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Experience-Dependent Plasticity and the Maturation of Glutamatergic Synapses

Review

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Glutamatergic synaptic currents undergo a characteristic pattern of maturation during early development. This pattern involves changes in the kinetics of N-methyl-D-aspartate (NMDA) receptor currents and, possibly, the formation of "silent" synapses that express only NMDA receptor currents and are later made functional by the addition of α-amino-3-hydroxy-5-methyl-4-isoxazole-proprionate (AMPA) receptor currents. These maturational changes in glutamatergic synapses have implications for the early development of neural networks (Cline et al., 1996) and for the mechanisms underlying long-term potentiation (LTP) of synaptic efficacy (Malenka and Nicoll, 1997). Here, we suggest that this pattern of synaptic maturation also has important implications for understanding how already functional networks are adaptively modified by the experience of the individual animal during later stages of development and possibly into adulthood.

Early in development, functional circuits are established by axonal pathfinding, target selection, synaptogenesis, and activity-dependent refinement of synaptic connections. Later in development, these initial circuits may undergo extensive adaptive modification by sensory and motor experience. This late developmental period occurs while the animal is a juvenile, after basic neural circuits are established and functioning but before the onset of sexual maturity. This juvenile period is marked by a high capacity for learning (Konishi, 1989; Kuhl, 1994; Brainard and Knudsen, 1998).

The neural basis for this learning is experience-dependent modification of neural circuitry that can involve changes in both the efficacy of existing synapses and the patterning of anatomical connections. Increasing evidence demonstrates that experience-dependent changes in anatomical connectivity can be substantial during late development (Feldman and Knudsen, 1997) and even in adulthood (e.g., Bailey and Kandel, 1983; Darian-Smith and Gilbert, 1994; Florence and Kaas, 1995). Because such anatomical changes involve the formation of new synapses, understanding the maturation of synaptic transmission at newly formed synapses may provide important insight into how experience modifies already functioning neural circuits. In this review, we discuss our current understanding of the maturation of glutamatergic transmission in early development, and we apply these principles to propose a general model for the role of NMDA receptors and the maturation of glutamatergic synapses in experience-dependent modification of neural circuits.

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Early Development of Glutamatergic Synaptic Currents

The majority of fast excitatory neurotransmission in the CNS is mediated by ionotropic glutamate receptors, which are divided into NMDA, AMPA, and kainate receptor subtypes on the basis of the biophysical properties of their currents, their sensitivity to different pharmacological agents, and the classification of their subunits into distinct genetic families. Both AMPA and NMDA receptors are usually colocalized at individual synapses, so that the synaptic release of glutamate typically activates both AMPA and NMDA receptor currents on the postsynaptic neuron (Nicoll et al., 1990). However, the ratio of AMPA to NMDA currents at a given synapse depends on the identity and maturational stage of the synapse (e.g., Hestrin, 1992; Mooney, 1992; Isaac et al., 1995; Liao et al., 1995). During early development, several distinct changes in the properties of glutamatergic synaptic currents have been proposed to occur that alter this ratio of AMPA to NMDA receptor currents. Here, we discuss the functional implications of two of these changes.

Changes in the Kinetics of NMDA Receptor Currents

The first developmental change, which is supported by a large body of evidence, is that the amount of current passed by NMDA receptors is initially much greater than in adults and then declines rapidly with age and synaptic activity. This phenomenon was first observed in layers IV–VI of the kitten's primary visual cortex in vivo, where visual responses are initially highly sensitive to blockade by the NMDA receptor antagonist 2-amino-5-phosphonovaleric acid (AP5), and this sensitivity declines abruptly with visual experience during the first weeks of life (Tsumoto et al., 1987; Fox et al., 1989, 1992). A basis for this effect was suggested by subsequent in vitro experiments, which showed that synaptic responses of layer IV neurons in rat visual cortical slices exhibit an NMDA receptor current whose duration declines severalfold over the first postnatal month (Carmignoto and Vicini, 1992). Similar developmental decreases in NMDA receptor current duration have been observed during early development in other structures, including the lateral geniculate nucleus (Ramoa and McCormick, 1994), the thalamocortical synapse in somatosensory barrel cortex (Crair and Malenka, 1995), and the superior colliculus (Hestrin, 1992). The developmental reduction in NMDA receptor current duration must involve a modification of the NMDA receptor complex itself, since it is observed in excised membrane patches in response to glutamate application (Hestrin, 1992; Carmignoto and Vicini, 1992), and recent evidence suggests that it is likely to reflect a developmental switch in the subunit composition of the NMDA receptor (Monyer et al., 1994; Flint et al., 1997).

