Glutamate transport by the excitatory amino acid transporters (EAATs) is coupled to the co-transport of 3 Na\(^+\) ions and 1 H\(^+\) and the counter-transport of 1 K\(^+\) ion, which ensures that extracellular glutamate concentrations are maintained in the submicromolar range. In addition to the coupled ion fluxes, glutamate transport activates an uncoupled anion conductance that does not influence the rate or direction of transport but may have the capacity to influence the excitability of the cell. Free Zn\(^{2+}\) ions are often co-localized with glutamate in the central nervous system and have the capacity to modulate the dynamics of excitatory neurotransmission. In this study we demonstrate that Zn\(^{2+}\) ions inhibit the uncoupled anion conductance and also reduce the affinity of L-aspartate for EAAT4. The molecular basis for this effect was investigated using site-directed mutagenesis. Two histidine residues in the extracellular loop between transmembrane domains three and four of EAAT4 appear to confer Zn\(^{2+}\) inhibition of the anion conductance.

Glutamate is the predominant excitatory neurotransmitter in the mammalian brain, and excitatory amino acid transporters (EAATs)\(^1\) serve the role of controlling extracellular glutamate concentrations to maintain normal neurotransmission. Five different glutamate transporters have been identified in humans, termed EAAT1–5 (1–3). The rat homologues of EAAT3 and GLT1 subtypes where glutamate transport (2, 9). The magnitude of the uncoupled anion flux relative to the glutamate-coupled ion fluxes varies with the different transporters, with the anion flux greatest for EAAT4 and EAAT5, followed by EAAT1 and then EAAT3 and EAAT2. Thus, electrophysiological measurements of glutamate transport have components derived from the ion-coupled transport conductance and the uncoupled chloride conductance. Zn\(^{2+}\) is found in a number of regions of the brain, with >90% bound to proteins such as various Zn\(^{2+}\) finger proteins. CHE-
Zn$^{2+}$ Modulation of Glutamate Transport

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Fig. 1. Alignment of the amino acid sequences of selected human and salamander glutamate transporters in the region of the putative Zn$^{2+}$ binding domain.

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In the presence of Zn$^{2+}$ was apparent at both positive and negative membrane potentials, the reduction in current amplitude was greater at positive potentials. A slightly different result was obtained for L-glutamate-evoked currents. In the absence of Zn$^{2+}$, L-glutamate generates a conductance ~50% of the conductance evoked by L-aspartate (Ref. 2, see Fig. 2B). In the presence of 100 μM Zn$^{2+}$, the reduction in the L-glutamate-evoked conductance was only apparent at positive potentials with little or no change in conductance at negative potentials (Fig. 2B). In subsequent experiments on EAAT4 and the various mutants of EAAT4, we have presented the results for the effects of Zn$^{2+}$ on L-aspartate-evoked conductances, because the larger conductance changes are more reliably measured than for L-glutamate and the extent of Zn$^{2+}$ modulation of the currents is greater. The onset of inhibition by Zn$^{2+}$ was rapid and reversible with washoff of Zn$^{2+}$ from the bath solution, which suggests a direct interaction between Zn$^{2+}$ and the transporter.

Inhibition of substrate-evoked currents by Zn$^{2+}$ could be due to inhibition of the coupled transport conductance or inhibition of the uncoupled anion conductance or both conductances. Under the conditions of this experiment and assuming that the stoichiometry of ion flux coupling for EAAT4 is the same as for EAAT3 and GLT1, a net inward flux of L-glutamate or L-aspartate is expected at membrane potentials up to +60 mV, and therefore any outward current at positive potentials is caused by the uncoupled anion conductance. The reduction in outward current at positive membrane potentials suggests that Zn$^{2+}$ inhibits the anion conductance. If the extracellular chloride ions are replaced with the more permeant anions bromide, iodide, or nitrate, significantly greater L-aspartate-evoked outward currents are observed, with a relative order of magnitude (and relative current amplitude at +60 mV) of NO$_3$ (>8.3) > Br$^-$ (3.75) > Cl$^-$ (1.0). Although 100 μM Zn$^{2+}$ reduced the anion conductance for all 4 anions, the degree of reduction varied, with the greatest reduction observed for iodide (76 ± 2%, n = 4), followed by chloride (66 ± 3%, n = 7) and bromide (66 ± 7%, n = 4) and with the smallest reduction observed for nitrate (48 ± 4%, n = 5) (Fig. 3B). In each case there was no significant change in reversal potential measured in the presence and absence of 100 μM Zn$^{2+}$. These results are consistent with Zn$^{2+}$ inhibiting the uncoupled anion conductance, and although there are variations in the extent of inhibition for different anions, Zn$^{2+}$ does not alter the relative anion permeability.

