sufficiently arousing to increase the ingestion of any stimulus, the same experiment was repeated with distilled water substituted for 0.03*M* sucrose as the taste stimulus. Under these circumstances the amount consumed by both decerebates and controls during deprivation did not differ from the amount consumed when they had just been fed (*19*).

Hunger has been operationally defined as an increase in food consumption as a function of food deprivation; satiation is defined conversely (*20*). Our data support the hypothesis that at least some of the normal control mechanisms of hunger and satiation are restricted to the caudal brainstem. Previously these mechanisms had been assigned exclusively to hypothalamic-forebrain structures.

The two experiments reported here are parallel in that they examine whether the response to a constant stimulus is altered as a function of changes in internal state; they differ in that in one case the viscerally applied stimulus is ongoing (food in the gut) and in the other the stimulus was applied previously (LiCl in the gut). The decerebrate rat required that the visceral stimulus be ongoing or present in order for ingestion of a taste stimulus to be replaced by rejection. It is conceivable that if the decerebrate animal were tested during rather than after the period of LiCl stimulation, the formerly accepted taste would be rejected. Although the hypothalamus or forebrain may be instrumental in controlling ingestion, the data suggest that aspects of this control may also be represented at other, more caudal levels of the mammalian brain.

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11. Decerebrates were fed by gavage three 12-ml meals daily. The diet consisted of equal parts of sweetened condensed milk and water. Rectal temperatures were recorded three to five times daily; hyperthermia was treated by wetting the fur with water and, in extreme cases, by exposing the wet animal to a fan to facilitate evaporative cooling.
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15. The taste stimulus, 0.1*M* NaCl (four rats) and 0.03*M* HCl (three rats) injected intraorally in 50-μl volumes, elicited an ingestion sequence before LiCl pairing. The NaCl and HCl (rather than sucrose) were used as paired taste stimuli to eliminate the possibility that daily tube-feedings of a sweetened milk diet might serve as extinction trials for a sucrose stimulus. Taste and LiCl (0.15*M*, 1.5 meq per kilogram of body weight, intraperitoneally) were paired once on each of four consecutive days ending 10 days before complete transection; LiCl was injected immediately after the presentation of the taste stimulus. The same taste stimuli were used for pairings before and after transection. The retention test took place on day 9 after the complete transection, and retention with exogenous arousal (tail pinch during and immediately before the test) on day 11. Acquisition and acquisition with exogenous arousal were each examined during four consecutive days of taste-LiCl pairings. The acquisition experiment began on day 15, and acquisition with exogenous arousal [intraperitoneal injections of *d*-amphetamine sulfate (0.5 mg/kg) given 1/2 hour before testing] on day 55. All responses were videotaped.
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19. The distilled-water control experiment began on day 79; two decerebrates and both controls were subjects. Average water consumption (in milliliters) for control and decerebrates, respectively, was 2.68 ml (standard error, 1.12), 0.63 (0.08) when sated; 2.75 (1.90), 0.85 (0.25) when deprived for 24 hours; and 2.70 (2.10), 0.70 (0.15) during 48-hour deprivation.
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Ponto-Geniculo-Occipital (PGO) Burst Neurons: Correlative Evidence for Neuronal Generators of PGO Waves

Abstract. *A newly discovered class of neurons, ponto-geniculo-occipital (PGO) burst neurons, has PGO wave relationships of phase-leading, stereotyped discharge bursts, and the highest reported discharge specificity and coherence; these neurons thus fulfill correlative criteria for output generator neurons for PGO waves. The PGO burst neurons are recorded in a discrete dorsal brainstem area in apposition to the brachium conjunctivum.*

Ponto-geniculo-occipital (PGO) waves are electroencephalographic spikes recorded in pons, lateral geniculate nuclei (LGN), and occipital cortex just before and during desynchronized sleep episodes. Because of their possible role in information generation and transmission from brainstem to forebrain sites in a number of behavioral and developmental conditions, PGO waves have attracted the interest of workers in sleep physiology, visual system function, pharmacology, and developmental plasticity (*1*). Studies employing lesion, cooling, and macropotential recording techniques have outlined the projection pathways of PGO waves from pons to LGN and to visual cortex (*2*), thus opening the way for investigations at the cellular level to provide critical information on the localization and function of neurons involved in PGO wave generation and transmission.