Thus, long-duration NMDA receptor currents give way to shorter-duration currents over the first few weeks of life, perhaps resulting from an activity-dependent switch in the subunit composition of the NMDA receptor. This progression would tend to cause a developmental reduction in the contribution of NMDA receptor currents to synaptic responses in vivo.

"Silent" Synapses during Early Development

A second change that has been proposed to occur during the maturation of glutamatergic synapses is more controversial, and involves an increase in AMPA receptor currents. A growing body of evidence suggests that early in development, many glutamatergic synapses express only NMDA receptor currents and lack AMPA currents entirely. Because the NMDA receptor passes current only at relatively depolarized postsynaptic membrane potentials due to a voltage-dependent blockade by magnesium ions (Nowak et al., 1984), these synapses generate little or no current when the postsynaptic cell is at a relatively hyperpolarized resting potential and thus have been termed "silent" synapses. Silent synapses can be revealed experimentally by depolarizing the postsynaptic cell above the threshold for NMDA receptor activation and observing an NMDA receptor current unaccompanied by an AMPA current. Synapses of this type are prevalent at early stages of development in several brain regions, including the optic tectum of *Xenopus laevis* (Wu et al., 1996), the rat's barrel cortex (Isaac et al., 1997), and the CA1 region of the rat's hippocampus (Isaac at al., 1995; Liao et al., 1995; Durand et al., 1996). In these systems, AMPA receptor currents begin to appear and increase in amplitude over the same time period as the changes in NMDA receptor currents described above. The appearance of AMPA receptor currents causes a rapid decrease in the number of silent synapses and a shift from synapses with purely NMDA receptor pharmacology to synapses with the mature combination of both AMPA and NMDA receptor currents.

The evidence supporting the existence of silent synapses in early development, though compelling, is not conclusive. An alternative explanation is that purely NMDAergic synapses do not exist, and instead, isolated NMDA receptor currents are observed when released glutamate diffuses to the synapse of interest from neighboring synapses on different postsynaptic cells. Such "spillover" of glutamate could selectively activate NMDA receptors, even if AMPA receptors coexist at the same synapse, because NMDA receptors have a higher affinity for glutamate than AMPA receptors, and the concentration of spilled-over glutamate would be relatively low (Kullmann and Asztely, 1998). In this view, the developmental reduction in the number of silent synapses would reflect a reduction in the amount of spillover occuring with age.

Although this issue has yet to be settled, a role for silent synapses as the starting point in the maturation of glutamatergic synapses remains quite attractive. This is in part because LTP of silent synapses causes the rapid appearance of AMPA receptor–mediated currents (Isaac et al., 1995, 1997; Liao et al., 1995; Durand et al., 1996), suggesting that ongoing LTP may occur during early development to cause the steady accumulation of AMPA receptor currents at young synapses. Because LTP is generally thought to be input specific, this mechanism would allow individual synapses that drive the postsynaptic cell appropriately to be made functional, while inappropriately targeted synapses would remain nonfunctional and therefore would not interfere with circuit function (Cline et al., 1996). An important test of this hypothesis that needs to be examined is whether treatments that prevent LTP induction result in the abnormal preservation of silent synapses during early development.

