Complete absence of evening melatonin increase in tetraplegics

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ABSTRACT Individuals with a spinal cord injury (SCI), especially with tetraplegia, experience poor sleep quality, and this may be related to impaired control of circadian rhythmicity. Here, we examined the evening onset of melatonin secretion, an important hormone for the initiation of sleep, in people with a complete cervical (tetraplegia) and thoracic (paraplegia) SCI, and age- and sex-matched able-bodied control participants. Multiple samples of salivary melatonin were obtained during the evening hours and analyzed by ELISA methods in 10 control participants, 9 individuals with paraplegia, and 6 individuals with tetraplegia. Sleep quality was assessed using questionnaires. Interactive effects of group and time were found for melatonin levels (P=0.022). In the control and paraplegia groups, the mean melatonin level increased significantly from 2.59 ± 1.04 and 4.28 ± 3.28 pg/ml at 7 PM to 10.62 ± 4.59 and 13.10 ± 7.39 pg/ml at 11 PM, respectively (P<0.001). In the tetraplegia group, melatonin level was 5.25 ± 3.72 at 7 PM but only 2.41 ± 1.25 pg/ml at 11 PM (P>0.05). Decreased sleep quality was more prevalent in individuals with tetraplegia (83%) and paraplegia (75%) compared with controls (20%; P=0.02). Unlike in the control and paraplegia groups, the evening increase in melatonin concentration was completely absent in the tetraplegia group. This provides biological insight into sleep regulation in humans and provides better understanding of the poor sleep quality in people with tetraplegia.—Verheggen, R. J., Jones, H., Nyakayiru, J., Thompson, A., Groothuis, J. T., Atkinson, G., Hopman, M. T., Thijssen, D. H. Complete absence of evening melatonin increase in tetraplegics. FASEB J. 26, 000–000 (2012). www.fasebj.org

Key Words: sleep quality · paraplegia · pineal gland

Individuals with a spinal cord injury (SCI) demonstrate a high prevalence of sleep disturbances, especially in cervical SCI (15-40%), which markedly affects the quality of life (1–3). The underlying mechanism for these sleep disturbances is currently unknown. A potential explanation relates to melatonin, which is a secretory product of the pineal gland and plays a central role in the regulation of sleep (4–7). Secretion of melatonin demonstrates an endogenous circadian rhythmicity, which is influenced by the light-dark cycle. Melatonin levels typically begin to increase 2-3 h before sleep (5, 8). Previous studies found that an altered melatonin release during evening hours is related to sleep disturbances (3–5). Secretion of melatonin is regulated via a neural pathway from the suprachiasmatic nuclei (SCN) to the pineal gland, which passes through the cervical spinal cord (5, 6). Since this anatomical connection might be compromised in cervical SCI, individuals with tetraplegia may have an altered release of melatonin (3, 9), which may contribute to sleep disorders.

Although an altered melatonin level in individuals with tetraplegia has been hypothesized before (9–11), these preliminary case and pilot studies assessed a limited number of cases, measured melatonin using urine analysis and at limited time points, did not measure the evening rise or rhythms in melatonin, and did not measure other outcomes related to melatonin (e.g., sleep quality). Notably, previous researchers only examined daytime levels of melatonin (and not the characteristic and clinically relevant evening rise before nocturnal sleep). No previous study performed a large, comprehensive study of the evening rise in melatonin in individuals with an SCI. Therefore, we assessed melatonin release in individuals with a cervical or a thoracic SCI and age- and sex-matched able-bodied controls. We hypothesize that individuals with tetraple-
gia demonstrate an impaired evening onset of melatonin, which contributes to an impaired quality of sleep.

MATERIALS AND METHODS

Participants

We recruited 15 male individuals with a motor and sensory complete SCI [American Spinal Injury Association Impairment Scale (AIS); ref. 12] and 10 age- and gender-matched able-bodied controls. Individuals were classified by SCI as those with paraplegia, with a thoracic spinal cord lesion between T4 and T12 (n=9), and tetraplegia, with a cervical spinal cord lesion between C4 and C7 (n=6). The SCI was of traumatic origin and present for at least 5 yr. All individuals were otherwise healthy and reported no sleep disorders (e.g., sleep apneoa). Individuals who used medication to aid sleep, noninflammatory steroidal drugs, or antihistaminics were excluded. Before testing, all individuals provided informed consent to participate and the study was approved by the Radboud University Nijmegen Medical Centre Ethics Committee.

