pressures, as surrogates for ICP, in glaucoma patients who underwent lumbar punctures support the idea that a lower ICP or a higher translaminar pressure difference is an even more important risk factor for glaucoma.

Physiological IOP and ICP are dynamic, and so is the translaminar pressure difference. Whereas the circadian (24-hour) variation in IOP is well known, a circadian pattern of ICP or translaminar pressure difference is less clear, with only a few reports in the literature. Some of those studies, performed in conscious and partially restrained Sprague-Dawley rats, suggested a nocturnal elevation in ICP. A light–dark ICP elevation of 3.9 mm Hg (5.3 cm H2O) was reported. When IOP was monitored by telemetry in conscious, freely moving Sprague-Dawley rats, the light–dark IOP elevation was approximately 5.3 mm Hg.

Although the rat optic nerve head has a less developed lamina cribrosa than that of a primate, it has similar structural proteins. Considering the magnitudes of light–dark ICP and IOP changes in rats, one may speculate that the circadian variation of translaminar pressure difference in this species is rather small. How significantly the endogenous translaminar pressure difference varies would be important in the understanding of orbital pressure relationships and tissue physiology at the lamina cribrosa. In the present study, we used telemetry to investigate the circadian change in ICP in conscious, freely moving Sprague-Dawley rats and estimated the circadian change in translaminar pressure difference.

METHODS

The study adhered to the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research and was approved by the Institutional Animal Care and Use Committee. Male Sprague-Dawley rats 8 to 10 weeks of age (250–300 g) were obtained from the Charles River Laboratories (Hollister, CA). Before the experiment, the rats were entrained for at least 2 weeks to a standard light–dark cycle with overhead fluorescent lights (200–300 lux) turned on at 6 AM and off at 6 PM. Food and water were freely available, and the housing temperature was maintained at 25°C.

A battery-powered telemetric pressure transmitter (model PA-C20; Data Sciences International, St. Paul, MN) was implanted subcutaneously in the dorsal midscapular region, with the light–dark entrained rat under general anesthesia (intramuscular 100 mg/kg ketamine and 10 mg/kg xylazine). The catheter to the pressure transmitter was connected to a brain infusion cannula (Alzet, Cupertino, CA). A mid-sagittal incision was made on the scalp to visualize the landmarks of bregma and lambda. One hole was drilled to accommodate the brain.
infusion cannula, with its tip inserted into the lateral ventricle at 0.96 mm caudal to the bregma, 2.0 mm on one side of the sagittal suture, and 3.5 mm below the dura, with a stereotoxic headholder (model 900; David Kopf Instruments, Tujunga, CA). Flange of the brain infusion cannula was tightly glued on the parietal bone with a tissue adhesive (Vetbond; 3M, St. Paul, MN). A hydrostatic continuity between the lateral ventricle and the retrolaminar subarachnoid space is expected. It has been verified that when the opening of the pressure recording catheter is set at the eyeball, having a height close to the lateral ventricle, the systemic hydrostatic influence on the pressure transmitter is not significant.

After surgery, the rat was allowed to recover in an individual cage in the standard light–dark condition. Collection of data began 24 to 48 hours after surgery, to allow time for physiological ICP to regain and stabilize. In nine successful preparations, data collection continued for 2 to 10 days until the pressure-recording system failed or was terminated. A longer data collection period was avoided because the subcutaneous packet housing the pressure transmitter may break spontaneously from two postoperative weeks onward. Telemetric data of ICP (in mm Hg) and locomotor activity (in arbitrary units of counts per minute) at 120 Hz were received. Two-minute averages of ICP and locomotor activity were archived continuously every 5 minutes. The pressure range (peak minus trough) in the 2-minute time interval was recorded. To examine the circadian patterns of ICP and locomotor activity, we calculated averages at each of the 24 hourly time points by using all the data collected to account for the variations among different days.

The light–dark differences were calculated from the means for the 12-hour light period (6 AM–6 PM) and the 12-hour dark period. The paired \( t \)-test was used to compare the means of ICP, pressure range, and locomotor activity. \( P < 0.05 \) was considered statistically significant.

Data were also collected under an acute 24-hour constant dark condition from six of the nine rats in the ICP monitoring group, after a consistent daily pattern of locomotor activity had been well established. In the other three rats, the recording system failed before the experiment could be performed under the acute constant dark condition. The acute constant dark condition was achieved by replacing one pressure transmitter within 33 cm of each other, and this limitation prevented simultaneous recording from two postoperative weeks onward.