It should be noted that both of these phenomena, the change in the time course of NMDA receptor currents and the addition of AMPA receptor currents, make the proportion of synaptic current mediated by the NMDA receptor initially high and then decline with use. Thus, both phenomena may contribute to the changing relative contribution of AMPA and NMDA receptor currents to sensory responses in vivo. Indeed, for the thalamocortical synapse in rat barrel cortex and the retinotectal synapse in *Xenopus*, two systems in which both mechanisms have been examined, changes in both the proportion of silent synapses (Wu et al., 1996; Isaac et al., 1997) and the duration of NMDA receptor currents (Crair and Malenka, 1995; Cline et al., 1996) occur during the same early developmental period.

The Retinotectal Synapse in *Xenopus laevis*

These early maturational changes in glutamatergic synaptic physiology have been studied carefully at the retinotectal synapse in *Xenopus*. In *Xenopus* tadpoles, neurogenesis occurs in a restricted region at the caudal edge of the developing optic tectum, so that immature neurons are found in the caudal tectum and progressively more mature neurons are found further rostrally (Wu et al., 1996). This rostrocaudal developmental gradient allows glutamatergic synaptic maturation to be studied by recording from tectal neurons at different rostrocaudal locations in a single animal.

Using whole-cell voltage-clamp recording techniques, Wu et al. (1996) found that neurons in the caudal tectum, which were recently formed and morphologically immature, exhibited robust NMDA receptor currents but very low levels of AMPA receptor currents, with some neurons exhibiting no detectable AMPA receptor currents at all. In contrast, more mature neurons in the rostral tectum showed prominent AMPA receptor currents. Furthermore, by comparing synaptic failure rates at hyperpolarized and depolarized potentials, it is possible to estimate the fraction of synapses on each neuron that exhibit currents mediated solely by NMDA receptors. A strong correlation was observed between position along the rostrocaudal axis and the fraction of synapses exhibiting purely NMDAergic synaptic currents (Wu et al., 1996). Because the synapses onto immature cells in the caudal tectum are newly formed, these results support the hypothesis that many or all glutamatergic synapses are formed as purely NMDAergic, silent synapses, and that these synapses are then converted to synapses with both AMPA and NMDA receptor components. In this view, the small proportion of silent synapses that persists in the rostral, mature tectum may reflect the continuing formation of retinotectal synapses, which occurs throughout larval life (Cline et al., 1996). In addition, immature tectal neurons were found to have NMDA receptor currents with durations twice as long as those of mature neurons, confirming that changes in NMDA receptor kinetics also occur during this early developmental period (Cline et al., 1997).

Though these experiments demonstrate elegantly the maturational changes occurring at glutamatergic synapses during early development, they do not address the important functional question of whether these changes are use dependent and can therefore be regulated independently for each synapse, which would provide a powerful mechanism for adjusting the functional properties of developing networks (Cline et al., 1996), or whether instead these changes reflect the developmental stage of the postsynaptic neuron and therefore occur in parallel for all synapses onto a given tectal cell.

Development of Learned Auditory Responses in the Owl's Inferior Colliculus

The capacity for different synapses to mature independently has been suggested by experiments in the inferior colliculus of the barn owl (*Tyto alba*), where altered experience during late stages of development can cause the appearance of novel auditory responses mediated by newly functional synaptic inputs. Neurons in the owl's external nucleus of the inferior colliculus (ICX) are tightly tuned for binaural sound localization cues, including interaural time difference (ITD), the microsecond difference in arrival time of a sound at each of the owl's ears. ICX neurons are arranged into a map of ITD and receive input via a topographic projection from the central nucleus of the inferior colliculus (ICC), which contains a similar ITD map (Konishi et al., 1988).

The tuning of ICX neurons for ITD and other sound localization cues is calibrated by vision during a sensitive period that ends late in development, at the age of sexual maturity (Brainard and Knudsen, 1993, 1998). During the sensitive period, existing circuits can be substantially modified by altered visual experience. For example, when owls are subjected to a sustained horizontal displacement of the visual field by wearing prismatic spectacles, ICX neurons acquire novel auditory responses, termed "learned responses," to values of ITD outside of their normal tuning range (Brainard and Knudsen, 1993; Feldman and Knudsen, 1997). During the first few weeks of prism experience, many neurons simultaneously express both learned responses and responses to their normal ITD range ("normal responses") that had been expressed before prism attachment. This results in broad ITD tuning curves containing both types of responses. With additional prism experience, normal responses are eliminated and ITD tuning curves become centered on the learned response.