As a first step in defining the neuronal network involved in the chain of events leading to PGO wave generation, it is important to identify the set of neurons forming the last link of this chain, that is, to identify a set of output neurons for PGO wave generation. Once such neurons have been identified one can work backward in the PGO generation network, tracing the inputs to these final stage or output cells. We reason that criteria for identification of such output generator cells for PGO waves should in-

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clude: high discharge coherence with PGO waves (discharge bursts associated with each wave); high discharge specificity (relative absence of discharge at other times); a fixed phase lead of discharge bursts relative to PGO waves; and evidence of projection to sites where PGO waves are recorded. Furthermore, output cells might evince a particularly stigmatic, stereotyped discharge pattern in contrast to other neurons in the PGO generation network.

In previous studies we found some neurons in the giant cell field of the pons [gigantocellular tegmental field (FTG)] that increased discharge rate up to 900 msec before the onset of PGO waves. While this impressively long phase lead is compatible with these cells playing a role in the initiation of events leading to PGO wave generation, the discharge coherence and specificity were not impressive and the phase-leading discharges were variable in both intensity and duration of lead, suggesting these cells were not output generator neurons for PGO waves (*3*).

Some cells in locus coeruleus and subcoeruleus have been noted to fire at shorter intervals before PGO waves, but with low coherence and specificity (*4*). Recently, some neurons in the nucleus parabrachialis lateralis have been reported to have good specificity and a fixed latency discharge pattern, but only moderate coherence (*5*). Thus, while all of these cells may be part of a PGO generation network, none have the qualities expected of neurons serving as the output generators for PGO waves.

Table 1. Temporal sequence of PGO wave and unit events. All times are relative to the peak of PGO waves recorded in LGN; averages are from all 13 units and ipsilateral PGO waves (with a minimum of a 1-second separation from preceding PGO waves); S.D., standard deviation.

Time (msec) (mean ± S.D.)	Event
−46.5 ± 4.4	First PGO burst cell discharge
−39.3 ± 4.5	Peak in unit discharge; LGN EEG still at baseline
−34.0 ± 1.2	PGO wave begins
0.0	PGO wave peak (reference point, t_0)

We now report a class of neurons whose discharge shows the highest degree of coherence with PGO waves yet discovered, and whose PGO wave relationships of specificity and a fixed phase-leading discharge pattern make them prime candidates for output generators for PGO waves. We call these neurons PGO burst neurons. Defining characteristics of this class of cells are: discharges in bursts of two to six spikes tightly linked to PGO waves; a first spike that occurs, with minimal variability, 12 msec before the onset of PGO waves and 45 msec before the PGO wave peak in LGN recordings; a high degree of PGO wave coherence; and high PGO wave specificity. This report describes the discharge characteristics and anatomical localization of PGO burst cells (*6*).

Extracellular recordings of single cell potentials were obtained with metal microelectrodes in unanesthetized and head-restrained cats as previously described (*7*). Standard macroelectrodes were implanted to record electrooculogram (EOG), nuchal electromyogram (EMG) and frontoparietal electroencephalogram (EEG); a set of four electrodes was implanted in each LGN to record PGO waves and to stimulate with a constant current stimulator. Placement of the LGN electrodes was guided by the evoked potential response recorded from them during strobe stimulation of the retina. We used conventional criteria to define state (*8*). Correlations between PGO waves in the LGN and unit acitvity were documented by means of frequency-modulated tape recordings, photographic and paper records, and by a computer program that detected PGO waves, averaged the wave forms, cross-correlated them with unit firings, and provided autocorrelograms for both PGO waves and the unit discharges (*9*). Stationarity of unit discharge–PGO wave relationships was indicated by consistent results on repeated recordings (up to 16) of successive transition periods from synchronized to desynchronized sleep. We mea-