Experimental design

In this cross-sectional study, melatonin levels were assessed in saliva, collected under dim light conditions in the evening hours (7 PM and then every 30 min from 8 to 11 PM). Physical activity level (heart rate recorder, diary, and activity monitor) was measured continuously during a 24-h period, starting at 9 AM the day of melatonin assessment and ending at 9 AM the following day. Questionnaires were adopted to assess sleep quality [Pittsburgh Sleep Quality Index (PSQI)] and excessive daytime sleepiness [Epworth Sleepiness Scale (ESS)]. Participants were instructed to perform their normal daily activities but to refrain from structured exercise and/or physically demanding activities.

Measurements

Procedure

Before the experiment, all participants received written information and completed the sleep questionnaires. Before data recording commenced, detailed instructions of the procedures and equipment was provided both verbally and in writing. Data recording started at 9:00 AM and continued until 9:30 AM the following day. For practical reasons, instruction and provision of the equipment to the individuals with an SCI were performed at their homes. All participants were instructed to engage in their normal daily activities. In addition, participants were instructed to stay indoors from 6 PM onwards under dim light conditions to ensure a constant and stable environmental condition within and between participants, required for adequate assessment of melatonin in saliva.

Melatonin

Saliva samples were collected at 7 PM and then every 30 min between 8 and 11 PM in 70-ml containers (HD-PE; Sarstedt, Rommelsdorf, Germany). Immediately after the saliva was collected, the container was stored at -20 °C. Saliva sampling took place in accordance with recent guidelines (6, 13). Briefly, 1 h before and during the collection period, participants remained under dim light conditions in their homes, avoiding all physical activities. Curtains were kept closed, and watching television and using a computer were permitted. The consumption of bananas, alcoholic beverages, chocolate, coffee, and tea was prohibited in the 24-h period before collection and during the experiment, as this may interfere with analysis of melatonin. For the same reason, brushing of teeth, drinking of substances other than water, and eating was not allowed during the collecting period. At 15 min before each sample, the participants rinsed their mouths with fresh water. Saliva was immediately stored at -20 °C following each sample, and all samples were transported back to the laboratory on dry ice and were stored at -80 °C after each test. Posttest analysis of melatonin was performed using duplicate samples from an ELISA kit (direct saliva melatonin ELISA; Buhlmann, Schonenbuch, Switzerland). All data points from a single participant were analyzed in a single series. The correlation of saliva melatonin levels to other samples (plasma and urine) has been determined as acceptable (13). The dim light melatonin onset (DLMO), the time at which the melatonin secretion commences, was calculated from the melatonin data to assess circadian phase of melatonin rhythm (6, 8). In plasma, the DLMO is defined as the time point at which the increasing melatonin concentration reaches a threshold value of 10 pg/ml (14). Nevertheless, for saliva, in accordance with previous studies, we used a threshold value of 4 pg/ml for salivary melatonin to identify the DLMO (15, 16).

Quality of sleep and sleepiness

Before participation, participants completed the validated and frequently used PSQI (17) and ESS (18) questionnaires to assess quality of sleep and excessive daytime sleepiness, respectively. The PSQI is a self-rated questionnaire that assesses sleep quality and disturbances over a 1-mo period of time, giving way to 7 component scores (based on the scoring of 19 items): subjective sleep quality, sleep latency, duration of sleep, sleep efficiency, disturbances in sleep, use of sleep medication, and daytime dysfunction (17). Based on these individual results, a general score, between 0 and 21, is calculated that indicates the quality of sleep. A score >5 corresponds with impaired sleep quality. The ESS is a self-administered questionnaire that provides an assessment of the general level of daytime sleepiness or sleep propensity. Participants score on a 0-3 scale how likely they would be to doze off during 8 situations during a normal day (18). A total score of 9 or higher corresponds with excessive sleepiness during the day.

Physical activity

Accelerometry An accelerometer was used (SenseWear Pro3; BodyMedia, Pittsburgh, PA, USA) to continuously monitor physical activity levels and to control for excessive changes in physical activity levels within participants. The accelerometer was worn around the right upper arm throughout the 24-h measuring period. Physical activity was expressed in metabolic equivalent (MET) units. Previous studies have demonstrated that this accelerometer is valid and accurate to measure energy expenditure in free-living situations (19–21). In addition, by taking skin heat flux into account, the accelerometer also provides information of sleep duration. A recent study found that accelerometry is a valid tool for sleep duration and efficiency (22). Activity levels were calculated as mean METs during daytime (9 AM to 11 PM), nighttime (11 PM to 7 AM) and evening hours (6 to 11 PM).