The acquisition of learned responses reflects synaptic modification occurring in the ICX (Brainard and Knudsen, 1993) and appears to involve a systematic anatomical change in the topography of the ICC–ICX projection, such that ICX neurons acquire abnormal inputs from locations in the ICC that encode the learned range of ITDs (Feldman and Knudsen, 1997). This finding strongly suggests that new synaptic connections develop to mediate learned responses. By comparing the pharmacology of learned responses, which are presumably mediated by circuits incorporating recently formed synapses, with that of normal responses, which are thought to be mediated by the preexisting ICX circuitry, it is possible to ask the question: is the development of glutamatergic synaptic transmission recapitulated when novel synaptic connections form as a consequence of experience-dependent plasticity late in development?

In vivo iontophoresis of glutamate receptor antagonists has shown that excitatory synaptic transmission of auditory responses in the ICX is mediated by both NMDA and non-NMDA, presumably AMPA, receptors (Feldman and Knudsen, 1994). In owls raised with normal vision, the proportion of auditory-evoked action potentials blocked by AP5 is constant across the entire range of ITDs to which a neuron responds, indicating that the relative contribution of NMDA and AMPA receptor currents to ICX responses (the NMDA/AMPA current ratio) is uniform across the synapses mediating these responses (Feldman and Knudsen, 1998). In contrast, in owls in which learned responses have been recently induced by prism experience, learned responses are much more sensitive to NMDA receptor antagonists than are normal responses expressed by the same ICX neurons (Feldman et al., 1996; Feldman and Knudsen, 1998). Both responses are equally sensitive to broad-spectrum glutamate receptor antagonists, however, indicating that synapses mediating learned responses have a higher NMDA/AMPA current ratio than synapses mediating normal responses. This increased NMDA/AMPA current ratio persists from the time learned responses first appear at about 80 days of age until the owls mature, at just over 200 days of age, when the NMDA/AMPA current ratio of learned responses declines to the same ratio exhibited by normal responses (Feldman and Knudsen, 1998).

Learned auditory responses in these juvenile owls therefore display a pharmacological profile that is similar to maturing glutamatergic synapses during early development: they initially exhibit a high NMDA/AMPA current ratio, and after an extended period this ratio declines to the value observed in the adult. Whether the high initial NMDA/AMPA ratio reflects an initial enhancement of NMDA receptor currents at synapses mediating learned responses, an initial paucity of AMPA receptor currents, or some other cause, is unknown. One possibility is that the synapses mediating learned responses form during prism experience as synapses with long-duration NMDA receptor currents, and that the duration of these currents then falls with age or synaptic activity. Another possibility is that synapses form during prism experience as silent synapses, and that learned responses develop when a subset of these silent synapses are reinforced by an LTP-like process, causing the appearance of enough AMPA receptor current to elicit a reliable postsynaptic response. Learned responses mediated by such synapses would be expected to have an NMDA/AMPA current ratio that is higher than that of the older, more mature synapses mediating normal responses on the same ICX neurons. With additional prism experience, more reinforcement could gradually occur, increasing the AMPA receptor component at these synapses until the NMDA/AMPA ratio falls to within the normal range. It should be noted that in both of these models, learning involves the formation of new synapses (either in a directed or a nondirected manner) and not simply the adjustment of the efficacy of existing synapses.

The attainment of normal pharmacology could also

be triggered by an extrinsic maturational signal related to the end of the juvenile period of enhanced plasticity, which closes at about the same age as when the NMDA/AMPA current ratio reaches the normal ratio (Brainard and Knudsen, 1998). Because this age is also coincident with sexual maturation, one candidate signal is the level of sex hormones, which increases when birds become sexually mature (Marler et al., 1987). Song learning in zebra finches is known to be regulated in this manner: low levels of steroid hormones are permissive for song learning when animals are juveniles, and when levels increase, either during normal sexual maturation or through experimental manipulation, song learning is arrested (Bottjer, 1991).

