Tonic Activity of Metabotropic Glutamate Receptors Is Involved in Developmental Modification of Short-Term Plasticity in the Neocortex

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INTRODUCTION

Developmental modifications of synaptic properties are an important determinant of function in the immature brain. One important property, presynaptic release probability, decreases during postnatal development in many synapses of the CNS. This is supported by previous reports that short-term plasticity (STP) induced by paired- or multiple-pulse stimulation in these synapses generally shows depression at early stages of development, but this converts to facilitation at later stages. This switch in STP is accompanied by an increase in the rate of failure of action potentials to cause release of neurotransmitter from the presynaptic terminals (Bolshakov and Siegelbaum 1995; Choi and Lovinger 1997; Pouzat and Hestrin 1997; Kalnins and Sakmann 1999). The switch from short-term depression to short-term facilitation and the increase in the failure rate indicate a decrease in release probability in the maturing presynaptic terminal (Pananceau et al. 1998; Stevens and Wang 1995; Thomson 2000). However, the mechanisms that underlie this developmental change in release probability remain to be elucidated.

Metabotropic glutamate receptors (mGluRs) act as powerful regulators of synaptic transmission in the CNS (Anwyl 1999). At resting conditions, a low level of free glutamate exists in the perisynaptic extracellular space (Danbolt 2001). This ambient glutamate could act on some mGluRs because of their high affinity to glutamate (Meldrum 2000). Recently, it was reported that blocking mGluRs enhanced the baseline synaptic response in both glutamatergic and GABAergic synapses in the CNS. This was accompanied by a decrease in paired-pulse facilitation (Bandrowski et al. 2003; Cao et al. 1997; Losonczy et al. 2003; Piet et al. 2003; Schrader and Tosker 1997), implying that tonic activity of presynaptic mGluRs regulates the release probability of synapses. However, the physiological relevance of tonic mGluRs activity in the developing brain has not been explored.

Ambient glutamate concentration is mainly controlled and regulated by glutamate transporter activity and extracellular space (Danbolt 2001). Blockade of glutamate transporters increases ambient glutamate concentration and presynaptically reduces baseline synaptic transmission. This reduction of baseline synaptic transmission is blocked by mGluR antagonists and mimicked by application of glutamate (Kidd and Isaac 2000; Maki et al. 1994; Oliet et al. 2001). The activity of transporters is likely age dependent as the effect of blockade of glutamate transporters on synaptic transmission was not found in the mature slice (Isacson and Nicoll 1993). This age dependence was further supported by the finding that expression of glutamate transporters in neocortex is regulated developmentally (Furuta et al. 1997). In addition, the extracellular space around the synapse also undergoes developmental changes as it has been reported to be larger in immature brain compared with mature brain (Tashiro et al. 2003; Vaughn 1989).

We hypothesized that the ambient glutamate concentration is subject to developmental regulation and would increase during cortical maturation. Acting via mGluRs, this would result in reduction of release probability during postnatal cortical development. To test this hypothesis, we have studied the effect of modulators of mGluRs and glutamate transporters on glutamatergic synaptic transmission and STP at different stages of development, which is the subject of this report.
postnatal cortical development. We found that tonic activity of mGluRs receptors increased during development, and the increase was, in part, due to a developmental decrease in glutamate transporter activity.

**METHODS**

Coronal brain slices were obtained from 13- to 42-day-old rats using procedures described previously (Roper et al. 1997). The animal was anesthetized by inhalation of isoflurane and decapitated, and the brain was rapidly removed. Slices (400-μm thick) were cut at the rostrocaudal level of the anterior commissure using a Vibratome (Technical Products International, St. Louis, MO). Slices were incubated on cell culture inserts (8 μm pore diameter, Becton Dickinson, Franklin Lakes, NJ) covered by a thin layer of artificial cerebrospinal fluid (ACSF, see following text) containing 1 mM Ca²⁺ and 6 mM Mg²⁺ and surrounded by humidified 95% O₂-5% CO₂ atmosphere at room temperature (22°C). For recording, a single slice, after ≥1 h incubation, was transferred to a submerged recording chamber with continuous flow (2–3 ml/min) of ACSF that contained (in mM) 124 NaCl, 26 NaHCO₃, 1.25 NaH₂PO₄, 2.5 KCl, 2 CaCl₂, 1 MgCl₂, and 10 glucose, gassed with 95% O₂-5% CO₂ giving pH 7.4. All experiments were carried out at room temperature (22°C).

