Medullary Respiratory Neural Activity During Hypoxia in NREM and REM Sleep in the Cat

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Lovering, Andrew T., Jimmy J. Fraigne, Witali L. Dunin-Barkowski, Edward H. Vidruk, and John M. Orem. Medullary respiratory neural activity during hypoxia in NREM and REM sleep in the cat. J Neurophysiol 95: 803–810, 2006. First published September 28, 2005; doi:10.1152/jn.00615.2005. Intact unanesthetized cats hyperventilate in response to hypocapnic hypoxia in both wakefulness and sleep. This hyperventilation is caused by increases in diaphragmatic activity during inspiration and expiration. In this study, we recorded 120 medullary respiratory neurons during sleep in hypoxia. Our goal was to understand how these neurons change their activity to increase breathing efforts and frequency in response to hypoxia. We found that the response of medullary respiratory neurons to hypoxia was variable. While the activity of a small majority of inspiratory (58%) and expiratory (56%) neurons was increased in response to hypoxia, the activity of a small majority of preinspiratory (57%) neurons was decreased. Cells that were more active in hypoxia had discharge rates that averaged 183% (inspiratory decrementing), 154% (inspiratory augmenting), 155% (inspiratory), 230% (expiratory decrementing), 191% (expiratory augmenting), and 136% (expiratory) of the rates in normoxia. The response to hypoxia was similar in non-rapid-eye-movement (NREM) and REM sleep. Additionally, changes in the profile of activity were observed in all cell types examined. These changes included advanced, prolonged, and abbreviated patterns of activity in response to hypoxia; for example, some inspiratory neurons prolonged their discharge into expiration during the postinspiratory period in hypoxia but not in normoxia. Although changes in activity of the inspiratory neurons could account for the increased breathing efforts and activity of the diaphragm observed during hypoxia, the mechanisms responsible for the change in respiratory rate were not revealed by our data.

INTRODUCTION

Hypoxia is common in disease and in health at altitude. Some studies have found that hypoxia stimulates and then depresses breathing in anesthetized and chemodenervated preparations, and the responses of medullary respiratory neurons under these conditions of respiratory depression and central apnea have been described (England et al. 1995; Richter et al. 1991). Other studies, including our study of the intact unanesthetized cat in both wakefulness and sleep (Lovering et al. 2003a), have described a sustained hyperventilation in response to hypoxia without a secondary depression. In our study, the hyperventilation to hypoxia was the result of an increased frequency and, more importantly, an increased depth of breathing. Frequency increased in NREM sleep in hypoxia primarily because of a reduction in the duration of inspiration. In REM sleep, the frequency of breathing was not different in normoxia and hypoxia. Tidal volume increased in hypoxia in all states because of increased airflow rates associated with changes in the profiles of inspiratory and expiratory airflow. Whereas inspiratory airflow rates are typically greatest at the end of inspiration in normoxia, they tend to be greatest in early inspiration in hypoxia. Similarly, expiratory airflow rates are normally greatest early in the phase, but in hypoxia, they are constant throughout the phase and are sometimes greatest toward its end. The causes of these changes in flow profiles can be seen in the activity of the diaphragm, which in hypoxia has a greater rate of rise at the onset of inspiration, and greater peak amplitude, and greater postinspiratory inspiratory activity (PIIA) that continues into the first half of expiration (Lovering et al. 2003a).

Our objective here was to study the activity of central respiratory neurons in intact unanesthetized animals to determine the mechanisms of the frequency changes, increased efforts, and changes in diaphragmatic activity that occur in response to hypoxia. The results showed generally greater neuronal activity in hypoxia and changes in discharge profiles that could account for the increased efforts and changes in diaphragmatic activity and thus airflow. However, the mechanisms underlying the change in respiratory rate in response to hypoxia were not apparent from our results.

METHODS

Subjects

Five adult cats (3.2–5.3 kg) were prepared for recordings of electroencephalographic (EEG), pontogeniculooccipital (PGO), diaphragmatic electromyographic (EMG), and medullary respiratory neural activity. Tracheal fistulas were created and headcaps containing a connector for electrodes were attached to the animals’ skulls. The headcap contained also standoffs that were used to immobilize the animal’s head during recordings. The animals recovered from surgery for 1 mo before experimentation. The Animal Care and Use Committee of Texas Tech University School of Medicine approved all surgical and experimental procedures.