Diary For general cross validation of physical activity and sleep, participants kept a diary and reported their physical activity level (heart rate recorder, diary, and activity monitor) was measured continuously during a 24-h period, starting at 9 AM the day of melatonin assessment and ending at 9 AM the following day. Questionnaires were adopted to assess sleep quality [Pittsburgh Sleep Quality Index (PSQI)] and excessive daytime sleepiness [Epworth Sleepiness Scale (ESS)]. Participants were instructed to perform their normal daily activities but to refrain from structured exercise and/or physically demanding activities.
activities throughout the 24-h recording period at 30 min intervals. Participants also reported the times they retired to bed and when they awoke.

**Statistical analysis**

Our primary hypothesis was that individuals with tetraplegia and paraplegia do not show a statistically significant increase in salivary melatonin concentration. Using data published by Burgess and Fogg (8), we estimated that the mean melatonin level for healthy subjects at -1 h before sleep onset is 7 pg/ml and the associated sd is 5 pg/ml. With a total sample size of 25 subjects, distributed across 10 control participants, 9 individuals with paraplegia, and 6 individuals with tetraplegia, it was estimated that the statistical power to detect a difference of 7 ± 5 pg/ml between groups is 82%

All data were analyzed using the Statistical Package for the Social Sciences (SPSS, version 16; SPSS Inc., Chicago, IL, USA). Data are presented as means ± sd unless stated otherwise. Melatonin data were analyzed using a group: (control vs. paraplegia vs. tetraplegia) × time (7:00-8:00-8:30-9:00-9:30-10:00-10:30-11:00 PM) linear mixed model analysis. According to recent guidelines, we adopted the least significant difference approach to multiple comparisons (23, 24). The level of statistical significance was set at α = 0.05.

**RESULTS**

There were no significant differences in physical characteristics [age, body mass, height, or body mass index (BMI)] among the 3 groups and no difference in duration of the SCI between the paraplegia and tetraplegia groups (Table 1). During the experiment, control participants reported an earlier time of waking and shorter sleeping period compared with participants with paraplegia or tetraplegia (Table 1). The time to wake of individuals with tetraplegia during a normal day (0837±0101) was significantly later compared with both controls (0651±0101) and individuals with paraplegia (0748±0110; P=0.014).

**Melatonin**

Due to insufficient amount of saliva, we excluded 2 time points (8:30 and 9:00 PM) in 1 individual with tetraplegia, 1 time point (8:00 PM) in 1 individual with paraplegia, and 1 time point (10:30 PM) in 1 control individual. A significant group vs. time interaction was evident in melatonin levels (P=0.022). Melatonin levels generally increased (P=0.001) during the evening in both the control and paraplegia groups, while melatonin levels in the tetraplegia group remained relatively constant throughout the evening. Melatonin levels in control participants and participants with paraplegia were significantly higher than in participants with tetraplegia at the 10:30 and 11:00 PM time points (P=0.015 and P=0.003, respectively). Post hoc analysis revealed that a significant and comparable increase in melatonin levels was observed in control participants (from 2.59±1.04 to 10.62±4.59 pg/ml) and participants with paraplegia (from 4.28±3.28 to 13.10±7.39 pg/ml), while participants with tetraplegia demonstrated no change in melatonin levels across the same time period, starting with melatonin levels of 5.25 ± 3.72 at 7:00 PM and ending with 2.41 ± 1.25 pg/ml at 11:00 PM (Fig. 1).

Interpolation of a linear regression line of the melatonin data to identify the DLMO did not reveal any significant differences (P=0.34) between control participants (2002±0050) and participants with paraplegia (1949±104). It was not possible to calculate the DLMO.