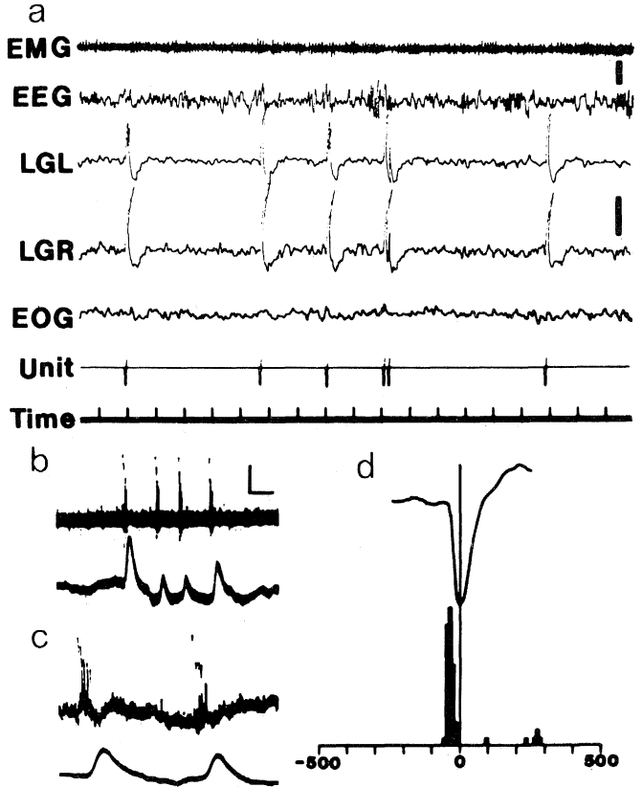

Fig. 1. (a) This inkwriter record of a transition period shows the consistent phase-linking between PGO waves recorded in the left (*LGL*) and the right lateral geniculate (*LGR*) nuclei and the discharges of a PGO burst cell (*Unit*). See text for other abbreviations. Time in seconds. Voltage calibration: LGN channels, 200 μV; other channels (upper right), 100 μV. (b and c) Oscilloscope photos of a PGO burst cell (upper trace) and ipsilateral LGN PGO waves (lower trace) showing stereotyped unit discharge bursts and tight phase-linking to the PGO waves. Each burst has five spikes and the initial spike occurs about 45 msec before the PGO peak. Time calibration: (b) 200 msec; (c) 50 msec. Voltage calibration for both unit records is 100 μV (negativity up) and 200 μV for the PGO records. Simultaneous occurrence of a negative field potential (which may reflect depolarizing input) and unit burst is evident in the less filtered unit record in (c) (lower − 3-dB point, 1 Hz). (d) Cross-correlation between 12 isolated transition period PGO waves (average wave form is displayed, amplitude, 220 μV; peak, time 0) and the discharges of a PGO burst cell (maximum, 17 discharges per bin). Time in milliseconds; bin width, 10 msec. Note the extremely tight and virtually noiseless coupling between PGO burst cell discharge and PGO waves.

sured coherence as the percentage of PGO waves preceded by a unit discharge burst and specificity as the percentage of unit discharges occurring in bursts preceding PGO waves. The data base for this report includes 13 PGO burst cells in three cats and the analysis of 70 transition and desynchronized sleep periods.

Figure 1a shows a polygraphic record segment of one PGO burst unit during a typical transition period. Coherence is 100 percent in this segment; for the entire transition period, discharge bursts preceded 32 out of 36 PGO waves (coherence, 89 percent). In this record there is also a high specificity of discharge: no bursts occur except in relation to PGO waves in the displayed segment and for the entire transition period only one burst occurred without a succeeding PGO wave. In the six units with the technically best recordings, coherence values ranged from 60 to 93 percent and averaged 80 percent; specificity values ranged from 79 to 99 percent and averaged 91 percent (*10*). The PGO burst neurons were silent or had very low discharge rates in synchronized sleep and quiet waking without eye movements (< 0.5 spike per second), but often discharged single spikes in relation to eye movements or sudden arousal.

Figure 1, b and c, and Table 1 illustrate the consistent phase relationships between PGO burst cell discharge and ipsilateral PGO waves: the first spike precedes PGO wave onset by about 12 msec, and precedes the PGO wave peak by 45 msec. The PGO burst cells were remarkably uniform in their discharge characteristics, having very similar cross-correlograms with PGO waves (Fig. 1d).