To measure the effects of Zn$^{2+}$ on the ion-coupled transport conductance, oocytes expressing EAAT4 were incubated in a buffer in which chloride ions were completely replaced with the impermeant anion gluconate for >40 h. This procedure has been reported to reduce the intracellular chloride concentration of the oocyte to <4 mm (9) and allows transport conductances to be measured in the absence of a significant uncoupled anion conductance. Application of L-aspartate to oocytes in chloride-free buffer generates inward currents at potentials up to +60 mV, as opposed to an outward current measured under standard conditions. At ~60 mV, currents measured under both chloride-free and standard conditions were inward but differed in relative amplitude. The L-aspartate-evoked current measured under chloride-free conditions was 15 ± 3 nA (n = 7) compared with 74 ± 8 nA (n = 3, from the same batch of oocytes) under standard conditions, which confirms previous observations that under standard conditions a majority of the L-aspartate-evoked conductance is caused by activation of a chloride conductance. Under chloride-free conditions, co-application of 100 μM Zn$^{2+}$ with 100 μM L-aspartate generated a similar conductance compared with 100 μM L-aspartate alone.
Zn\(^{2+}\) Modulation of Glutamate Transport

**Fig. 2.** Zn\(^{2+}\) inhibits the substrate-activated conductance of EAAT4. Current voltage plots of substrate elicited conductances of EAAT4 measured in the presence of Zn\(^{2+}\) (I\(100\ \mu M\) substrate + 100 \(\mu M\) Zn\(^{2+}\) in buffer) − I(buffer); squares. l-aspartate elicited conductances (A) and l-glutamate elicited conductances (B) measured in standard ND96. The data presented in both A and B are normalized to the current elicited by 100 \(\mu M\) l-aspartate at −100 mV and represent mean currents ± S.E. from five cells.

(Fig. 3C), which suggests that Zn\(^{2+}\) has no effect on the coupled transport component of the currents mediated by EAAT4. Thus, Zn\(^{2+}\) inhibition of the substrate-gated conductance of EAAT4 is most likely to be due to inhibition of the uncoupled anion conductance.

In further experiments on EAAT4 and EAAT4 mutants, we have not distinguished between the coupled transport and the uncoupled anion components of the conductance and have assumed that Zn\(^{2+}\) has a selective effect on the uncoupled anion conductance. The EC\(_{50}\) for l-aspartate activation of the chloride conductance measured in the presence of 100 \(\mu M\) Zn\(^{2+}\) (5.1 ± 0.5 \(\mu M\), n = 7) was increased compared with the EC\(_{50}\) measured in the absence of Zn\(^{2+}\) (3.4 ± 0.5 \(\mu M\), n = 7, p = 0.05 2-tailed t test) (Fig. 4A), which suggests that Zn\(^{2+}\) modulates the interaction between l-aspartate and EAAT4. At −100 mV, Zn\(^{2+}\) caused a maximal inhibition of 58 ± 10\% (n = 4), whereas at +60 mV a maximal dose of Zn\(^{2+}\) inhibited the current by 81 ± 5\% (n = 4) (Fig. 4B). The IC\(_{50}\) values for Zn\(^{2+}\) inhibition of the anion conductance also differed at the different membrane potentials. At −100 mV, the IC\(_{50}\) was 86 ± 29 \(\mu M\) (n = 4) and at +60 mV the IC\(_{50}\) was 38 ± 10 \(\mu M\) (n = 4).