**TABLE 1. Subject characteristics in control, paraplegia, and tetraplegia groups**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Paraplegia</th>
<th>Tetraplegia</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>44 ± 11</td>
<td>49 ± 9</td>
<td>43 ± 11</td>
<td>0.47</td>
</tr>
<tr>
<td>Body mass/weight (kg)</td>
<td>86 ± 16</td>
<td>76 ± 13</td>
<td>79 ± 14</td>
<td>0.52</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>183 ± 9</td>
<td>181 ± 7</td>
<td>182 ± 4</td>
<td>0.79</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.5 ± 3.3</td>
<td>23.2 ± 3.6</td>
<td>24.2 ± 3.6</td>
<td>0.34</td>
</tr>
<tr>
<td>Duration of injury (yr)</td>
<td>22 ± 9</td>
<td>23 ± 15</td>
<td>0.87</td>
<td></td>
</tr>
<tr>
<td>Sleep during normal day (self-reported)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to sleep (hh:mm)</td>
<td>23:21 ± 00:41</td>
<td>23:51 ± 01:26</td>
<td>23:32 ± 01:09</td>
<td>0.62</td>
</tr>
<tr>
<td>Lying awake (hh:mm)</td>
<td>00:16 ± 00:11</td>
<td>00:31 ± 00:33</td>
<td>00:20 ± 00:20</td>
<td>0.39</td>
</tr>
<tr>
<td>Time to wake (hh:mm)</td>
<td>06:51 ± 01:01</td>
<td>07:48 ± 01:10</td>
<td>08:37 ± 01:01</td>
<td>0.014*</td>
</tr>
<tr>
<td>Total sleep (hh:mm)</td>
<td>07:01 ± 00:47</td>
<td>06:53 ± 01:08</td>
<td>07:20 ± 01:04</td>
<td>0.69</td>
</tr>
<tr>
<td>Sleep during experiment (self-reported)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to sleep (hh:mm)</td>
<td>23:29 ± 00:27</td>
<td>23:24 ± 00:33</td>
<td>23:33 ± 00:26</td>
<td>0.85</td>
</tr>
<tr>
<td>Time to wake (hh:mm)</td>
<td>06:59 ± 00:16</td>
<td>07:48 ± 00:38</td>
<td>08:00 ± 00:45</td>
<td>0.003*</td>
</tr>
<tr>
<td>Total sleep (hh:mm)</td>
<td>07:30 ± 00:22</td>
<td>08:25 ± 00:40</td>
<td>08:27 ± 01:02</td>
<td>0.01*</td>
</tr>
<tr>
<td>Sleep during experiment (activity monitor)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to sleep (hh:mm)</td>
<td>23:55 ± 00:45</td>
<td>24:03 ± 00:42</td>
<td>23:46 ± 01:57</td>
<td>0.27</td>
</tr>
<tr>
<td>Lying awake (hh:mm)</td>
<td>00:06 ± 00:05</td>
<td>00:04 ± 00:04</td>
<td>00:08 ± 00:06</td>
<td>0.37</td>
</tr>
<tr>
<td>Time to wake (hh:mm)</td>
<td>07:12 ± 00:42</td>
<td>07:32 ± 00:26</td>
<td>07:58 ± 00:59</td>
<td>0.13</td>
</tr>
<tr>
<td>Total sleep (hh:mm)</td>
<td>06:40 ± 00:48</td>
<td>06:14 ± 01:13</td>
<td>07:39 ± 03:5</td>
<td>0.56</td>
</tr>
<tr>
<td>Total lying (hh:mm)</td>
<td>07:32 ± 00:35</td>
<td>07:33 ± 00:45</td>
<td>08:42 ± 2:26</td>
<td>0.20</td>
</tr>
</tbody>
</table>

Data are presented as means ± sd; n = 10 (control group), n = 9 (paraplegia group), and n = 6 (tetraplegia group). P value represents a 1-way ANOVA among 3 groups, except for the comparison of duration of injury (unpaired t test). *P <0.05.
in participants with tetraplegia since they did not reach the DLMO threshold level of 4 pg/ml.

**Sleep questionnaires**

Individuals with tetraplegia, but also those with paraplegia, tended to report a poorer sleep quality on the PSQI compared with control participants \((P = 0.06; \text{Table 2})\). The prevalence of poor sleep was significantly higher in individuals with an SCI compared with controls \((P = 0.02; \text{Table 2})\). Individuals with tetraplegia reported the highest mean scores and prevalences for excessive sleepiness on the ESS, although this did not reach statistical significance \((\text{Table 2})\).