Whole cell recordings were made from pyramidal neurons in layer IV/V of neocortex under visual control using infrared differential interference contrast (IR-DIC) videomicroscopy with a fixed-stage microscope (Axioskop-FS; Zeiss, Oberkochen, Germany) equipped with a 40×, 0.8-W water-immersion objective. Patch electrodes had a resistance of 3–5 MΩ when filled with internal solution containing (in mM) 120 K-glucuronate, 8 NaCl, 10 HEPES, 4 MgATP, 0.3 Na,GTP, and 0.2 EGTA (pH = 7.3 with KOH, osmolarity = 290–300 mOsm). Pyramidal neurons were identified by their triangular somata, a single apical dendrite and regular spiking pattern in response to a depolarizing current pulse in current-clamp configuration. Some recorded neurons were further characterized by successful biocytin staining using 0.1% biocytin in the electrode filling solution. Neurons were voltage-clamped at −68 mV using an Axopatch 1D amplifier (Axon Instruments, Foster City, CA). GABAergic input was blocked by adding the GABA_{α} receptor blocker, picrotoxin (50 μM, Sigma, St. Louis, MO) to the bath solution.

To evoke monosynaptic excitatory postsynaptic currents (EPSCs), a glass electrode (3–5 MΩ) filled with ACSF was placed in layer IV/V 50–70 μm away from the cell bodies that were being recorded. Five-pulse trains at 20 Hz were given to elicit EPSCs. The interval between trains was 10 s. Monosynaptic currents were identified by their constant latency and a single peak for all five responses. Stimulation strength was adjusted to induce the first response with an amplitude ~100 pA. For minimum stimulation, the intensity of stimulation was adjusted to have two to three failures in each 5-pulse train. Series resistance (14–25 MΩ) was monitored continuously by applying a hyperpolarizing pulse before each stimulus. The recordings were discarded if a change of series resistance ~10% occurred. (2S,2′R,3′R)-2-((2′,3′-dicarboxycyclopentyl)glycine (DCG-IV; Tocris Cookson, Ballwin, MO), L-1-(+)-2-amino-4-phosphonobutyric acid (L-AP4; Tocris Cookson), L-trans-pyridoline-2,4-dicarboxylate (tPDC; Sigma) and dihydrokainate (DHK; Sigma) were first dissolved in water as stock solution and then diluted into bath solution to the desired concentration. 2S-2-amino-2-(1S,2S-2-carboxycycloprop-1-yl)-3-(xanth-9-yl) propanoic acid (LY341495; Tocris Cookson) was dissolved in 100% dimethyl sulfoxide (DMSO; Sigma). The final concentration of DMSO in bath solution was <0.01%. At this concentration, DMSO did not affect synaptic transmission. In experiments where tPDC and DHK were used, bi-2-amino-5-phosphonopentanoic acid (AP5, 50 μM, Tocris Cookson) was added in solution to block N-methyl-D-aspartate (NMDA) receptors. Data were acquired and stored using pClamp 8 (Axon Instruments) and analyzed using Clampfit 8 and Origin 6 software. Short-term plasticity was quantified by normalizing the amplitude of all five responses to that of the first response. All values were expressed as means ± SE. The paired or unpaired Student’s two-tailed t-test was used to test the significance of changes. Statistical significance was set at P < 0.05.

Slices containing biocytin-filled cells were kept in 4% paraformaldehyde overnight at 4°C, rinsed in PBS (0.1 M) two times for 30 min, and then incubated in 0.1% ExtraAvidin peroxidase (Sigma) in PBS solution overnight. Slices were treated with 3% H₂O₂ for 5 min, rinsed with PBS and acetate buffer, and then reacted for 10 min with a solution of 0.5 mg/ml 3,3′-diaminobenzidine (Sigma), 4%Ni-DAB chromagen and 0.2 μl/ml 30% H₂O₂ in sodium acetate buffer. Slices were then rinsed in sodium acetate buffer, dehydrated, mounted onto slides, and coverslipped.