**Fig. 3.** Zn\(^{2+}\) selectively inhibits the anion conductance of EAAT4. A. l-aspartate elicited conductances measured as in Fig. 2, but in a buffer in which 96 mM NaCl was replaced with 96 mM NaI. The data represent the mean currents ± S.E. from four cells and in for each cell the current measurements are normalized to the current because of 100 \(\mu M\) l-aspartate at 0 mV. B, the percent reduction in slope conductance (over the range 0–40 mV) because of 100 \(\mu M\) Zn\(^{2+}\) in which the 96 mM NaCl in the extracellular buffer was changed to 96 mM NaBr, NaI, or NaNO\(_3\). C, l-aspartate elicited conductances measured from oocytes that had been incubated in a chloride-free buffer (gluconate substituted for chloride) for >40 h prior to recording. Recordings were then made in the same chloride-free buffer. Data represent the mean ± S.E. of current measurements from five cells.

Mutations of Histidine 154 and Histidine 164 Abolish Zn\(^{2+}\) Sensitivity of EAAT4—We have previously identified two histidine residues in the large extracellular loop between transmembrane domains 3 and 4 of EAAT1 that form part of the Zn\(^{2+}\) binding site. Alignment of the amino acid sequences of EAAT4 with EAAT1 shows that both histidine residues are conserved between the two transporters. In the following experiments we have used site-directed mutagenesis to investigate whether the conserved histidine residues also form the Zn\(^{2+}\) binding site on EAAT4 that mediates inhibition of the anion conductance.

The two histidine residues were mutated to alanine to remove the imidazole group that is thought to interact with Zn\(^{2+}\). In addition the second histidine residue, at position 164, was changed to glutamate because a glutamate residue is found at this position of the glutamate transporter EAAT5. Application of l-aspartate to oocytes expressing the EAAT4 mutants, H154A, H164A, and H164E generated dose-dependent conductances that reversed direction at similar membrane potentials to that of wild type EAAT4 (Table I). This suggests that the mutations have not caused significant structural changes to the pore of the transporter. In contrast to wild type EAAT4, co-application of 100 \(\mu M\) Zn\(^{2+}\) with 100 \(\mu M\) l-aspartate to oocytes expressing the EAAT4 mutant, H154A, had no significant effect on the conductance compared with l-aspartate alone (Fig. 5) or the EC\(_{50}\) for l-aspartate-evoked conductance. This suggests that the mutation has selectively disrupted Zn\(^{2+}\) modulation of the substrate-activated anion conductance. Similar results were also observed for the second site mutants H164A.
and H164E (Fig. 5). Thus, histidines residues at positions 154 and 164 appear to influence Zn\(^{2+}\) affinity for EAAT4, which is analogous to the results observed for EAAT1 (16).

Cysteine residues have also been identified in other proteins as forming Zn\(^{2+}\) binding sites and as EAAT4 contains two cysteine residues we investigated whether either of these two residues play a role in mediating the effects of Zn\(^{2+}\) on EAAT4. Application of 100 \(\mu\)M L-aspartate to oocytes expressing the EAAT4 C194A and EAAT4 C356A mutants showed similar current-voltage relationships to the wild type EAAT4, and co-application of 100 \(\mu\)M Zn\(^{2+}\) caused similar reductions in the conductance as observed for the wild type EAAT4. Thus, the C194A and C356A mutations do not appear to alter the functional properties of the transporter or the sensitivity to Zn\(^{2+}\), and are unlikely to form part of the Zn\(^{2+}\) binding site on EAAT4.

In most cells expressing EAAT4, but not in uninjected oocytes, application of Zn\(^{2+}\) alone appears to block a constitutive conductance. This constitutive conductance could be an intrinsic property of EAAT4 or could be because of the expression of an endogenous oocyte protein as a consequence of overexpression of the transporter. The following observations suggest that an endogenous oocyte ion channel mediates the constitutive conductance. First, if the constitutive conductance were an intrinsic property of the transporter it would be expected that there should be a correlation between the amplitude of the leak conductance and the amplitude of the anion conductance. The amplitude of the constitutive conductance was variable both between, and within, batches of oocytes. The amplitude of the leak conductance blocked by 100 \(\mu\)M Zn\(^{2+}\) varied from 250% of the substrate-activated anion conductance to <5% of the anion conductance. Second, application of the glutamate transport blocker TBOA to oocytes expressing EAAT4, at concentrations that inhibit the substrate-activated anion conductance, does not block the constitutive conductance. Third, the amplitude of the Zn\(^{2+}\)-blocked leak conductance does not appear to influence any of the transporter-mediated functional properties, such as the EC\(_{50}\) for Zn\(^{2+}\) inhibition of the anion conductance or the extent of inhibition. Fourth, the same variability in amplitude of the leak conductance observed for EAAT4 was also observed for the EAAT4 mutants, EAAT4 H154A, EAAT4 H164A, EAAT4 H164E, EAAT4 C194A, and EAAT4 C356A. Finally, other researchers have also described various Zn\(^{2+}\)-blocked conductances in oocytes (20) that could be responsible for the leak conductance in oocytes expressing EAAT4. Although we cannot completely rule out the possibility that the constitutive conductance, or some proportion of the conductance, is an intrinsic property of the transporter that functions independently of the transport function, the above observations make this interpretation unlikely.

