can be seen in the PD trace from the spikes in the LP trace. When a brief depolarizing current is applied to the PL cell (Fig. 2C), the expected LP burst is inhibited, and the next PD burst occurs prematurely because of the absence of the usual inhibition. A similar response occurs if the PL neuron is hyperpolarized instead (Fig. 2D).

Thus during the typical pyloric pattern seen in active preparations, the PL neuron acts to help terminate the LP burst (Fig. 1B), allowing the PD neuron to fire sooner. The hyperpolarization of the PL neuron during the PD burst may also retard the LP depolarization and burst, thus modulating circuit activity during the hyperpolarizing part of the PL cycle when neurons are thought to be ineffective.

Finally, neuromodulators are known to modulate selectively the range of the normal voltage excursion and the firing patterns of these stomatogastric neurons (*12*). Such regulation should be capable of modifying the relative strengths of the mixed chemical-electrical synaptic connection, allowing one or the other effect to dominate. In other systems, modulators have been demonstrated to affect electrical coupling (*13*) and synaptic transmission (*14*), raising the possibility of even more marked shifts in the relative effectiveness of the electrical and chemical components of this mixed synapse. Thus this synaptic pair may be capable of switching its computations between full-wave rectification, half-wave rectification, and simple chemical inhibition or electrical coupling depending on modulatory input to this simple two-cell circuit and, by so doing, may modulate the patterned output of its larger neural network.

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8. Data are from six preparations, including both isolated stomatogastric ganglia and combined preparations (those with commissural and esophageal ganglia left attached). Data in Fig. 1B are from an isolated ganglion; Fig. 1, C and D, and Fig. 2 are from a combined preparation. Single- and double-barreled intracellular microelectrodes were used with either separate microelectrodes or separate barrels for injecting current and measuring voltage (*4*).
9. Hyperpolarization out for hyperpolarization in is also characteristic of a reduction in tonic chemically mediated excitation, which is not found in this network. Properties of electrical coupling and of mixed electrical-plus-excitatory chemical synaptic connections are reviewed by M. V. L. Bennett [in *Handbook of Physiology,* Section 1, *The Nervous System,* vol. 1, *Cellular Biology of Neurons,* J. M. Brookhart *et al.*, Eds. (American Physiological Society, Bethesda, MD, 1977), part 1, pp. 357–416.
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Technical Comments

Asymmetry of Neural Feedback in the Organization of Behavioral States

The nucleus locus coeruleus sends norepinephrine-containing projections to the entire cerebral cortex. Gary Aston-Jones *et al.* (*1*) show that this nucleus does not receive reciprocal projections back from the cortex. The overall connectivity pattern of this nucleus leads them to conclude that the widespread norepinephrine innervation of cortex is under a restricted set of afferent controls emanating mostly from a few medullary and hypothalamic nuclei.

We demonstrated this type of asymmetry in the connectivity of the nucleus basalis, which is the source of cholinergic projections for all cortical areas in the brain (*2*). Our studies in the rhesus monkey showed that the forebrain projections to this nucleus arise from a surprisingly restricted set of limbic and paralimbic regions. In contrast, the numerous sensory-motor and association areas of cortex which also receive cholinergic innervation send virtually no reciprocal projections back into the nucleus basalis. We concluded that the vast majority of the cortical surface has no direct feedback control over the cholinergic input that it receives, whereas a handful of limbic and paralimbic areas can exert monosynaptic control not only over the cholinergic input that they receive but also over the cholinergic projections that reach all other parts of the cerebral cortex. This pattern of connectivity implied that the nucleus basalis was poised to act as a cholinergic relay for modulating the activity of the entire cortical surface according to the prevailing motivational state encoded by the limbic and paralimbic regions of the brain.

Aston-Jones *et al.* show that the principle of asymmetrical neural control also holds for the nucleus locus coeruleus. An analogous arrangement is likely to exist in the connectivity of the brainstem raphe nuclei and of the substantia nigra–ventral tegmental area complex, which provide the cerebral cortex with serotonin and dopamine innervation, respectively. This pattern contrasts sharply with the great majority of corticocortical and corticothalamic connections that are reciprocal in a more symmetrical fashion.