**RESULTS**

**Short-term plasticity switched from depression to facilitation during postnatal development**

We performed whole cell recordings from layer IV/V pyramidal neurons and monosynaptic EPSCs were evoked by 5-pulse (20 Hz) train stimulation. In agreement with previous reports (Reyes and Sakmann 1999), we found that STP at the early stage of development (P13–17) consistently showed depression. However, the depression gradually switched to facilitation during the first month of postnatal development. By P28, STP showed facilitation of responses two to five in the train, as illustrated in Fig. 1, A and B. In agreement with
previous work (Reyes and Sakmann 1999), our data with minimal stimulation showed an increase in the failure rate during development, which is inversely correlated with short-term depression (data not shown). Because STP is determined largely by presynaptic mechanisms (Pananceau et al. 1998), our results support the idea that the release probability of CNS synapses is downregulated during postnatal development (Bolshakov and Siegelbaum 1995; Choi and Lovinger 1997; Pouzat and Hestrin 1997; Reyes and Sakmann 1999).

**Activation of presynaptic mGluRs suppressed EPSCs at both developmental stages**

Synaptic transmitter release is strongly regulated by presynaptic mGluRs. Among eight types of mGluR, mGluR2/3 has been extensively studied both in hippocampus and cortex and has been consistently shown to depress synaptic response by reducing release probability (Anwyl 1999; Schoepp 2001). We tested the effect of activation of mGluR2/3 on synaptic transmission using the agonist, DCG-IV, to see if it changed during postnatal development. We found that application of DCG-IV (2–4 μM) reversibly suppressed stimulus-evoked EPSCs at both P13–17 and P28–42 (Fig. 2, A and B). As shown in Fig. 2C, it suppressed the first EPSC to 37% of control in the younger group (n = 9) and to 31% of control (n = 10) in the older group. This effect was not different between the two age groups (P > 0.05). As shown in Fig. 2C, the effect of DCG-IV on EPSC amplitude and STP was completely blocked by LY 341495 (2 μM, n = 5 for P13–17, n = 7 for P28–42). As illustrated in Fig. 2, A and B, DCG-IV produced a conversion of short-term depression into short-term facilitation at the early stage and a further increase in facilitation at the late stage. In an attempt to address issues of specificity between group II and group III mGluRs, we examined the effect of t-AP4, a group III-specific activator on EPSP amplitude. At P13–17, t-AP4 (50 μM) produced a modest reduction in amplitude of the initial EPSCs (84 ± 3% of pretreatment, n = 11, P < 0.05). A similar effect was seen at P28–42 (87 ± 4% of pretreatment, n = 9, P < 0.05).

**Antagonism of mGluRs enhanced EPSCs at P28–42 but had no effect at P13–17**

We used a LY341495, an mGluR antagonist that is most potent at mGluR2/3 (Kingston et al. 1998), to test the effect of tonic activity of mGluRs on synaptic transmission and STP. LY341495 (2 μM) rapidly, reversibly, and significantly enhanced the amplitude of evoked EPSCs in most of cells recorded at the late stage (P28–42), although the magnitude of the enhancement varied from cell to cell (Fig. 3B). On average, the amplitude of the first EPSC was enhanced by 31% (n = 17, P < 0.05; Fig. 3I). This enhancement was accompanied by a significant decrease in short-term facilitation (Fig. 3, C and G), with some cells even converting from facilitation to depression, indicating an increase in release probability. The decrease of short-term facilitation was inversely correlated with the enhancement of the first EPSC (Fig. 3H). However, LY341495 had no significant effect on either EPSC amplitude or STP at the early stage (P13–17), as shown in Fig. 3, D–F. On average, the amplitude of the first EPSC at P13–17 was 101% of control after LY341495 (n = 14; Fig. 3I). These results indicated that the effect of LY341495 was age dependent. We then examined the effect LY431495 on EPSCs at an intermediate age (P19–P25). As shown in Fig. 3I, at P19–25, LY 341495 had a relatively small but significant effect. On average, it enhanced the first EPSC amplitude to 114% of control (n = 13, P < 0.05). These results indicated that there is a progressive increase in tonic activity of mGluRs during development.