Implications for the Formation of Synapses during Late Development and in Adulthood

The findings discussed above have implications for synaptic transmission in structures that retain the capacity for synaptogenesis in the juvenile period and even into adulthood. Where synapse formation is ongoing, as in the optic tectum of larval *Xenopus* (Cline et al., 1996) and in the hippocampus of adult rats (Woolley and McEwen, 1992), the relative contributions of NMDA and AMPA receptors to normal synaptic transmission may reflect not only an intrinsic, age-dependent NMDA/AMPA ratio associated with synapses in that region, as is traditionally thought, but may also depend critically on the rate of ongoing synaptogenesis. Where synapse formation is induced by altered experience or loss of peripheral input (e.g., Darian-Smith and Gilbert, 1994; Florence and Kaas, 1995), the NMDA/AMPA current ratio would be predicted to vary with the amount of synaptic reorganization that is occurring.

This possibility suggests an intriguing hypothesis for why learned responses in the barn owl exhibit a high NMDA/AMPA current ratio for so long and return to an apparently normal ratio at an age corresponding to the end of the sensitive period of enhanced plasticity. One interpretation for the modification of ICC–ICX synaptic connectivity during the sensitive period is that ongoing synaptogenesis occurs in the ICX throughout this period, with new synapses that mediate learned responses being selectively retained. Because newly formed synapses have a relatively high NMDA/AMPA receptor current ratio, continual addition of newly formed synapses to mediate learned responses might keep the NMDA receptor–mediated proportion of these responses high as long as new synapses continue to be created. Only when synaptogenesis slows or comes to a halt, as might occur with the close of the juvenile period, would maturation of the existing synapses reduce the NMDA/AMPA current ratio of learned responses to the ratio observed for normal responses.

General Model for Glutamatergic Synaptic Maturation in Experience-Dependent Plasticity

Together, these observations suggest the following general hypothesis: during early development, neural networks are established by genetically specified cues and activity-dependent processes. Glutamatergic synapses that form during this period display a rapid, activity-dependent maturation of NMDA and AMPA receptor currents, so that by the time basic networks have been established, glutamatergic pharmacology is much like that observed in the adult. Subsequently, there occurs an extended, late period of development during which established networks are modified by experience, in part through the formation and selective stabilization of novel glutamatergic synapses. These novel synapses are created initially as either synapses with long-duration NMDA receptor currents and/or as silent, purely NMDAergic synapses, recapitulating the maturation of glutamatergic synaptic currents in early development. In either case, the high NMDA/AMPA current ratio of such synapses would be beneficial in enabling rapid activity-dependent adjustment of synaptic strength by NMDA receptor-dependent mechanisms (Katz and Shatz, 1996). If novel synapses were formed as silent synapses, an additional advantage would be gained: because synapses would be made functional only if they were appropriately targeted, the presence of inappropriate synapses would not adversely affect the performance of the preexisting circuit (Cline et al., 1996). Thus, large-scale adaptive adjustments could be made, for example, by nondirected axonal outgrowth and synapse formation, followed by the selective activation of appropriate synapses. In this model, network optimization could proceed without jeopardizing normal function, an essential feature if plasticity is to occur in a circuit that is necessary for the survival of the animal. This is certainly the case for the barn owl, in which ICX plasticity takes place at an age when juvenile owls have left the nest and depend on sound localization to find their prey. Finally, by the end of the late developmental period, which coincides with sexual maturation, the capacity for synaptogenesis is dramatically restricted, reducing the ability of many networks to adapt to novel changes in sensory or motor experience. Within the juvenile period, this restriction may occur earlier for low order networks and at progressively later ages for high order networks (Fox and Zahs, 1994).

A prediction of this model is that, except for brain regions in which the capacity for synaptogenesis persists throughout life, experience-dependent changes in neural circuits in the adult will be mediated primarily through changes in the efficacy of the synapses that exist at the end of the juvenile period. Thus, experience during the juvenile period may be critical in establishing the repertoire of connectional states available to the adult nervous system (Knudsen, 1998).

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