Figure 2 shows the histological localization of PGO burst cells on a microelectrode descent at lateral 1.6 that passed through the cerebellum and ended in the central tegmental field in close approximation to the brachium conjunctivum. A microlesion (arrow) marks the recording site of one PGO burst cell; another burst cell was recorded 0.1 mm distant. Rather than inclusion in any one nuclear group, the critical anatomical localizing feature was proximity to the brachium conjunctivum. All PGO burst cells were recorded in a discrete dorsal brainstem area that extends between 1.4 and 4.0 mm from the midline and lies along the border of the brachium conjunctivum as it passes through the marginal nucleus and the anterior pole of the locus coeruleus to enter the central tegmental field. Only this area has been positive for PGO burst cells, although the brainstem region we have sampled in

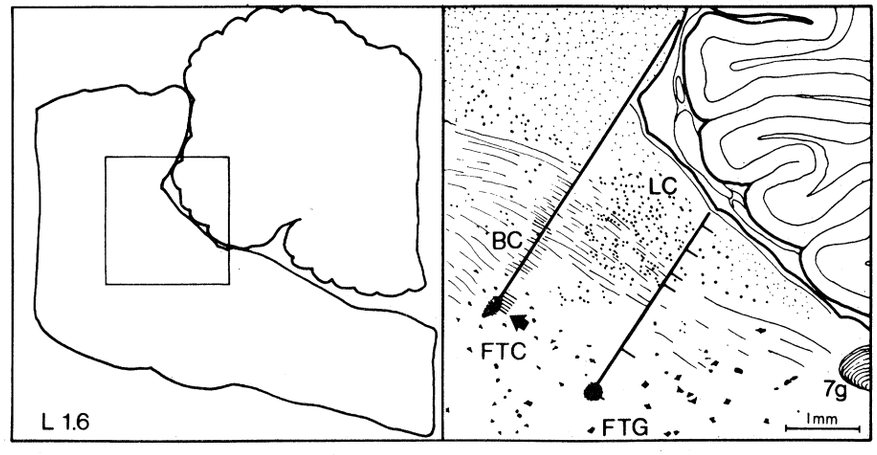

Fig. 2. Histological reconstruction in a sagittal section of a microelectrode descent with a microlesion near the site of recordings of two PGO burst cells (arrow) and a more posterior descent negative for burst cells (see text). The anterior descent was typical of those yielding PGO cells in that it ran parallel to the posterior border of the brachium conjunctivum (*BC*), indicated in the drawing by the densely packed fibers just anterior to the locus coeruleus (*LC*) and ended in the dorsal part of the central tegmental field (*FTC*). Other positive descents were found more laterally at the same depth and in the same relationship to the brachium conjunctivum.

over 100 descents in this and other experiments is quite large, extending rostro-caudally from the red nucleus to the ponto-medullary junction and from the midline to 4 mm laterally (*11*).

The combination of the extraordinarily strong correlational linkage between PGO burst cell discharge and lateral geniculate nucleus PGO waves reported here, and the evidence obtained with horseradish peroxidase of direct projection to LGN of some cells in the area of the brachium (*12*) suggested that the cells we recorded might project directly to LGN. In six PGO burst cells we thus attempted antidromic activation from the electrodes used for PGO recording in the LGN. No cells were antidromically activated but five of the six cells examined responded orthodromically at latencies of 5 to 25 msec. One of these showed a state-dependent orthodromic driving: it could be driven in desynchronized sleep but not in waking by stimulation of the LGN. In recent experiments we have observed that LGN electrical stimulation during desynchronized sleep produces both evoked PGO waves and PGO burst cell discharge that has the same burst characteristics and phase as with spontaneous PGO waves.

Further antidromic stimulation tests at different LGN sites will have to be conducted to enable us to determine whether monosynaptic projections from burst cells to LGN exist; the latency measurements (Table 1) suggest slow conduction velocities but by no means rule out monosynaptic projection. If the projections are polysynaptic to LGN, a possible site for interposed neurons is the perigeniculate or reticular thalamic nucleus (*13*). A third possibility is that the PGO burst cells we have recorded may project to visual cortex or to some other component of the PGO conduction system.

With respect to theories of PGO wave generation, the high coherence of these cells (all > 50 percent) gives no support to the notion derived from cooling and macropotential studies that there are isolated bilateral PGO generators with separate pathways through the mesencephalon (*14*). That hypothesis implies that each PGO burst cell should only discharge before 50 percent of the PGO waves. Our data indicate that the likelihood of such a 50 percent discharge coherence being true is less than 1 in 10 billion (*15*).

