Inhibitory Effect of Ondansetron on Glycine Response of Dissociated Rat Hippocampal Neurons

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Accepted for publication March 23, 1999 This paper is available online at http://www.jpet.org

ABSTRACT
We examined the effect of ondansetron, an antagonist of type 3 serotonin receptors, on the whole cell response of freshly isolated hippocampal CA1 pyramidal neurons of neonatal and “mature” rats to glycine using the gramicidin perforated patch technique. Ondansetron depressed the current induced by subsaturating concentrations of glycine (ICly) in a concentration-dependent manner. The ondansetron concentration needed to depress ICly induced by 30 μM glycine to half amplitude was 25 μM. Ondansetron (54 μM) shifted the glycine concentration-response curve to the right in a parallel manner, increasing the EC50 for glycine from 40 ± 3 μM to 70 ± 5 μM. Ondansetron increased the time constant of activation of ICly without affecting the time constant of deactivation. When examined under current clamp conditions, glycine induced depolarization and hyperpolarization in neonatal and mature neurons, respectively; ondansetron also suppressed these responses to glycine. The data suggest that ondansetron competitively inhibits the glycine receptor.

Materials and Methods

Isolation of Neurons and Electrophysiological Recording. Hippocampal CA1 pyramidal neurons were prepared as described previously (Ye et al., 1997). Briefly, 5- to 11-day old (neonatal group) and 24- to 30-day old (mature group) Sprague-Dawley rats were decapitated. Their brains were quickly excised and placed into iced sucrose. The brain was then glued to the chilled stage of a vibratome (Campden Instrument, LTD, Cambridge, England) and sliced to a thickness of 400 μm. Slices were transferred to standard solution containing: 140 mM NaCl, 5 mM KCl, 1 mM MgCl2, 2 mM CaCl2, 10 mM glucose, and 10 mM HEPES; pH was adjusted to 7.4 with Tris base and osmolarity to 320 mM/kg with sucrose. The brain was then glued to the chilled stage of a vibratome (Campden Instrument, LTD, Cambridge, England) and sliced to a thickness of 400 μm. Slices were transferred to standard solution containing 1 mg pronase/6 ml and incubated (31°C) for 20 min. After an additional 20-min incubation in 1 mg thermolysine/6 ml, mi...
cropunches of the hippocampal CA1 region were isolated and transferred to a 35-mm culture dish. Mild trituratation of these tissue punches through heat-polished pipettes of progressively smaller tip diameter served to dissociate single neurons. Within 20 min of trituration, isolated neurons had attached to the bottom of the culture dish and were ready for electrophysiological experiments. The experimental protocol was approved by the Institutional Animal Care and Use Committee.

Glicineperfused patch technique (Abe et al., 1994) was used to record the glycine-induced whole cell response (Axopatch 1D; Axon Instruments, Foster City, CA). Glicine (Sigma Chemical Co., St. Louis, MO) was dissolved in methanol (2 mg/ml; J.T. Baker, Inc. Phillipsburg, NJ), and then diluted in the pipette solution to a final concentration of 5 to 10 μM. The progress of perfusion was evaluated by monitoring the decrease in membrane resistance. Drugs were applied after the membrane resistance had stabilized; this usually took from 1 to 10 min. pCLAMP software (Axon Instruments) delivered voltage clamp protocols and wrote digitized current records to disk. The patch electrode had a resistance between 3 and 5 MΩ when filled with solution containing: 120 mM CsCl, 21 mM TEA-Cl, 4 mM MgCl2, 11 mM EGTA, 1 mM CaCl2, and 10 mM HEPES (pH 7.2). All glycine-induced responses were recorded in the standard external solution at an ambient temperature of 20 to 23°C. Junction potential was nulled immediately before forming the Giga-seal. In most experiments, series resistance before compensation was 15 to 25 MΩ. Routinely, 80% of the series resistance was compensated resulting in 3 mV error for 1 nA of current.