**DISCUSSION**

\(\text{Zn}^{2+}\) Inhibition of the Anion Conductance of EAAT4—\(\text{Zn}^{2+}\) is found throughout the brain and may modulate the actions of glutamate by influencing the activity of NMDA receptors (12, 13), Ca\(^{2+}\) channels (14), and also glutamate transporters (15, 16). The actions of Zn\(^{2+}\) are most clearly demonstrated in the mossy fibers of the hippocampus where Zn\(^{2+}\) is co-released with glutamate upon stimulation (11). Whereas there are a number of physiological and pathological implications of Zn\(^{2+}\) modulation of excitatory neurotransmission, Zn\(^{2+}\) may also be used to study potential mechanisms for modulation of various proteins, including glutamate transporters. In this study we have used Zn\(^{2+}\) as a molecular probe to identify the molecular basis for differential modulation of the coupled and uncoupled conductance states of the glutamate transporter EAAT4.

There are two distinct types of conductances associated with glutamate transporter function: a coupled flux of Na\(^{+}\), K\(^{+}\), and glutamate ions (7, 8); and an uncoupled anion conductance that requires the presence of L-glutamate and Na\(^{+}\) ions (2, 9, 21, 22). The relative contributions of the two components vary with the different transporter subtypes, and the effects of Zn\(^{2+}\) on these conductances also vary between transporter subtypes. In the case of EAAT1, we have previously demonstrated that Zn\(^{2+}\) inhibits the coupled Na\(^{+}\), K\(^{+}\), and glutamate fluxes with little, if any, effect on the uncoupled anion conductance, whereas application of Zn\(^{2+}\) to oocytes expressing EAAT2 or EAAT3, does not appear to modulate any of the transporter-associated conductances (16).\(^2\) In the present study we have investigated the actions of Zn\(^{2+}\) on the uncoupled anion conductance and the coupled substrate transport conductance of the EAAT4 subtype.

We have demonstrated that Zn\(^{2+}\) inhibits the uncoupled anion conductance of EAAT4 and also causes a small, but

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\(^2\) R. J. Vandenb  unpublished observations.
The kinetic parameters presented for EAAT4 and the EAAT4 mutants were calculated for L-aspartate elicited currents. The EC50 values are for L-aspartate dose responses measured at −100 mV. The IC50 values are for Zn2+ dose responses at the indicated membrane potentials and %inhibition values are the maximal inhibition values at the indicated membrane potentials. Zn2+ did not change the reversal potential of either of the mutants or wild type transporters, and the values obtained for each of the mutants were not significantly different from wild type.

| Transporter | EC50 (−100mV) | IC50 (−100mV) | IC50 (+60mV) | %Inhib. (−100mV) | %Inhib. (+60mV) |
|-------------|----------------|----------------|---------------|------------------|------------------|
| EAAT4       | 3.4 ± 0.5 b    | 5.1 ± 0.5 b    | µM            | 38 ± 10          | 58 ± 10          |
|             | n = 7          | n = 7          | µM            | n = 4            | n = 4            |
| EAAT4-H154A | 6.2 ± 3.7      | 6.5 ± 3.2      | 100 µM        | >1mM             | >1mM             |
|             | n = 4          | n = 4          | 1mM           | n = 7            | n = 7            |
| EAAT4-H164A | 2.6 ± 1.2      | 3.0 ± 1.1      | 100 µM        | >1mM             | >1mM             |
|             | n = 4          | n = 4          | 1mM           | n = 6            | n = 6            |
| EAAT4-H164E | 3.5 ± 1.3      | 3.5 ± 1.3      | 100 µM        | >1mM             | >1mM             |
|             | n = 6          | n = 6          | 1mM           | n = 14           | n = 14           |
| EAAT4-C194A | 2.5 ± 0.2 c    | 3.9 ± 0.4 c    | ND            | 60 mV            |
|             | n = 5          | n = 5          | ND            | 100 mV           |