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Surgical procedures

The animals were initially anesthetized with acepromazine maleate (2.5 mg im) and ketamine (17 mg/kg im). Surgery was performed under aseptic/antisepsis conditions. A midline incision was made from below the cricoid cartilage to just above the suprasternal notch, and the sternothyroid, sternothyroid, and sternomastoid muscles were retracted to expose the trachea. The trachea was opened longitudinally and the cut edges of the rings were sewn to the skin margins on the corresponding side. A tracheal tube was inserted, and anesthesia was maintained by administration of 1–2% halothane in O2.

The animal was placed in a supine position. An incision was made caudal to the costal margin from the xiphoid process to the mid-axillary line. Four EMG electrodes (Teflon-coated multistranded stainless steel wires; Cooner AS 632) were implanted within crural and semimedianus regions of the right diaphragm. The electrodes were placed medially as possible to avoid intercostal muscle activity contamination. The EMG wires were run subcutaneously to the back of the neck where they were routed to the skull.

The animal was placed in a stereotaxic frame, and a midline incision exposed the dorsal skull. Four EEG electrodes (4–40 stainless steel screws with multistranded Cooner (AS 632) stainless steel leads) were screwed into the skull over medial occipital and parietal cortices bilaterally. Two tripolar electrodes, one in each hemisphere of the brain, were implanted stereotaxically at coordinates A6.4, L10, and H +2.5. These are the coordinates of the fibers of the optic tract where they enter the lateral geniculate body of the thalamus. PGO wave recordings are optimal when the electrode tip in these fibers is referred to an electrode in the overlying lateral geniculate body.

EEG and PGO electrodes, and 4–40 anchor screws, were cemented to the skull. A prefabricated headcap containing standoffs for immobilization of the head was fixed to the skull with dental cement. Gold Cinch pins were crimped to the ends of the diaphragmatic, EEG, and PGO electrode wires and were inserted into a connector block. The connector block was then attached to the headcap.

In a separate operation under anesthesia as in the preceding text and using aseptic techniques, a small craniotomy (5 mm diam) was made in the occipital bone. The craniotomy was made using stereotaxic coordinates that allowed access to medullary respiratory groups (Orem 1980). The animal was allowed to recover for ≥2 wk before experimentation.

Recording procedures and experimental protocol

On nights before recording sessions, the animals were housed in a cold (0°C) environment to reduce sleep. This consolidated sleep during recording sessions the following day. During recordings, the trachea was intubated with a 4.0 mm endotracheal tube that was attached to a Validyne pneumotachograph. Total dead space of the tracheal tube and pneumotachograph was 8 ml, which is approximately equal to the dead space of the upper airway. Pressure levels in the tube were measured using a volumetric pressure transducer. Tidal O2 and CO2 were measured with an O2 analyzer (Beckman OM-11) and infrared CO2 analyzer (Beckman LB-2). Tidal O2 and CO2 percentages, EEG, EMG, and PGO activity, airflow and intratracheal pressures were recorded on paper (Astro-Med 9500) and on magnetic tape. Diaphragmatic activity was amplified with a Grass P511 amplifier set to pass frequencies from 0.3 to 30 kHz.

Medullary inspiratory neurons were recorded in control and experimental conditions in 230 sessions over a period of 25 mo. Only one penetration with the microelectrode was made during a session (day). Penetrations were defined by reference to a point on the head-restraint plate. Tungsten microelectrodes (impedances: 1–10 MΩ) were used to record extracellular action potentials. The microelectrodes were mounted in a hydraulic microdriven and driven through the cerebellum into the medulla. Signals were led to a high-impedance probe (Grass HIPS11) and via a preamplifier (Grass P511) to paper and tape recording devices.