Neither do these results support the hypothesis that catecholamine-containing neurons of the middle and caudal locus coeruleus play an active, excitatory role in PGO wave generation (*16*), because the discharge pattern of the PGO burst cells is quite different from that reported of neurons in portions of the locus coeruleus not bordering the brachium (*17*). In fact, since many locus coeruleus neurons, as well as those in dorsal raphe, decrease discharge rate with PGO onset, these neurons may instead act in a permissive, disinhibitory manner in PGO wave generation (*18*).

We propose the following hypothesis about events leading to LGO wave generation: the sequence begins with the activation of FTG cells, possibly as a result of disinhibition by locus coeruleus and raphe cells. The FTG cells then activate the burst cells directly or, more likely, indirectly via vestibular and oculomotor

system connections. The PGO burst cells form the final link in the chain, acting as output generators for the PGO waves by integrating information from other pontine systems and transmitting it to forebrain.

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Physostigmine: Improvement of Long-Term Memory Processes in Normal Humans

Abstract. *Nineteen normal male subjects received 1.0 milligram of physostigmine or 1.0 milligram of saline by a slow intravenous infusion on two nonconsecutive days. Physostigmine significantly enhanced storage of information into long-term memory. Retrieval of information from long-term memory was also improved. Short-term memory processes were not significantly altered by physostigmine.*

Studies in humans and animals have implicated cholinergic processes in memory functioning. Investigations with both anticholinergics and cholinomimetics indicate that fluctuations in cholinergic activity can profoundly affect storage and retrieval of information in memory. Small doses of cholinesterase inhibitors have been reported to facilitate maze learning in rats (*1–3*). In humans the anticholinergic agent scopolamine produces learning impairments similar to those found in people with senile dementia (*4*). The acetylcholinesterase inhibitor physostigmine enhanced both storage and retrieval of information in a patient with impaired cognitive function (*5*). However, any enhancement of human memory is apparently limited to a narrow dose range of physostigmine (*6, 7*).

In this study normal subjects received low doses of either physostigmine or saline placebo. When the subjects received physostigmine they showed a significant improvement in storage of information compared to their performance when they received the placebo. These results have implications for the treatment of people with a variety of memory disorders.

The subjects were 19 normal male volunteers (18 to 35 years) who gave their informed consent to participate in this study. They were chosen according to their performance on a verbal learning task identical to the test used to measure the effect of physostigmine. Subjects were excluded if their performance on the screening task indicated there was no opportunity for improvement (*8*).

The subjects received 1.0 mg of physostigmine or 1.0 mg of saline on two nonconsecutive days. The order of infusions was randomized. Physostigmine or the saline placebo was administered by a constant infusion over 60 minutes. Approximately 20 minutes prior (−20) to the start of either infusion the subjects received 0.5 mg of methscopolamine bromide subcutaneously in order to block the peripheral effects of physostigmine. When the pulse rate reached 100 beats per minute the infusion was begun.

The experiment was designed (Table 1) so that we could measure short-term (STM) and long-term (LTM) memory functions. Two tests of STM were used: the digit span and memory scanning task of Sternberg (*9*). The digit span task determines the capacity of STM by measuring the maximum number of digits that a subject can recall correctly after a single presentation (*10*). Digit span measured 9 minutes after (+9) the start of infusion with physostigmine (when the subjects had received 0.15 mg) was 6.8 digits, and with saline was 6.9 digits. The memory scanning task measures the rate of processing in STM. Subjects make decisions about the contents of STM and register those decisions allowing measurement of the response speed. Two components of response time can be distinguished: one is a function of STM processing speed and one is a function of stimulus encoding and motor response processes. A dose of 0.75 to 1.0 mg of physostigmine had no significant effect on either component (*8*). Thus, physostigmine, compared to saline, had no quantifiable effect on any aspect of STM functioning.

We assessed LTM functioning by means of two verbal learning tasks (*10*). The first tested the hypothesis that physostigmine would enhance the ability to retrieve information from LTM. Thirty minutes prior to either infusion the subjects were given two learning trials on a list of 15 concrete nouns. The 15 nouns were presented verbally to the subject at the rate of one word per 2 seconds. The subject tried to recall the 15 words at the

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