**Chemical Application.** Solutions of glycine (Sigma Chemical Co.) and ondansetron hydrochloride (Glaxo Wellcome Inc., Hertfordshire, England) were prepared on the day of experiments. These solutions were applied to a dissociated neuron with a superfusion system via a multibarreled pipette as described previously (Ye et al., 1997). The tip of the superfusion pipette was normally placed 50 to 100 μm away from the cell, a position that allowed rapid as well as uniform drug application and preserved the mechanical stability of the cell. By keeping the dead volume small and the flow rate high, solution exchange could be accomplished within 15 ms. Throughout all experimental procedures the bath was continuously perfused with the standard external solution.

**Data Analysis.** Data were statistically compared using Student’s t test or ANOVA, as noted. Statistical analyses of concentration-response data were performed using the nonlinear curve-fitting program (Sigma Plot). For all experiments, average values are expressed as mean ± S.E.M.

**Results**

**Ondansetron Inhibits Glycine Current (I Gly).** The effects of ondansetron on I Gly were tested with glicineperforated patch technique (Abe et al., 1994). Glicine forms pores permeant only to monovalent cations. Therefore, the concentration of intracellular Cl− and proteins is virtually undisturbed. As for hypothalamic neurons (Abe et al., 1994), the reversal potential for I Gly of neonatal rat hippocampal neurons was between −50 and −10 mV with an average value of −25 ± 10 mV (n = 7). At a holding potential negative to the reversal potential, glycine induced inward current. As expected, I Gly was sensitive to strychnine. For example, 20 nM strychnine depressed I Gly to 50% (data not shown). As illustrated in Fig. 1, 10 to 54 μM ondansetron suppressed the peak current induced by 30 μM glycine. I Gly completely recovered after ondansetron washout (Fig. 1A, e). On average, 13.5, 27, and 54 μM ondansetron decreased the peak amplitude of current induced by 30 μM glycine by 41 ± 3% (n = 6), 48 ± 1% (n = 9), and 54 ± 6% (n = 7), respectively. Ondansetron inhibition of current activated by 30 μM glycine was observed in all neurons tested (n = 50), and exhibited a clear concentration dependence (Fig. 1B). Fit of the Hill equation to the concentration-response data of Fig. 1B indicated that the IC50 for ondansetron reduction of peak current induced by 30 μM glycine was 25 μM. Interestingly, there is a remarkable difference in the effects of ondansetron on the peak versus steady state I Gly. Figure 1A (also Figs. 2 and 3) shows that ondansetron has essentially no effect on the current at the end of the pulse.

**Ondansetron Inhibited Only Current Induced by Subsaturating Concentration of Glycine.** To test the hypothesis that ondansetron inhibits I Gly by a competitive mechanism, the effects of ondansetron were tested on current induced by 10 to 1000 μM glycine. Figure 2 shows typical I Gly records obtained without (A) and with (B) ondansetron. Ondansetron (54 μM) depressed I Gly induced by 10 and 30 μM glycine. However, ondansetron had no effect on the current induced by 1 μM glycine. On average, 54 μM ondansetron decreased the amplitude of peak current activated by 10, 30, and 1000 μM glycine by 85 ± 5% (n = 6), 59 ± 5% (n = 7), and 6 ± 4% (n = 5), respectively. Figure 2C summarizes the concentration-response relationships for glycine (10–1000 μM) in control and in the presence of 54 μM ondansetron. The EC50 and Hill coefficient of glycine was 40 μM and 1.9 in the absence of ondansetron and 73 μM and 1.8 in the presence of 54 μM ondansetron, respectively. The Lineweaver-
Burke plot of Fig. 2D indicates that ondansetron competes with glycine for binding to the GlyR.

**Ondansetron Has a Stronger Effect on I_{Gly} When Applied with a Prepulse.** To determine the mechanism of ondansetron action on I_{Gly}, we compared ondansetron’s effect on I_{Gly} when it was preapplied to neurons for 5 s before coapplication with glycine (++ paradigm, Fig. 3A, b) to its effect without this prepulse (−+ paradigm, Fig. 3A, c). Superimposition of records a, b, and c produced Fig. 3A, d. This composite record reveals that ondansetron has a stronger effect on the peak I_{Gly} with the +++ paradigm. To determine the proper preincubation time, we evaluated ondansetron’s effect with preincubation of 1 to 50 s. Although the inhibitory action of ondansetron on I_{Gly} significantly increased with preincubation time within 3 to 5 s, there was no significant change in the range of 5 to 50 s (data not shown). This suggests that ondansetron is at equilibrium with the receptor with 5-s preincubation time. To examine the possibility that ondansetron affects the receptors when they are not activated, we applied ondansetron alone for 5 s before the application of glycine alone (+ − paradigm), as illustrated in Fig. 3B, b. Superimposition of records a and b produced Fig. 3B, c.