![Figure 2](http://jn.physiology.org/)

**FIG. 2.** Activation of metabotropic glutamate receptors 2/3 (mGluR2/3) receptors by (2S,2R,3'R)-2-(2,3'-dicarboxycyclopropyl)glycine (DCG-IV) depresses EPSCs at both early and late stages of postnatal development. A: data from a representative neuron shows that DCG-IV (2 μM) reduced EPSC amplitude at the early stage (P13–17). After application of DCG-IV, STP turned from depression (white circle) to facilitation (black circle). Calibration bar: 50 pA/50 ms. Inset: superimposed traces from the cell before (thin trace) and after (thick trace) DCG-IV. B: data from a representative neuron show that, at the later developmental stage (P28–42), DCG-IV reduced EPSC amplitude and enhanced the magnitude of short-term facilitation. Inset: superimposed traces from the cell before (thin trace) and after (thick trace) DCG-IV. C: group data showing reduction in amplitude of the first EPSC by DCG-IV at both stages (n = 9 for P13–17, n = 10 for P28–42). 2S-2-amino-2-(1S,2S-2-carboxycycloprop-1-yl)-3-(xanth-9-yl) propanoic acid (LY341495; 2 μM), a potent mGluR2/3 antagonist, blocked the effect of DCG-IV at both stages (n = 5 for P13–17; n = 7 for P28–42). Asterisks, a significant difference from the pretreatment condition (P < 0.05).

![Figure 3](http://jn.physiology.org/)
Blockade of glutamate transporter activity depressed synaptic responses in at P13–17 but not at P28–42

Tonic activity of mGluRs is maintained by ambient glutamate in the extracellular space. Our results suggested that ambient glutamate levels might be higher in the more mature animals (P28–42) than in the immature group (P13–17). Two major factors regulate the ambient glutamate concentration: glutamate transporters and the size of the extracellular space (Danbolt 2001). We tested a possible role for glutamate transporters using the glutamate transporter inhibitor, tPDC. tPDC is a potent, but nonspecific, inhibitor of both glial and neuronal glutamate transporters (Bridges et al. 1991). As shown in Fig. 4, A–D, tPDC (300 μM) significantly decreased the amplitude of the first EPSC and reduced short-term depression at P13–17 (13 of 16 neurons). The average amplitude of the first EPSC was depressed to 73% of control (n = 16, P < 0.05; Fig. 4F). The reduction of short-term depression was negatively correlated with the change in amplitude of the first EPSC (r = 0.84).

FIG. 3. LY341495, an antagonist of mGluRs, enhanced EPSC amplitude and reduced facilitation at the late stage (P28–42) but had no effect at the early stage (P13–17). A: data from a representative neuron at P13–17 were taken during 5-pulse stimulation at the time indicated by “a” and “b” in B. Each trace represents an average of 20 consecutive trials. Calibration bar: 50 pA/50 ms. B: data from the same neuron demonstrate that application of LY341495 (2 μM) increased EPSC amplitude at the late stage. C: data from the same cell as A and B show that short-term facilitation was reduced by LY341495 (○, pretreatment; ●, posttreatment). D: data from a representative neuron at the early stage (P13–17) were taken during 5-pulse stimulation at times marked by “a” and “b” in B. Each trace represents an average of 20 consecutive trials. Calibration bar: 50 pA/50 ms. E: data from the same neuron show that application of LY341495 had no effect on EPSC amplitude in the P13–17 group. F: data from the same neuron as D and E show that STP was not affected by LY341495 at P13–17 (○, pretreatment; ●, posttreatment). G: group data from P28–42 animals confirm that short-term facilitation was reduced by LY341394 (○, pretreatment; ●, posttreatment; Ⅺ, posttreatment; n = 17). H: group data from P28–42 neurons before and after exposure to LY341495 show an inverse correlation between percentage change in amplitude of the initial EPSC and the percentage change in amplitude of EPSC2 relative to EPSC1 (r = –0.84). I: group data showing the effect of LY341495 on amplitude of the first EPSC at different stages of postnatal development (P13–17, n = 14; P19–25, n = 13; P28–42, n = 17). *, a significant difference from the pretreatment condition (P < 0.05).