The ascending corticopetal connections of the nucleus basalis, locus coeruleus, brainstem raphe, and substantia nigra are organized in such a way that a relatively small group of cells (under a restricted set of

descending neural controls) can rapidly and perhaps uniformly influence the information-processing state throughout the cerebral cortex. This is in keeping with the behavioral affiliations (for example, vigilance, motivation, mood, and memory) that have been attributed to these nuclei (*3*). It appears that the principle of asymmetrical neural feedback may be an important common denominator in the neuroanatomical organization of behavioral states.

M-MARSEL MESULAM
Behavioral Neurology,
Beth Israel Hospital,
330 Brookline Avenue,
Boston, MA 02215

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Response: Mesulam (*1*) emphasizes interesting and important similarities between the anatomic circuitries of the noradrenergic nucleus locus coeruleus (LC) and the cholinergic nucleus basalis systems. Both groups of cells widely innervate the neocortical mantle and thereby presumably exert global influences on cortical processing. However, there is a marked asymmetry in the neocortical connections of these cell groups: the LC receives no direct input from neocortical areas, and the basalis receives direct input from only a few.

Mesulam proposes that such asymmetrical circuitry may also hold for other nonthalamic cortical afferents and that a principle of asymmetrical neural feedback may characterize anatomic circuits involved in the organization of behavioral states. While this is an intriguing suggestion with substantial merit and is similar to our own functional analyses (*2, 3*), there are additional considerations. For example, brain areas other than the nonthalamic cortical afferent nuclei are asymmetrically connected with their targets, but may lack direct involvement in behavioral state processes (for example, retinal-thalamic and cortico-tectal pathways). The same is true for some cortical afferents, such as the occipital cortex, which projects to frontal, temporal, and parietal lobes but itself receives few reciprocal projections. Thus, other factors, such as functional attributes of afferents to, and discharge properties of, the neurons in question, must also be considered in functional analyses.

In this context, we have found that there are pronounced physiological differences between LC and basalis neurons in both rats and monkeys. LC cells are markedly homogeneous for physiological properties, exhibiting slow impulse conduction velocities, characteristic wide spike waveforms, tonic changes in activity as a function of behavioral state, and phasic responses to a wide array of sensory stimuli (*3, 4*). The major afferents to LC receive inputs consonant with these properties; for example, paragigantocellularis receives inputs from many sensory modalities (*5*) and it potently excites LC cells (*6*), indicating that this nucleus may serve as the sensory relay area for LC phasic activity (*2, 3*). In contrast, cortically projecting nucleus basalis neurons are markedly heterogeneous in terms of impulse conduction velocity, spike waveforms, spontaneous activity, and certain sensory-behavioral discharge properties (*7, 8*). Taken together, these results suggest that individual LC neurons are homogeneous in terms of intrinsic physiologic properties and afferent control, resulting in concerted discharge properties, while nucleus basalis neurons may be heterogeneous along these same dimensions. There are also differences in the patterns of cortical termination by these two cell groups: individual LC neurons broadly innervate different cortical areas (*4*), while single basalis neurons have more restricted cortical terminal fields (*7, 9*).

These anatomic and physiological distinctions may indicate significant functional differences between the LC and basalis systems. Thus, LC neurons may act more or less in unison to exert a concerted, global influence on brain activity and behavioral state [for example, vigilance (*3, 10*)], while basalis neurons, by virtue of their physiological heterogeneity and restricted terminal fields, may exert more differentiated control of select target areas (*7*). Additional studies of these two important cortical afferents are needed to further delineate their properties and to help determine whether functional similarities outweigh the differences.

GARY ASTON-JONES
Department of Biology,
New York University,
New York, NY 10003
MICHAEL T. SHIPLEY
Department of Anatomy and Cell Biology,
University of Cincinnati College of Medicine,
Cincinnati, OH 45267

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