**Physical activity**

Physical activity levels among control, paraplegia, and tetraplegia groups did not differ significantly different during the day \((1.4 \pm 0.2, 1.5 \pm 0.4, 1.4 \pm 0.5 \text{ METs, respectively}; 1\text{-way ANOVA}, P = 0.63)\); evening \((1.2 \pm 0.2, 1.3 \pm 0.2 \text{ and } 1.3 \pm 0.5 \text{ METs, respectively}; 1\text{-way ANOVA}, P = 0.55)\); and night \((0.9 \pm 0.1, 1.0 \pm 0.1 \text{ and } 1.0 \pm 0.1 \text{ METs, respectively}; 1\text{-way ANOVA}, P = 0.73)\).

**DISCUSSION**

The aim of this study was to assess the release of melatonin in individuals with an SCI (both paraplegia and tetraplegia) compared with age- and gender-matched able-bodied control participants. First, we observed that individuals with paraplegia demonstrate a similar increase in melatonin during the evening hours as controls. Second, an important observation in our study was that individuals with tetraplegia demonstrate no change in melatonin levels during the evening hours. In addition, our study confirmed the higher prevalence of poor sleep quality in individuals with an SCI, especially tetraplegia. Taken together, the results of this study demonstrate that individuals with tetraplegia elicit no change in melatonin during the evening, while a normal evening increase in melatonin is evident in individuals with paraplegia. This finding may form the basis for the frequently reported poor sleep quality in people with tetraplegia.

An important observation in our study is that individuals with tetraplegia, in contrast to controls and individuals with paraplegia, demonstrated no increase in melatonin in the evening. Our findings are in line with two previous case studies that reported an absence of melatonin rhythm in individuals with tetraplegia across a 24-h period \((9, 10)\). However, we have specifically focused on the increase in melatonin during the evening hours, where it is believed to contribute to the initiation of sleep. An evening increase in melatonin is thought to be an integral component of the sleep onset period, since melatonin mediates soporific and hypothermic effects \((4, 6, 25–27)\). The absence of an increase in melatonin in individuals with tetraplegia corresponds well with impaired core body temperature rhythmicity, which was recently shown by our group \((28)\). In the present study, we also observed a high prevalence of poor sleep quality in individuals with tetraplegia and excessive daytime sleepiness compared with control participants. Nevertheless, the sleep characteristics assessed with the use of accelerometry, albeit only measured during one nocturnal sleep period, did not reflect this difference between the groups. This could suggest that individuals with tetraplegia perceive more disturbed sleep due to a lack of soporific effects that are usually associated with melatonin release. Collectively, these data demonstrate a lack of melatonin release during the evening hours in individuals with tetraplegia, which likely plays a key role in the poor sleep quality evident in this group.

The pathophysiological mechanism that underlies our finding of the absent melatonin rhythm in individ-

**Figure 1.** Melatonin levels \((\text{mean} \pm \text{se})\) in saliva during evening hours, between 7 PM \((19:00)\) and 11 PM \((23:00)\), in control \((\text{C, solid circle, } n =10)\), paraplegia \((\text{P, solid square, } n =9)\), and tetraplegia \((\text{T, open square, } n =6)\) groups. \(*P < 0.05; \text{post hoc analysis: } T < P = C\); \(^* P < 0.05 \text{ vs. baseline (19:00)\).}"

**TABLE 2.** Sleep characteristics in control, paraplegia, and tetraplegia groups

<table>
<thead>
<tr>
<th>Sleep questionnaire</th>
<th>Control</th>
<th>Paraplegia</th>
<th>Tetraplegia</th>
<th>(P)</th>
<th>\textit{Post hoc}</th>
</tr>
</thead>
<tbody>
<tr>
<td>PSQI (mean score)</td>
<td>3.7 (\pm) 22</td>
<td>6.8 (\pm) 2.8</td>
<td>7.0 (\pm) 4.6</td>
<td>0.06</td>
<td>\textit{C} &lt; (P = T)</td>
</tr>
<tr>
<td>PSQI (prevalence poor sleep)</td>
<td>20%</td>
<td>75%</td>
<td>83%</td>
<td>0.02*</td>
<td></td>
</tr>
<tr>
<td>ESS (mean score)</td>
<td>6.2 (\pm) 3.3</td>
<td>6.8 (\pm) 3.4</td>
<td>9.8 (\pm) 3.4</td>
<td>0.12</td>
<td></td>
</tr>
<tr>
<td>ESS (prevalence sleepiness)</td>
<td>20%</td>
<td>22%</td>
<td>50%</td>
<td>0.21</td>
<td></td>
</tr>
</tbody>
</table>