The activity of single respiratory neurons was studied first during sleep and wakefulness while the animal breathed room air (Lubbock, TX, altitude: 1,000 m). After these control recordings, the animals breathed a hypoxic gas mixture (F1O2 = 0.10–0.11 O2 in N2; P1O2 = 63–69 mmHg). CO2 levels were allowed to decrease as a function of ventilation (hypocapnic hypoxia). We attempted to continue the exposure to low oxygen until a complete sleep-wakefulness cycle was obtained, but this was not always possible. In particular, it was difficult to obtain REM sleep in hypoxia because the low carbon dioxide levels associated with hyperventilation reduce the amount of REM sleep and prevent its occurrence (Lovering et al. 2003b). The exposure to hypoxia therefore lasted for many minutes, and the responses of neurons described herein were not immediate responses but rather the response after minutes to hours of exposure. Recording sessions lasted ~4 h. We have shown that intact unanesthetized adult cats hyperventilate to hypoxia throughout this period (Lovering et al. 2003a). Although REM sleep in hypoxia was the most difficult condition to obtain, there were cases when neuronal activity was recorded during hypoxia but not normoxia in REM sleep. In some of these cases, for various reasons, e.g., limitations in the time remaining for recording, the animals were switched to hypoxia before a control REM period was obtained. In other cases, a new respiratory neuron appeared while recording another neuron during hypoxia and no REM sleep was obtained in subsequent recordings in normoxia.

Recordings of extracellular action potentials can change with slight movements of the animal or with changes in cerebral blood flow as occurs in REM sleep. The present experiments required lengthy recordings. Often these were associated with changes in amplitude of the action potentials. To ensure that the data were from the same neuron, we discriminated the action potentials on the basis of amplitude and then superimposed the action potentials using the standard pulse generated by the Dataview pulse height discriminator. If these averages did not show a refractory period or revealed multiple waveforms in association with the standard pulse, the samples were excluded from analysis.

On-line data analysis

Cycle-triggered histograms, and the signal strength and consistency of the respiratory component of the activity of a cell (η2 value) were determined for each cell during recording sessions. Procedures for constructing cycle-triggered histograms and calculating the η2 value of the activity of a cell have been published (Orem and Dick 1983). η2 values assigned to cells were determined in NREM sleep during periods of regular breathing in normoxia. Respiratory neurons were classified as inspiratory or expiratory based on when they discharged in relation to airflow and diaphragmatic activity during NREM sleep in normoxic conditions. Decrementing neurons had peak activity during the first half of their phase of activity (inspiration or expiration) and then progressively declined throughout the rest of the phase. Augmenting neurons increased their activity gradually throughout the phase with peak activity late in the phase. Neurons the patterns of which were not clearly augmenting or decrementing were classified as simply inspiratory or expiratory. Late inspiratory and expiratory neurons discharged only at the end of their respective phase. Few phase-spanning neurons were obtained in this study. However, we were able to study seven cells with activity that peaked late in expiration and that continued into early inspiration. These cells correspond to preinspiratory neurons as described by Schwarzacher and associates (1995), and we have adopted here that name for them.

Off-line data analysis

Diaphragmatic activity, PGO activity, EEG activity and airflow were digitized off-line from analog recordings at 1,000 samples/s using a Cambridge Electronic Designs (CED) Micro 1401 device in conjunction with CED Spike2 (v4.10). Neural activity was digitized at 20,000 samples/s.

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Mean interspike intervals and the SD of the interspike intervals, along with the results of statistical analyses, are presented in the tables in Results and supplemental data. The figures show average instantaneous discharge rates throughout the respiratory cycle. Interspike intervals were determined for each cell, when possible, in NREM and REM sleep during normoxia and hypoxia. Data from relaxed wakefulness and NREM sleep were combined because cats adapted to the apparatus were relaxed and drowsy during wakefulness, and the EEG showed frequent episodes of light sleep interspersed with wakefulness. Alert, sustained wakefulness was infrequent. Thus all data reported herein are designated as either from NREM or REM sleep. We analyzed episodes of activity in NREM sleep that contained consecutive breaths that were not interrupted by augmented breaths, swallows, movements, coughs, and vocalization. In REM sleep, all breaths in the period were analyzed. Differences between mean interspike intervals were tested using the $t$-test. All comparisons were made within specific states of consciousness (e.g., REM sleep in normoxia vs. REM sleep in hypoxia). Results were considered significant when $P < 0.05$. Interspike interval data for individual cells is provided as supplemental data. Here, based on the statistical analyses in the preceding text, the responses of cells to hypoxia, compared with normoxia, were grouped according to cell type and classified as increased, decreased, or unchanged.