a EC50 calculated from transport current measurement made in the presence of 100 µM Zn2+. b For the wild type EAAT4 and the C194A mutant the EC50 for L-aspartate activated conductances were significantly different measured in the presence and absence of 100 µM Zn2+. c For the C194A mutant, the %inhibition is the value obtained for 100 µM Zn2+. d ND, not determined. 
*NI, no inhibition at 300µM Zn2+.

FIG. 5. Histidine mutations in EAAT4 at positions 154 and 164 abolish Zn2+ sensitivity of EAAT4. Current-voltage plots for L-aspartate elicited responses in oocytes expressing the EAAT4 mutants H154A, H164A, H164E, and C194A were measured in the absence of Zn2+ (10 µM L-aspartate in ND96) — I(ND96; squares) and the presence of Zn2+ (100 µM L-aspartate + 100 µM Zn2+ in ND96) — I(100 µM Zn2+ in ND96; circles). Current measurements are normalized to the current elicited by L-aspartate at −100 mV. Data represent mean ± S.E.

significant, increase in L-aspartate EC50. Although Zn2+ reduced the amplitude of the anion conductances of EAAT4, Zn2+ did not change the reversal potentials of the anion conductances when carried by chloride, bromide, iodide or nitrate ions. The lack of changes in anion permeability suggests that Zn2+ binds to a site on EAAT4 that is distinct from the pore region of the transporter. The IC50 for Zn2+ inhibition of the anion conductance decreased with an increase in membrane potential from 86 µM at −100 mV to 38 µM at +60 mV and the extent of maximal inhibition of the anion conductance also changes from 58% at −100 mV to 81% at +60 mV. These observations could be explained if the time spent in transport mode compared with anion-conducting mode is also dependent on membrane potential. At positive membrane potentials, the anion-conducting mode may predominate and as Zn2+ selectively inhibits the anion conductance of the transporter, the measured effects of Zn2+ may be more apparent at these membrane potentials.

Molecular Basis for Differential Zn2+ Modulation of Glutamate Transporter Subtypes—We have previously demonstrated that two histidine residues within the extracellular loop between transmembrane domains 3 and 4 form part of the Zn2+ binding site on EAAT1. Mutations of either of these histidine residues to alanine do not alter the glutamate transport kinetics of EAAT1 but do diminish the effects of Zn2+ on EAAT1 and therefore these Zn2+ binding site residues are unlikely to form part of the pore through which glutamate, Na+, K+, H+ and possibly Cl− ions pass during the transport process. We have now extended this work to include a description of the Zn2+ binding sites on the EAAT4 subtype of excitatory amino acid transporters.

Alignment of the amino acid sequences of the EAATs shows that the two histidine residues of EAAT1 that bind Zn2+ are conserved in EAAT4. Mutation of either of these histidine residues to alanine abolishes Zn2+ inhibition of the anion conductance of EAAT4 and also Zn2+ modulation of L-aspartate EC50, which demonstrates that Zn2+ interacts with EAAT4 at a similar binding site to that of EAAT1. Although the Zn2+ binding sites are similar on EAAT1 and EAAT4, the effects of Zn2+ are different. In the case of EAAT1, Zn2+ inhibits the coupled fluxes of L-glutamate, Na+, K+, and H+ with minimal effect on the anion conductance (16), whereas for EAAT4 Zn2+ causes a small increase in EC50 for L-aspartate with no change in the level of inhibition of L-aspartate transport and significant inhibition of the anion conductance. There are a number of possible explanations for these differences. Wadiche and Kavanaugh (23) have demonstrated that glutamate transporters do not simultaneously function as a coupled transporter and an anion channel, but rather the transporters are likely to switch between the two modes of function. As the chloride conductance dominates the combined coupled transport/uncoupled chloride channel conductance in the cases of EAAT4, it may be predicted that the time spent in the anion channel mode is significantly greater than the transporter mode compared with EAAT1. Thus, Zn2+ modulates the dominant process, i.e. the anion conductances of EAAT4 and the coupled glutamate, Na+, K+, H+ fluxes of EAAT1.

