Commentary

Integrating information at single synaptic connections

P. Read Montague
Division of Neuroscience, Baylor College of Medicine, Houston, TX 77030

One target of modern neuroscience research has been the nature of neural plasticity in the mammalian brain. Although it is difficult to assign reasons for such a focus, the intense interest in neural plasticity may have arisen because it raises the head in so many different contexts—e.g., development, learning, and behavior. In this fashion, it provides a unifying issue for research at multiple levels of description. This commentary will not deviate from this preoccupation with plasticity and will focus on the relationship between mechanisms of synaptic modulation and the kinds of information potentially available at single synaptic connections.

In the developing mammalian brain, activity-dependent mechanisms of synaptic function operate in part to organize spatial patterns of synaptic connections (1–4). This activity-dependent plasticity appears to be driven by regularities in patterns of neural activity that exist over developmental periods ranging from days to months. Long-term changes in synaptic function thought to influence this developmental plasticity resemble correlational or coincidence-detecting mechanisms known to induce long-term changes in synaptic strength in the hippocampus and cerebral cortex (5–8). Other work has shown that a similar kind of “coincidence-based” plasticity appears to operate on a much shorter time scale where changes in receptive field properties of neurons in the visual cortex can be induced during the course of a single experiment (9). A similar short-term plasticity has been demonstrated in an in vitro preparation of visual cortex (10). In the adult mammalian brain, rather dramatic plasticity in cortical organization has been observed on both short and long time scales (11).

Much of this work on neural plasticity has focused on how different pre- and postsynaptic events change transmission properties of glutamatergic connections. There are, however, other well-known influences of synaptic function—in particular, neuromodulatory systems. In the mammalian brain, neuromodulatory systems are known to influence developmental plasticity, synaptic plasticity, and ongoing learning and memory (e.g., see refs. 12–15). The neuromodulatory systems to which I refer are localized in small nuclei in the midbrain and basal forebrain and possess output connections that innervate widespread target regions and deliver various neurotransmitters—e.g., dopamine, norepinephrine, acetylcholine, and serotonin. Although there are many differences among these systems, they are sometimes collectively referred to as diffuse ascending systems. A variety of evidence from distinct levels of analysis has cast these systems as modulators of the state of target cells through their influence on both synaptic plasticity and cellular excitability.

Although experimental evidence supports a role for these systems in gating synaptic plasticity and influencing the transfer characteristics of target neurons, these two putative roles are not tantamount to a description of the kinds of information that could be carried by activity in these pathways. This is a critical consideration and serves to highlight the importance of the work reported in this issue by Huang and Kandel (16). I begin with a brief description of the Huang and Kandel result.

It is known that long-term potentiation (LTP) in area CA1 in the mammalian hippocampus exhibits both an early component, which is transient, and a later, longer-lasting component, which depends on cAMP cascades and protein synthesis. Dopamine has been implicated as a player in the late phase of LTP. In 1984, Gribkoff and Ashe (17, 18) reported that dopamine had a number of effects on transmission at the CA3 to CA1 connection in the mammalian hippocampus. These effects included a late, long-lasting potentiation of the population spike and increased neuronal excitability evinced by increased spontaneous activity. Later in 1991, Frey et al. (19) reported that blockers of the D1/D5 dopamine receptor could block the late stage of LTP. Huang and Kandel have put together these results with their own and shown that D1/D5 agonists alone can induce a long-lasting potentiation of the field excitatory postsynaptic potential that is occluded by potentiation induced by cAMP agonists. These effects depend on intact protein synthesis. The potentially important functions of LTP, dopamine action, and the constellation of effects that can ensue from either make this a notable and interesting result. This particular set of results becomes even more interesting when one considers a major source of the dopamine input to area CA1, the ventral tegmental area (VTA) and other mesencephalic dopamine nuclei. I focus on the VTA.

The VTA is a dopaminergic nucleus in the midbrain that is a major source of dopamine projections to limbic structures (20, 21) and to the prefrontal cortex (22). The VTA is also known to be a self-stimulation site (23) that appears to report on the reinforcing properties and/or behavorial salience of sensory stimuli (24). Over the past 9 years, Schultz and colleagues (24–27) have recorded successfully from VTA neurons in alert primates while the animals learned various conditioning tasks. These workers have shown that activity in a subset of VTA neurons appears to relate to elements of the learning tasks. This latter set of observations gives additional meaning to the results showing that dopamine can mediate the late component of LTP through cAMP production. If dopamine delivery to the hippocampus is directly related to identifiable elements of a learning task, then the changes in synaptic efficacy induced by dopamine delivery could also be interpreted in relation to elements of a learning task and the learning exhibited by the monkey.