For representation of average values of neural activity, airflow waveforms, and diaphragmatic activity, both inspiration and expiration during each respiratory cycle were divided into 1,000 bins, and these bins were averaged across cycles from multiple breaths. Neuronal activity was converted to a step-wise function of firing frequency over time. For each time moment between impulses, the frequency was equal to the inverse value of the current interspike interval. Then the averages of inspiratory and expiratory activity were combined into one 1,000-bin file. The proportion of bins allotted to inspiratory and expiratory activity were combined on one 1,000-bin file. The proportion of bins allotted to inspiratory and expiratory activity were based on the average values of $T_I$ and $T_E$ respectively (custom script in Spike2). Cycle-triggered histograms (1,000-bin resolution) were constructed using the transition from expiratory to inspiratory airflow, or from inspiratory to expiratory airflow, as the trigger-event. Comparisons of activity pattern profiles were made by aligning these cycle-triggered histograms of neural activity and airflow in normoxia and hypoxia. The neural activity was aligned at the transition from expiration to inspiration for inspiratory neurons and vice versa for expiratory neurons (see Fig. 3). These alignment configurations allowed for determination of alterations in activity including changes in timing of activity as well as changes in profile in response to hypoxia with respect to the normoxia controls.

NREM and REM sleep and wakefulness were defined on the basis of standard EEG criteria (Orem et al. 1977).

**RESULTS**

Data were obtained from 403 respiratory neurons. Of these neurons, 120 were recorded in both hypoxic and normoxic conditions in NREM sleep. Of these 120, 19 neurons were recorded in both hypoxic and normoxic conditions during REM sleep. All neurons were located within the ventral respiratory group (Fig. 1).

**Ventilatory response to hypoxia**

The cats in this study hyperventilated as previously reported (Lovering et al. 2003a). The hyperventilation was the result of significant increases in diaphragmatic activity during both
inspiration and expiration (Figs. 2, 4, and 7). The increases in diaphragmatic activity resulted in changes in airflow profile from augmenting and decrementing flows during inspiration and expiration respectively to more constant flows during both phases of the cycle (Figs. 2, 4, and 7).

Neural response to hypoxia

The majority of all types of neurons, with the exception of preinspiratory neurons, were more active during hypoxia (Table 1). Inspiratory cells that were more active in hypoxia had discharge rates that averaged 164% of the rates in normoxia [inspiratory decrementing (I dec) 183%; I augmenting (I aug) 154%; and I 155%]; expiratory cells that were more active in hypoxia discharged at rates that averaged 186% of the rates in normoxia [expiratory decrementing (E dec) 230%; E augmenting (E aug) 191%; and E 136%; Table 1]. However, inspiratory and expiratory cells with increased activity constituted small majorities within their populations. In the case of inspiratory cells, 58% were more active in hypoxia than in normoxia, whereas 15% and 27% were less active or equally active in the two conditions, respectively. Similarly, only 56% of expiratory cells were more active in hypoxia. The others were either less active (24%) or unchanged (20%). In contrast to other populations (Figs. 2 and 3), the majority (57%) of preinspiratory cells were less active (discharge rates of only 40% of rates in normoxia) in hypoxia (Fig. 4).

Figure 3 illustrates the activity changes of individual cells of various types that were more active during hypoxia.

| Table 1. Discharge rate change to hypoxia of different types of respiratory neurons in NREM and REM sleep |
|-------------------------------|------------------|------------------|------------------|
| Cell Type | Rate Change | % Normoxia NREM | % Normoxia REM |
| Pre-I | Increased | 197 ± 94 (2) | 63 ± 32 (4) |
| | Decreased | 40 ± 23 (4) | |
| | Unchanged | 92 (1) | |
| I dec | Increased | 183 ± 72 (5) | |
| | Decreased | 122 ± 13 (2) | |
| | Unchanged | 116 ± 48 (5) | 116 (1) |
| I aug | Increased | 154 ± 46 (31) | 126 ± 17 (3) |
| | Decreased | 69 ± 14 (6) | 74 ± 11 (3) |
| | Unchanged | 100 ± 13 (14) | 101 ± 10 (3) |
| I | Increased | 155 ± 33 (10) | 384 ± 415 (4) |
| | Decreased | 59 ± 14 (6) | 59 (1) |
| | Unchanged | 116 ± 48 (5) | 116 (1) |
| E dec | Increased | 230 ± 96 (6) | |
| | Decreased | 68 ± 36 (2) | |
| | Unchanged | 114 ± 6 (2) | |
| E aug | Increased | 191 ± 87 (10) | |
| | Decreased | 56 ± 20 (4) | |
| | Unchanged | 103 ± 11 (5) | |
| E | Increased | 136 ± 105 (3) | |
| | Decreased | 76 ± 15 (2) | |
| | Unchanged | 114 ± 6 (2) | |