FIG. 4. Blockade of glutamate transporter activity reduces EPSC amplitude and short-term depression at an early stage (P13–17) but has no effect at a later stage (P28–42) of postnatal cortical development. A: data from a representative neuron at P13–17 were taken during 5-pulse stimulation at the time indicated by “a” and “b” in B. Each trace represents an average of 20 consecutive trials. Calibration bar: 50 pA/50 ms. B: data from the same neuron show that application of trans-pyrrolidine-2,4-dicarboxylate (tPDC; 300 μM) reduces EPSC amplitude. C: data from the same cell as A and B show that tPDC converted short-term depression to short-term facilitation (○, pretreatment; ●, posttreatment). STP was measured based on an average of 20–30 consecutive trials before and after treatment. D: group data at P13–17 confirm the effect of tPDC on STP at this age (○, pretreatment; ●, posttreatment; n = 16). E: group data at P13–17 before and after exposure to tPDC show a negative correlation between the percentage change in amplitude of EPSC1 and the percentage change in amplitude of EPSC2 relative to EPSC1 (r = –0.88; n = 16). F: group data show the effect of tPDC on EPSC amplitude at different ages (P13–17, n = 16; P21–25, n = 11; P28–42, n = 11), LY341495 blocked effect of tPDC at P13–17 (n = 7). *, a significant difference from the pretreatment condition (P < 0.05).
potential might re
1991; Maki et al. 1994). Therefore this effect on the membrane
cortical pyramidal neurons. Antagonism of mGluRs reduced
regulation of release probability in excitatory synapses of
activity plays an important role in the developmental down-
ning, that blockade of glutamate transporters reduced syn-
aptic responses and short-term depression at P13–17 but had no
effect at P28–42, indicates that diminished transporter activity
may contribute to higher ambient glutamate levels in the
mature neocortex.

Previous immunocytochemical and morphological data add
support to the proposition that ambient glutamate levels may
rise during postnatal neocortical development. Glutamate
transporters and size of the extracellular space are major
factors controlling the concentration of ambient glutamate
(Danbolt 2001). Both of them appear to undergo developmental
changes. It has been reported, in rat cortex, that expression of
the neuronal glutamate transporter reaches a maximum at
P5–16, then decreases with further maturation (Furuta et al.
1997). In addition, extracellular space around the synapses is
much larger in immature cortex compared with mature cortex,
thus promoting diffusion of glutamate (Tashiro et al. 2003;
Vaughn 1989). Smaller extracellular space and more complex
structures around synapses in mature cortex constrain the free
diffusion of glutamate and this would promote higher ambient
 glutamate concentrations around presynaptic terminal. The
sensitivity and density of presynaptic mGluRs may also affect
the tonic activity of mGluRs. However, it is not clear if the
sensitivity and density of mGluRs also undergo developmental
modification. Our current result, that an agonist of mGluR2/3
(DCG-IV), in the same concentration, depressed stimulus-
evoked EPSCs to a similar extent at P13–17 and P28–42,
suggests that changes in sensitivity or density of mGluRs might
not account for our findings. But we cannot rule out this
possibility based on our current data.

It appears that the activity of presynaptic mGluRs differen-
tially regulates synaptic transmission under different physio-
logical conditions with different demands. When synapses are
intensively stimulated, presynaptic mGluRs receptors can re-
spond to the increase of glutamate in the synaptic cleft and act
to prevent excessive increases in excitation (Scanziani et al.
1997). On the other hand, under resting conditions, mGluRs
can be tonically activated by ambient glutamate, which may
play an important role in setting the initial release probability
of cortical synapses. Different types of mGluRs have distinct
localization within the presynaptic terminal, indicating each
type might have distinct functional roles (Cartmell and Scho-
epp 2000; Lujan et al. 1997). mGluR2/3s are localized to the
preterminal axons and have a higher affinity for glutamate than
most other mGluRs (Meldrum 2000). Thus mGluR2/3 may be
better suited to sense low ambient glutamate levels and regu-
late initial release probability.

Our present results indicate that tonic activity of mGluRs is
subject to developmental regulation. This could help reconcile
perceived inconsistencies in previous studies that did not find
tonic activity of mGluRs (Kidd et al. 2002; Scanziani et al.
1997) due to the fact that, in those studies, immature animals
were used. It appears that the maturation of CNS synapses is
characterized by a progressive lowering of release probability.
It may be that higher release probabilities provide an important
 trophic effect in immature cortex where synapse formation is
important. Conversely, low release probabilities in mature
cortex may confer a wider dynamic range on the synapses, thus
promoting functional plasticity, and help in stabilizing the
neural network.