This composite record reveals that ondansetron applied in a + − paradigm has no effect on I_{Gly}.

**Ondansetron’s Action on I_{Gly} Has a Slower Onset than Offset.** To explore the kinetics of the ondansetron action, we applied a brief pulse of 54 μM ondansetron during a longer lasting pulse of 30 μM glycine. Ondansetron decreased I_{Gly} (Fig. 4). The kinetics of ondansetron’s effect. A, a, brief pulse of ondansetron (54 μM) reduced I_{Gly} in response to 30 μM glycine. A, b, control I_{Gly} in response to two consecutive pulses of glycine. A, c, control I_{Gly} in response to a continuously applied glycine pulse. A, d, both the onset and offset of ondansetron’s effect could be fit by a single exponential, as shown by the continuous lines. A, e, superimposition of traces a, b, and c. Note the onset and offset of ondansetron’s action is slower compared with the onset and offset of glycine alone. B, repeated pulses of ondansetron (54 μM) were applied during a continuous application of 30 μM glycine. Holding potential was −50 mV in both cases.
immediately and with cessation of ondansetron, IGly recovered (Fig. 4A, a). As the continuous lines of Fig. 4A, d show a single exponential could fit both the onset and offset of ondansetron’s effect. The time constant (n = 5) for onset and offset of the ondansetron effect was 1760 ± 30 ms and 385 ± 20 ms, respectively.

To further clarify the mechanism of the ondansetron effect, we recorded IGly under different conditions. Figure 4A, b was obtained when glycine was applied in two separate short pulses, and Fig. 4A, c when applied continuously. Superimposition of records of a, b, and c in A produced e. The composite record of Fig. 4A, e reveals three interesting phenomena. First, both the onset and offset of ondansetron’s action (trace a) was slower than that of glycine alone (trace b). Secondly, with continuous application of glycine, the receptor desensitized as indicated by the gradual decline of the current. In record b, IGly induced by the second pulse of glycine was greater than IGly of record c, indicating that some GlyRs recovered from desensitization during the wash-out period. Interestingly, the same phenomenon, although to a lesser extent, can be seen in record a. That is, immediately after a short pulse of ondansetron, IGly was greater than when glycine was continuously present. These data suggest that during the pulse of ondansetron some GlyRs not occupied by glycine recovered from desensitization. All these findings were reproduced in four additional neurons. Figure 4B shows that repeated pulses of ondansetron during a longer pulse of glycine depressed IGly to a similar extent. On average, 54 μM ondansetron inhibited current induced by 30 μM glycine by 51 ± 3%, 54 ± 2%, and 52 ± 3% in the first, second, and third application (n = 4).

**Ondansetron Does Not Increase Receptor Desensitization.** Ondansetron inhibition of IGly could result from ondansetron enhancement of receptor desensitization. To test this hypothesis, we studied the desensitization of IGly in the absence and presence of ondansetron. As shown in Fig. 5A, the decay rate of current activated by 30 μM glycine was decreased, rather than increased, by application of 27 μM ondansetron. For six neurons, 27 μM ondansetron significantly increased the time constant of desensitization (Student’s t test, p < .05).