Values are means ± SD. Late I and late E cells were grouped with inspiratory augmenting (I aug) and expiratory augmenting (E aug), respectively. *Rate of change for majority of this cell type. NREM, non-rapid-eye-movement; REM, rapid-eye-movement.

1 The Supplementary Material for this article (nine tables) is available online at http://jn.physiology.org/cgi/content/full/00615.2005/DC1.
greater rate of rise of activity. This is evident for the I dec and I aug cells in Fig. 3, A and B. In other cases, the active phase of the cell relative to airflow began earlier. This is evident in the case of the I aug, E dec, E and late E cells in Fig. 3, B, E, G, and H.

The distributions of discharge rates of different respiratory cell types overlapped considerably in hypoxia and normoxia in NREM sleep (Fig. 5). Except for preinspiratory and late expiratory cells, the distribution of frequencies of the individual cell populations shifted upward in hypoxia, but the changes were relatively small.

State effects

Nineteen inspiratory cells were studied during normoxia and hypoxia in both REM and NREM sleep. The response to hypoxia in NREM and REM sleep was quantified as the ratio of the hypoxia rate to the normoxia rate in the two states. A plot of these data in the two states showed that the points fell generally along the line of identity (Fig. 6), which indicates that the response to hypoxia was similar in the two sleep states. However, there was a tendency for responses to be slightly greater in NREM sleep, as indicated by the predominance of points to the right of the line of identity. Figure 6 shows also that 11 of the 19 cells did not increase their activity in response to hypoxia in REM sleep, whereas 8 of 19 cells did not increase their activity in NREM sleep. The proximity of most points to the line of identity indicates that cells that were less active in hypoxia in NREM sleep were less active in hypoxia in REM sleep.

Postinspiratory inspiratory activity (PIIA) of the diaphragm increases in response to hypoxia in NREM sleep (Figs. 2, 4 and

FIG. 3. Discharge profiles of inspiratory (A–D) and expiratory (E–H) neurons during normoxia (light traces) and hypoxia (heavy traces). Long dotted line for cells shown in A–D represents the transition from expiration (e) to inspiration (i). Long dotted line for cells shown in E–H represent the transition from inspiration (i) to expiration (e). Numbers of breaths (n) averaged to obtain discharge profiles in normoxia and hypoxia are shown in each frame. impulses per second. Two to 3 breaths of the raw data used to obtain the averaged traces in A, B, and H are shown in Fig. 2, A–C, respectively. Data are from NREM sleep.
but then decreases in REM sleep (Lovering et al. 2003a). This state effect was seen also in diaphragm recordings in this study and was associated with similar changes in the activity of some I aug \(n = 8\) and I neurons \(n = 5\) (Fig. 7). These neurons were active only during inspiration in normoxia but discharged throughout inspiration and much of expiration in hypoxia (Fig. 7). In REM sleep both the diaphragm and inspiratory neurons had less PIIA (Fig. 7).

**DISCUSSION**

The objective of the present study was to understand the neural basis for the changes in breathing during hypoxia. The
latter include an abrupt increase in diaphragmatic activity at the onset of inspiration and then ramping activity to a peak (Lovering et al. 2003a). This is a step-ramp pattern rather than the augmenting ramp pattern characteristic of normoxia. Also, postinspiratory inspiratory activity (PIIA) and respiratory rate increase in hypoxia—the latter primarily as the result of a decreased duration of inspiration.