If we compare the results of the human glutamate transporters expressed in oocytes with that observed for the actions of Zn2+ on glutamate transporters in the salamander retina there are a number of similarities, but also some distinct differences. In Muller cells
of the salamander retina the predominant transporter is homolo-
gous to EAAT1, and in these cells Zn$^{2+}$ inhibits glutamate trans-
port current, but in contrast to human EAAT1 Zn$^{2+}$ stimulates
the uncoupled chloride conductance. Furthermore, the $K_{0.5}$
for Zn$^{2+}$ modulation of the Muller cell transporter is 0.66 $\mu$M, which
is $\sim 10$–20-fold less than that observed for EAAT1. In other Zn$^{2+}$-
binding proteins the number of coordinating residues roughly cor-
relates with the affinity of Zn$^{2+}$. With 2 coordinating histidine
residues affinities range from 10–100 $\mu$M whereas with 3 coordinating
residues affinities in the range of 0.01–1 $\mu$M have been
observed (17). Thus, the higher affinity of Zn$^{2+}$ for the salamander
EAAT1 may be due to the presence of an additional coordinating
residue. If the amino acid sequences of the human and salamander
EAAT1 s are compared in the putative Zn$^{2+}$ binding site region a
number of subtle differences are apparent that could explain the
different effects of Zn$^{2+}$ (Fig. 1). The salamander EAAT1 contains
an extra histidine residue between the two histidine residues con-
served between the human and salamander EAAT1s that could
possibly influence the binding affinity or could create different
conformational changes when Zn$^{2+}$ is bound compared with Zn$^{2+}$
binding to EAAT1 such that the different functional effects are
created. The differences could also arise because of the expression
of other glutamate transporter subtypes or accessory proteins (24–
26) in the Muller cell with each subtype responding differently to
Zn$^{2+}$. In cone cells of the salamander retina, Zn$^{2+}$ inhibits the
chloride conductance associated with glutamate transporters of the
retinal cone cells (27). The predominant glutamate transporter in
cone cells is homologous to human EAAT5, but in oocytes express-
ing human EAAT4, Zn$^{2+}$ appears to stimulate the anion
conductance. 3

The quarternary structure of glutamate transporters is poorly
defined, but recent characterization of electron micrographs of X.
laevis oocyte membranes containing the EAAT3 transporters sug-
gests that transporters may exist as homomultimers consisting of
between 3–6 subunits, with 5 subunits the most favored option
(28). Furthermore, it was suggested that the subunits may function
as separate transporters, but the chloride channel function of the
transporters may arise through the association of the subunits to
form a central channel. The binding of substrate to each of the
subunits may alter the association of the subunits to change the
conformation of the central chloride channel and allow passage of
chloride ions. If this functional model is correct then the actions of
Zn$^{2+}$ offer a particularly interesting insight into the mechanisms
for differentially modulating the dual roles of glutamate transport-
ers. Thus, the functional role of Zn$^{2+}$ ions may be to modify the
association between subunits so as to change the rate of conforma-
tional changes required for the different modes of function of the
transporters.

Possible Physiological Roles of Zn$^{2+}$ Modulation of Gluta-
mate Transporters—The concentrations of Zn$^{2+}$ required to
modulate EAAT4 are within the reported concentration range of
the free extracellular Zn$^{2+}$ found in various regions of the brain.
EAAT4 is expressed predominantly in Purkinje cells of the cerebral
hemisphere, which also co-express EAAT3 (29,30). Whereas
Zn$^{2+}$ is found in the cerebellum, and numerous studies have
investigated the effects of exogenously applied Zn$^{2+}$ on synap-
tic neurotransmission in this region, the levels of free Zn$^{2+}$
found in regions accessible to the transporters under normal or
pathological conditions are not well established (10). If present
in sufficiently high concentrations, Zn$^{2+}$ would inhibit activa-
tion of the anion conductance of EAAT4, which may alter the
excitability of the Purkinje cells. An alternative suggestion for

3 W. Fairman and S. Amara, personal communication.
**Zn\(^{2+}\) Inhibits the Anion Conductance of the Glutamate Transporter EAAT4**
Ann D. Mitrovic, Fiona Plesko and Robert J. Vandenberg

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