Data are presented as means \(\pm\) sd; \(n = 10\) \([\text{control (C) group}]\), \(n = 9\) \([\text{paraplegia (P) group}]\), and \(n = 6\) \([\text{tetraplegia (T) group}]\). PSQI: 0-21, cutoff value 5; ESS: 0-24, cutoff value 9. \(P\) value represents a 1-way ANOVA for continuous variables and a \(\chi^2\) test for data representing prevalence. \(*P < 0.05\).
uals with tetraplegia most likely relates to the neural pathways involved in melatonin secretion. Melatonin is secreted in the pineal gland under the influence of an efferent neural pathway, originating from the SCN in the hypothalamus and passing through the cervical spinal cord and the superior cervical ganglion (5, 6, 8, 27), which is innervated by nerves originating from the ciliospinal center located at the spinal cord levels C8–T2. Neurologically motor and sensory complete SCI (AIS; ref. 12) below the spinal cord level T4, all demonstrated a preserved rhythmicity of melatonin, as was expected based on the level of the spinal cord lesion and in line with previous studies (9–11). The observation of a preserved DLMO corresponds with our previous observation of normal core body temperature rhythmicity in this group (28). Despite the preserved DLMO in individuals with paraplegia, a higher prevalence of poor sleep quality was observed, which is in agreement with previous studies (1–3). Therefore, it is unlikely that the poor sleep quality in individuals with paraplegia is related to melatonin, since this group demonstrated a preserved melatonin onset.

Clinical relevance
A logical clinical extension of our findings is the supplementation of patients with tetraplegia, but also paraplegia, with melatonin. This intervention may restore variables involved in the physiological circadian variation, contributing to normal day-night rhythmicity. Future studies, adopting a randomized controlled trial, should further examine this potential. It is also important to note that hypersensitivity of melatonin-receptors should further examine this potential. It is also important to note that hypersensitivity of melatonin-receptors in individuals with tetraplegia due to the lower levels of melatonin in this group may be a possibility. Thus supplementation of melatonin may result in an exaggerated response of these receptors.

Limitations
Due to the home-based setting of our study, some external variables could not be controlled. However, efforts were made to minimize potential influencing factors through written and oral information, and all measurements were performed within 3 mo to minimize the effect of daytime length and ambient temperature. Moreover, this study represents data collected in a free-living situation in which sleep characteristics are not influenced by a laboratory assessment. This also raises the question of whether the poor sleep quality in individuals with tetraplegia can be fully related to the lack of melatonin release during evening hours. Another consequence of the home-based assessment is that we were restricted to questionnaires to examine sleep quality, rather than electroencephalography or polysomnography. These latter techniques are highly valuable for assessment of sleep efficiency and sleeping patterns, while questionnaires provide important and valid information about sleep quality (32, 33).

In summary, individuals with a complete cervical spinal cord lesion demonstrate no increase in melatonin levels during the evening hours, while such a response was present in controls and individuals with a thoracic spinal cord lesion. This altered circadian rhythm of melatonin in individuals with tetraplegia may explain the baseline melatonin levels in individuals with tetraplegia as demonstrated in our study.

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In summary, individuals with a complete cervical spinal cord lesion demonstrate no increase in melatonin levels during the evening hours, while such a response was present in controls and individuals with a thoracic spinal cord lesion. This altered circadian rhythm of melatonin in individuals with tetraplegia may
potentially contribute to the high prevalence of poor sleep quality. Based on our results, we recommend future studies to examine the potential effects of exogenous melatonin as a potentially effective strategy to improve sleep quality in patients with cervical SCI.

This study was financially supported by Het Dwarslaesie Fonds (Dutch Spinal Cord Injury Foundation). D.H.J.T. was financially supported by the Netherlands Heart Foundation (2009T064). Author contributions were as follows: D.H.J.T., M.T.E.H., J.T.G., and H.J. designed the study; R.J.H.M.V. and J.N. performed the data collection; R.J.H.M.V., J.N., G.A., and A.T. performed the data (biochemical) analysis and statistical analysis; R.J.H.M.V., J.N., D.H.J.T., and H.J. drafted the manuscript; and all authors have critically revised the manuscript.

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