What sort of information could mesolimbic dopamine delivery carry? To answer this question, some of the Schultz results (27) must be examined in more detail. A number of tasks given to the animals required them to depress one of two levers to receive a juice reward. Each lever was positioned in front of the animal underneath a green instruction light, which indicated which lever was to be depressed. A third centrally positioned yellow light acted as a trigger; when it was illuminated, the animal was permitted to reach out and depress the lever indicated by the green instruction light. In one task, the green instruction light came on for 1 sec and was extinguished. After a period randomly varying from 2.5 to 3.5 sec, the trigger light came on and the animal was permitted to reach out and depress a lever. Initially, before the task was learned, a substantial fraction of dopamine neurons responded to the delivery of the juice with a transient increase in firing rate. After learning, very few dopamine neurons responded to the delivery of reward; however, an increased number of these neurons responded to the most consistent...
predicators of reward—i.e., the instruction light and trigger light. This group was careful to show that the activity in these dopamine neurons did not relate to the metrics of movements associated with each learning task.

These results show that (i) neural pathways carrying information about reward can drive changes in VTA activity and this drive is modifiable, and (ii) neural pathways whose activity represents the instruction and trigger lights can drive changes in VTA activity and this drive is modifiable. One extremely interesting finding in this work was observed when monkeys made mistakes and depressed the lever that was not indicated by the instruction light. In these cases, the dopamine cell activity was replaced by a complete cessation in firing at the time that the reward would have been delivered had the monkey depressed the correct lever. A similar cessation in activity was not generally seen in naive monkeys learning the task, a time when numerous mistakes would be made. These findings show that the output of these dopamine neurons can reflect the exact timing of reward contingencies in the presence of sensory cues that predict reward. Such information would presumably be passed to target hippocampal neurons to influence synaptic plasticity onto these cells.

Recent theoretical work suggests that fluctuating activity levels in a subset of VTA neurons can be interpreted as representing information about future expectations of reward rather than simply “print now” or “learn now” signals that code for the time course and magnitude of rewarding stimuli (28, 29). In particular, this work demonstrates how activity in the cerebral cortex can make predictions about future cortical activity and future receipt of reward and how activity levels in mesencephalic dopamine systems could represent errors in these predictions (refs. 28 and 29; unpublished observations).

The possibility that changes in dopamine delivery to hippocampal cells carries information concerning expectations of future events raises a number of interesting interpretations of the fact that dopamine application alone can induce a long-lasting potentiation of the glutamatergic drive onto CA1 neurons. In this context, it is possible that the synaptic strength changes in the hippocampus could represent information about future receipt of reward. At this early stage, many interpretations are possible; however, looking at the Schultz and the Kandel results together enriches the interpretation of observations in both domains.

The results reported by Huang and Kandel (16) also raise an important mechanistic issue. These authors note that, in an in vitro slice preparation, the late phase of LTD is mediated by heterosynaptically delivered dopamine, then how is the release of dopamine accomplished by stimulating afferent glutamate fibers? Somehow the stimulation of glutamatergic input to CA1 is capable of eliciting dopamine release. The effect could be due to stimulated dopamine fibers or it could be mediated through the glutamate released during stimulation. In particular, the release of dopamine could be due to direct activation of N-methyl-D-aspartate (NMDA) or other glutamate receptors on quiescent dopamine terminals. Alternatively, glutamatergic activity could, through NMDA receptor activation, elicit the production of nitric oxide, which could stimulate the release of neurotransmitter from surrounding presynaptic terminals (30–33). The subsequent release and binding of dopamine to D1/D5 receptors would then result in the production of cAMP, which would induce the late potentiation that is observed. This latter possibility is consistent with the observation that cAMP increases in CA1 subsequent to tetanic stimuli are blocked by NMDA receptor blockers (34).

It is probably reasonable to think that any given small volume of cortical or hippocampal tissue is integrating enormous amounts of information from multiple sources—e.g., cholinergic input, dopaminergic input, thalamic input, intracortical or intrahippocampal input, etc. The nature of the information from each source may differ dramatically. This likelihood highlights the need to consider both mechanistic and informational constraints when designing experiments or building models to understand the function of any brain.

I thank Drs. John Dani and Jim Patrick for helpful insights, criticisms, and witicisms. This work was supported by National Institute of Mental Health Grant R01MH52797-01.