Two mechanisms may underlie ondansetron-induced decrease of IGly decay rate. Ondansetron could act directly on the receptor channel to decrease desensitization. Alternatively, ondansetron could decrease the apparent concentration of glycine and indirectly cause a decrease in desensitization. To test these two hypotheses, we applied a saturating concentration of glycine and examined current desensitization with and without 54 μM ondansetron. Under this condition, ondansetron would not significantly change the apparent concentration of glycine. Thus, any change of the current decay rate would result from a direct action of ondansetron to the desensitization process. As illustrated by Fig. 5B the desensitization rate of the current activated by a saturating concentration (1 mM) of glycine did not significantly change in the presence of 54 μM ondansetron. Similar results were obtained in three other neurons. Thus, these data indicate that ondansetron has no effect on the desensitization process. Rather, ondansetron may decrease the apparent concentration of glycine and indirectly cause a decrease of desensitization.

**Ondansetron Decreases Receptor Activation Rate without Affecting Deactivation Rate.** The preceding data suggest that ondansetron may inhibit IGly by competing with the agonist for the same binding site on the GlyR. To further examine this hypothesis, we determined the activation and deactivation time constants of IGly in the absence and presence of ondansetron. To allow accurate measurement of time constants within the limits of the fast perfusion system (time constant of 9 ± 1.3 ms for solution changes in patch-clamped cells; Fig. 6A, inset), we used glycine concentrations of 30 μM or lower. As shown in Fig. 6A, in the presence of 0, 108, and 218 μM ondansetron, the activation time constant 5 was 284, 860, and 1003 ms, respectively. The activation time constants (Fig. 6B) were highly dependent on both glycine concentration (ANOVA p < .01; n = 6) and ondansetron concentration.
Fig. 6. Effect of ondansetron on activation and deactivation time constants of glycine-activated current. A, records of currents activated by 30 μM glycine in the absence and presence of 54 and 109 μM ondansetron. Both activation and deactivation of the current were well fitted using single-exponential equations (continuous curves). Horizontal bars indicate that we applied ondansetron for 5 s before and after application of glycine to eliminate the possible effect of the rates of onset and offset of ondansetron action on the measurement of the rates of activation and deactivation of the receptor by glycine. Note that both 54 and 109 μM ondansetron had relatively little effect on deactivation time constant (τ_{rec}), but greatly increased the activation time constant (τ_{act}). Inset shows the time constant for solution change in a patch-clamped cell. The external solution containing 100 μM kainate was abruptly changed from 140 mM Na⁺ to 10 mM Na⁺ plus 130 mM N-methyl-D-glucamine (NMDG). B, graph plotting averaged τ_{rec} values as a function of glycine concentration in the absence (○), and presence of 54 (●), and 109 μM (■) ondansetron. The average τ_{rec} of glycine induced current was highly dependent upon ondansetron concentration (ANOVA, p < .01). Holding potential was −50 mV. C, graph plotting average τ_{act} values as a function of glycine concentration in the absence (○), and presence of 54 (●), and 109 μM (■) ondansetron. Average τ_{act} of I_{Gly} depends on glycine concentration (ANOVA, p < .05; n = 5), but was independent of ondansetron concentration (ANOVA, p > .25; n = 5).

Ondansetron Depression of I\textsubscript{Gly} Is Independent of Voltage. To explore the voltage dependence of ondansetron’s action, we studied the current-voltage relationships (I-V) of I\textsubscript{Gly} in the absence and presence of ondansetron with a voltage ramp protocol. As illustrated in Fig. 7, over the voltage range of +20 to −70 mV, the I-V curves are linear. Ondansetron depressed I\textsubscript{Gly} to a similar extent at all voltages tested. Thus, the effect on I\textsubscript{Gly} is not voltage dependent. Furthermore, the glycine-activated channel remained selectively permeable to Cl⁻ because the reversal potential of I\textsubscript{Gly} was approximately −31 mV with or without ondansetron.