In any pharmacological study, issues of specificity are im-
portant to consider when interpreting results. Although it is
most potent at mGluR2/3, L341495 at a concentration of 2
µM likely blocks the group III mGluRs, mGluR6–8, as well
(Kingston et al. 1998). However, it has been reported that
mGluR6 is confined almost entirely to the retina (Nakajima et
al. 1993). mGluR7 is highly expressed in cerebral cortex and
localized in active zones of presynaptic terminal (Bradley et al.
1998). But glutamate has a low affinity at mGluR7 (EC50 >
0.5 mM; thus at resting conditions, it may not be activated by ambient glutamate concentrations of 0.5–2 μM (Cartmell and Schoepp 2000; Meldrum 2000). mGluR8 is highly expressed in the olfactory bulb and, to a lesser extent, in the cerebral cortex (Duvoisin et al. 1995). Similar to mGluR2/3, mGluR8 has a high affinity for glutamate and may also be localized in presynaptic terminals (Schoepp 2001). Therefore it is possible that presynaptic mGluR8 is tonically activated at resting conditions and plays a role in reducing transmitter release probability. However, we observed that L-AP4, a group III mGluR-specific agonist at 50 μM, only slightly reduced evoked-EPSC amplitude. At this concentration of L-AP4, mGluR8s should be maximally activated (Cartmell and Schoepp 2000). Therefore we feel that mGluR2/3s are primarily responsible for the effects that are being reported in this article and this is consistent with other reports on the effects of group II mGluRs on synaptic activity in the neocortex (Bandrowski et al. 2003). However, mGluR8 activity may be contributing to our findings as well.

Similar issues of specificity can be raised in connection with glutamate transport blockers. tPDC was chosen in the present study because it is reported to be the most potent and specific in blocking glutamate transporter activity. In comparison, another commonly used glutamate uptake inhibitor, DHK, is less potent and has been shown to act directly on postsynaptic glutamate receptors (Bridges et al. 1991; Isaacscon and Nicoll 1993; Maki et al. 1994). We also found that DHK caused a depolarization that was not blocked by the NMDA receptor antagonist, AP-5, suggesting an action on postsynaptic AMPA receptors. Our results showed that blocking glutamate transporters, on average, reduced short-term depression at P13–17 but did not convert it to the facilitation that was seen in mature cortex. This indicates that other factors are also important in the developmental regulation of ambient glutamate concentration. This is plausible because developmental changes in the extracellular space could also play a major role in reducing ambient glutamate concentration. Glutamate transporters are localized in both neuron and glial cells (Danbolt 2001). While our results here give no direct information about which type of glutamate transporter accounts for our result, the neuronal glutamate transporter is the most likely candidate because it undergoes a developmental change as indicated in previous immunocytochemical work (Furuta et al. 1997). Some early work on brain slices from adult animals did not detect a consistent and significant effect on synaptic transmission by blocking glutamate transporters (Hestrin et al. 1990; Isaacscon and Nicoll 1993). But in culture preparations and younger animals, blocking glutamate transporter activity clearly decreases synaptic responses (Kidd and Isaac 2000; Maki et al. 1994). Our results would suggest that one explanation for this discrepancy would be an age-dependent reduction in activity of glutamate transporters.

Other factors could be contributing to altered ambient glutamate levels in the slices. One possibility is that the older slices were less healthy and, therefore their homeostatic mechanisms for extracellular glutamate were impaired. It is recognized that it is more difficult to get healthy slices from older animals than from younger ones. Although we recorded from deep (30–90 μm beneath the surface of the slice) and healthy cells to eliminate the effect caused by the damage during the slice preparation; we cannot rule out the possibility that tissue trauma caused a decrease in the function of glutamate transporters. In vivo developmental studies would be important to address this issue.

In summary, our results show that tonic activity of mGluRs is an important factor in maturation of synaptic function in the neocortex. This increase in tonic activity is due, in part, to a decreased activity of glutamate transporters. These findings contribute to our understanding of how excitatory synapses go from high release probability with short-term depression to low release probability with short-term facilitation. This appears to be an important step in the functional maturation of excitatory synapses in the neocortex. Ultimately, this may have important implications for our understanding of the dynamic functional differences between mature and immature cortex.

G R A N T S

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R E F E R E N C E S


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