Variable response to hypoxia

We recorded single medullary respiratory neurons during sleep in normoxia and hypoxia. As seen by other authors using different preparations (Nesland et al. 1966; St. John and Bartlett 1979; St. John and Bianchi 1985; St. John and Wang 1977), our results were diverse. Regardless of the cell type, inspiratory or expiratory, some cells were excited by hypoxia but others were not. The reasons may be numerous. Cells having similar activity patterns may be located in different regions of the ventral respiratory column and can therefore have different roles in respiration that may require different response to hypoxia. However, using decerebrate, cerebellectomized, paralyzed, vagotomized and ventilated cats, St. John and Bianchi (1985) have found that bulbospinal and laryngeal neurons of the ventral medullary respiratory group had a variable response to hypoxia. Thus even in a case where the location of the neurons is known and the neural projections are established, the variability could not be explained. Also in-phase inhibition could account for differences in response to hypoxia. For example, I aug cells that were less active in hypoxia may be inhibitory to other I aug cells, and their inactivity allows the latter to be more active (Ballantyne and Richter 1984; Parkis et al. 1999; Zuperku and McCrimmon 2002). It is possible also that some cells are depressed directly by hypoxia (Richter et al. 1991; St. John and Wang 1977), whereas others are excited by peripheral chemoreceptor input. Also some cells may be more
sensitive to central chemoreceptors, which are inactivated by hypocapnia, whereas others are more sensitive to peripheral chemoreceptors, which are activated by hypoxia.

**Step-ramp diaphragm pattern**

The majority of I dec, I aug, and I neurons were more active in hypoxia than normoxia, and in the case of I aug cells, the pattern of activity was a step increase in activity followed by a ramping increase to peak activity at the end of inspiration. These changes parallel the increase of diaphragmatic activity and its step-ramp shape in hypoxia.

**Diaphragmatic PIIA in hypoxia**

Lawson et al. (1989) showed that stimulation of the peripheral chemoreceptors caused a reduction of the hyperpolarization, or an actual depolarization without spiking, of inspiratory neurons during early expiration. Others have reported increased diaphragmatic PIIA in response to hypocapnic, but not isocapnic, hypoxia (Sherrey et al. 1988; Smith et al. 1989). In a previous study, we showed that diaphragmatic PIIA increases in hypoxia in wakefulness and NREM sleep but is reduced in REM sleep (Lovering et al. 2003a). In this study, we found that some I aug and I neurons developed PIIA during hypoxia in NREM sleep, but this activity was reduced during REM sleep.

Theoretically PIIA could arise if E cells that are inhibitory to I cells became less active in hypoxia. Contrary to this idea, most E neurons were excited by hypoxia. The cause of PIIA therefore appears to be an increased excitation of I aug and I neurons that extends into early expiration.

**Increased rate of breathing in hypoxia**

It is not known how the brain stem oscillator changes rates. The rate of breathing increases in hypoxia, and the increase is a result primarily of decreases in the duration of inspiration (Lovering et al. 2003a). Although a mechanism is not known, changes in discharge profile (Figs. 2 and 3) may cause changes in timing. In the current study, decrementing, augmenting, and late inspiratory neurons increased their activity sooner and ended their activity more abruptly during inspiration in hypocapnic hypoxia in NREM sleep (i.e., left shift in activity). Previous works have found that late inspiratory neurons are active earlier in hypoxia (Batsel 1965; England et al. 1995) and Morris and associates found similar results in response to peripheral chemoreceptor stimulation (Morris et al. 1996). Thus a left shift in initiation and termination of inspiratory neural activity and other profile changes observed in the current study, e.g., advanced activity of E and late E cells, might affect timing.

**Conclusion**

The response of medullary respiratory neurons to hypoxia is heterogeneous. However, a common theme has emerged between all studies of respiratory neural activity in preparations with excitation of respiratory motor output in response to hypoxia; that is, despite excitation of the respiratory motor output, some respiratory neurons are depressed or unchanged in response to hypoxia. Furthermore, St. John and colleagues have found an almost identical increase in phrenic motoneuron activity in response to hypoxia and hypercapnia (St. John 1981; St. John and Bartlett 1979; St. John and Wang 1977). However, they found also that the same premotor respiratory neurons with a heterogeneous response to hypoxia had a homogeneous excitatory response to hypercapnia. Taken altogether, the data suggest that the heterogeneous response to hypoxia may represent an adaptive mechanism that allows for increased breathing efforts without complete activation of the respiratory network at a time when oxygen availability is compromised.

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