RESULTS

Figure 1 presents the 24-hour change patterns in ICP and locomotor activity in the nine light-dark–entrained Sprague-Dawley rats in the standard light–dark condition. The hourly average ICP was relatively constant throughout the 24 hours, in a range of 7.47 to 10.90 mm Hg, whereas locomotor activity showed more variation. Mean ICP, pressure range, and locomotor activity during the light and the dark periods, as well as the light–dark differences are summarized in Table 1. As expected, locomotor activity was higher during the dark period than during the light period in these nocturnally active rats. The ICP was \( 9.33 \pm 5.03 \) mm Hg (mean ± SD) during the light period and \( 9.22 \pm 5.03 \) mm Hg during the dark period. The light–dark ICP difference was \( -0.11 \pm 1.45 \) mm Hg (\( P = 0.823 \), paired \( t \)-test). Under the acute constant dark condition, the ICP difference between the light and dark periods (8.56 ± 5.61 mm Hg, \( n = 6 \)) and the subjective dark period (8.24 ± 5.88 mm Hg) remained small and statistically nonsignificant (\( -0.32 \pm 1.56 \) mm Hg, \( P = 0.636 \)), indicating that the absent light–dark ICP change was independent of the environmental light condition.

The light–dark ICP difference (95% CI, 1.00 to –1.23 mm Hg) was very small compared with a significant light–dark IOP elevation of 5.15 ± 4.47 mm Hg (\( P = 0.037 \)) in the six rats previously studied under the same standard laboratory conditions and subjected to IOP monitoring. Student’s \( t \)-test showed a significant difference between the light–dark variations in ICP and IOP (\( P < 0.01 \), Table 1). When mean pressure ranges and locomotor activities were compared between the rat ICP group and the IOP group, no statistically significant difference was found.

The transmalar pressure difference (IOP minus ICP) was calculated based on data obtained from the two rat groups. The hourly changes in the transmalar pressure difference for 24 hours are presented in Figure 2. The hourly average transmalar pressure differences varied from 9.48 (10–11 AM) to 20.80 (6–7 PM) mm Hg. Larger transmalar pressure differences were recorded during the early dark period. Variation in the 24-hour transmalar pressure difference was mainly due to the change in IOP, not to the change in ICP. The projected change in the transmalar pressure difference between the light period (mean, 11.84 mm Hg) and the dark period (mean, 17.10 mm Hg) was 5.26 mm Hg.

Cosine-fits of ICP, IOP, and related pressure ranges and locomotor activities were performed on the data from individual rats. Phase timings for the simulated variation of 24-hour rhythm were determined. The Rayleigh test indicated no synchronized phase timings for the 24-hour ICP data collected from the nine rats, although there were synchronized 24-hour rhythms for the pressure range (\( P < 0.001 \)) and locomotor activity (\( P < 0.01 \)) in the same group of rats. The phase timings for the 24-hour ICP data in the six rats housed under the acute 24-hour constant dark condition remained unsynchronized, verifying that there was no 24-hour ICP rhythm. In the six rats used for the IOP monitoring, the Rayleigh test detected syn-
chronized group phase timings for the 24-hour IOP, pressure range, and locomotor activity ($P/\text{H11021} 0.001$). Between the rat ICP and IOP monitoring groups, the difference in the phase timing of pressure range and locomotor activity was not statistically significant (Mann–Whitney rank-sum test, data not shown).

**DISCUSSION**

Results showed a relatively constant ICP in the light-dark–entrained, conscious, freely moving Sprague-Dawley rats. There was no significant difference in the ICP means between the light and dark periods. Mathematical simulation verified the absence of a 24-hour rhythm of the hourly ICP averages. In contrast, the locomotor activity and pressure range in the same rats showed higher means during the dark period than during the light period. Mathematical simulations also indicated 24-hour rhythms for locomotive activity and pressure range. The absence of a robust light–dark ICP difference was unrelated to the environmental light condition. The ICP difference remained very small and statistically nonsignificant in the acute 24-hour constant-dark condition, immediately after the switch from the standard light–dark condition. These observations support the concept that there is no circadian ICP rhythm in conscious, freely moving rats.

A variation in locomotor activity in light–dark conditions is expected in nocturnally active rats, including the Sprague-Dawley strain.21 Although our results agree with an observation that indicated no daily ICP pattern in conscious, freely moving rats.

Data are from rats entrained for the light period, 6 AM to 6 PM, and the dark period, 6 PM to 6 AM and are expressed as the mean ± SD.

$^* P < 0.01$; Student’s $t$-test against the ICP value for the same time period or category.
moving Sprague-Dawley rats in a stroke model, 22 a few other observations in conscious, but partially restrained Sprague-Dawley rats showed a substantial light–dark ICP elevation. 10–12 It is possible that limiting locomotor activity with experimental attachments would have modified the endogenous circadian ICP pattern. Another study parameter, the pressure range, is the pressure peak minus trough within each time interval of data collection. As second-to-second ICP pulse ranges are synchronous with heartbeats, 23 the ICP pressure ranges within the 2-minute interval of data collection should be affected by the locomotor activities and postures in the present study. Spontaneous locomotor activities and postural changes increased during the dark period in conscious, freely moving rats, as did the pressure ranges. These spontaneous effects would be equally applied to the ICP peak and trough, and the net effect on the mean ICP was small. Therefore, an increase in pressure range during the dark period did not lead to an increase in the mean ICP (Table 1).

Using telemetry to monitor IOP in another group of six Sprague-Dawley rats under the same laboratory conditions, we found that IOP varied significantly for 24 hours, and the light–dark IOP difference was significant, as has been reported. 14,24 In both rat IOP and ICP groups, there were 24-hour rhythms for locomotor activity and pressure range by mathematical simulation. However, there was no intergroup difference in the phase timings for these two study parameters. The only difference between the two rat groups was the absence of a 24-hour rhythm in ICP versus the presence of a 24-hour rhythm in IOP.

The projected circadian variation in transmamellar pressure difference is significant because of the change in IOP. The transmamellar pressure difference between the light and dark periods was approximately 5 mm Hg, and the largest hourly difference was approximately 10 mm Hg, which provides little support for the hypothesis that endogenous variation in the transmamellar pressure difference is insignificant in rats. Since no endogenous ICP increase can counterbalance the impact of a higher nocturnal IOP on the lamina cribrosa, this tissue is exposed to an endogenous fluctuation in transmamellar pressure difference up to 10 mm Hg. This new information adds to our knowledge of how timing in IOP elevation may affect the lamina cribrosa in rats. An IOP increase of several millimeters of mercury during the light period is probably tolerable by this tissue, as the change is within the physiological range. 25 However, a threshold for disturbance in the transmamellar pressure difference is more easily overrun during the dark period. An exogenously induced IOP increase or ICP decrease can cause a pressure imbalance. Time-dependent cellular responses at the lamina cribrosa due to the circadian change in transmamellar pressure difference will be interesting to explore in rat models with chronically elevated IOP. 26 Because of the limited similarities in the structure of the lamina cribrosa between rats and primates, biomechanical studies on the nonhuman primate optic nerve head subjected to time-dependent changes in IOP, ICP, and transmamellar pressure difference are warranted for more insight into the pathogenesis of glaucoma. 16

ICP can be modulated by changes in CSF production, resistance to CSF outflow, dural sinus pressure, and intracranial compliance. 27 Although circadian variation in ICP is insignificant, endogenous variations in the ICP regulatory factors may be significant. It has been demonstrated that human CSF pro-
duction exhibits a circadian pattern. The CSF production in the middle of the night is 2 to 3.5 times that in the late afternoon. However, this significant change in CSF production may not lead to a parallel day–night ICP pattern, because of the feedback regulations for ICP homeostasis. Keeping in mind that continuous ICP monitoring with implanted pressure sensors in humans can be justified only in severely neurologically affected patients, a prior study indicated that there was no detectable 24-hour ICP rhythm in head-injury patients. Like the circadian ICP variation in rats, a circadian ICP rhythm is probably absent in healthy, bed-rested humans.

Additional caution should be used when one considers the results obtained in the present study with human 24-hour ICP pattern. Clinical ICP information is usually obtained from the opening CSF pressure during lumbar puncture in the lateral decubitus body position.6–8 It is well known that local CSF pressure in humans is height-dependent.31,32 Upper body postures vary significantly in daily life: vertical while sitting and standing, near horizontal during sleep, and variable due to spontaneous physical activities. Different postures influence ICP and local CSF pressure in the subarachnoid space bathing the optic nerve. The hydrostatic continuity between cerebral ventricles and the retrostellar subarachnoid space may also be altered.33 An accurate transmamillary pressure difference should be calculated on the basis of IOP and the retrostellar CSF pressure in the same body position. One snapshot of CSF pressure from the lumbar puncture has its limitations in estimating the circadian pattern in human transmamillary pressure difference. Circadian patterns in human ICP and transmamillary pressure difference in humans in real life are currently unknown.

References