Ondansetron Suppresses Glycine-Induced Membrane Potential Changes. The ondansetron effect on the glycine response was also studied under current clamp conditions. As stated earlier, the average reversal potential of I\textsubscript{Gly} was −25 mV in the neonatal group. Because resting membrane potentials (−68 ± 2.5 mV, n = 5) are more negative than the reversal potential of glycine at this age, GlyR activation would produce membrane depolarization. As illustrated in Fig. 8A, glycine induced membrane depolarization. On average, 30 μM glycine induced 20 ± 5 mV (n = 6) depolarization. This effect of glycine was also concentration dependent, with an EC\textsubscript{50} of 40 μM, close to the EC\textsubscript{50} for I\textsubscript{Gly}. Ondansetron suppressed the depolarizing response induced by glycine (Fig. 8B). Figure 8C illustrates the concentration-response relationships of glycine in the absence and presence of ondansetron. Ondansetron shifted the curve to the right without affecting the maximal voltage change induced by glycine. Similar experiments were repeated in hippocampal...
neurons (Ye et al., 1997). Squires and Saederup (1999) demonstrated that ondansetron reversed the inhibitory effect of 1 μM GABA on [35S]β-butyrylphosphorothionate binding to whole rat forebrain membranes. In this study, we describe the depressant effects of ondansetron on the glycine-induced response of rat hippocampal pyramidal neurons.

The data indicate that ondansetron inhibits the glycine receptor by shifting the agonist concentration-response curve to the right in a parallel manner without affecting the maximal response to glycine. This effect could result either from competitive inhibition by ondansetron, or by interaction with an allosteric site on the receptor channel resulting in a decreased affinity of the receptor for glycine. The latter mechanism has been demonstrated for inhibition of GABA_A receptors by benzodiazepine site inverse agonists (Kemp et al., 1987). Competitive antagonists will decrease the activation rate of the receptor channel without changing its deactivation rate (Clements and Westbrook, 1991). Allosteric antagonists that decrease the affinity of the receptor for agonist will increase the deactivation rate without changing its activation rate (Li et al., 1997). In the present study, ondansetron decreased the activation rate without affecting the deactivation rate of I_{Gly}. This observation suggests that ondansetron may compete with the agonist for binding to the GlyR. The observation that I_{Gly} recovered after a brief pulse of ondansetron suggests that during the pulse, GlyRs were occupied by ondansetron instead of glycine.

There are several explanations for ondansetron’s weaker effect on steady state than peak I_{Gly}. For example, ondansetron may reduce desensitization of the GlyRs. That is, in the early part of the pulse, ondansetron occupied an agonist binding site of the GlyRs and thus prevented activation of the GlyR. Because desensitization of GlyRs is proportional to activation of GlyRs, there will be less desensitization. Consequently, the steady state I_{Gly} has a greater amplitude. This hypothesis is supported by the observation that ondansetron reduced desensitization of GlyRs (Fig. 5). Alternatively, there may be an rate competition between ondansetron and glycine. Presumably, in the + + paradigm, GlyRs were occupied by ondansetron. Therefore, less GlyRs were available to bind glycine when it arrived. However, as the pulse continued, glycine might bind by competing with ondansetron, as suggested by the gradual increase of I_{Gly} (Figs. 2B, b and 3A, b). If the resultant increment of I_{Gly} offsets the ondansetron depression of I_{Gly}, ondansetron would not affect the steady state current. The competitive nature of ondansetron’s effect supports this hypothesis.

In addition to competitive, noncompetitive block is also a major mechanism underlying receptor inhibition. Open-channel block and increase of desensitization are two common mechanisms underlying noncompetitive inhibition. Because ondansetron has a pK_a of 7.4 (Glaxo-Wellcome), it is 50% charged in the external solution used. Because ondansetron inhibited I_{Gly} only in the presence of agonist, ondansetron may act as an open channel blocker. However, two lines of evidence do not support this hypothesis. First, open-channel block by charged molecules is usually voltage dependent (Hille, 1992); ondansetron inhibition of I_{Gly} was independent of voltage. Conceivably, ondansetron could bind to a site within the ion channel beyond the influence of the membrane electrical field. In this case, ondansetron could be an open channel blocker but independent of voltage. This mech-
anism is unlikely, because ondansetron inhibition can be overcome by increasing the concentration of glycine. Analysis of the current-voltage relationships reveals that ondansetron did not change the ion selectivity because the reversal potential of \( I_{\text{Gly}} \) did not alter in the presence of ondansetron.

Secondly, use dependence is a feature often associated with an open channel blocker. However, repeated application of ondansetron suppressed \( I_{\text{Gly}} \) to a similar extent. Although ondansetron could depress \( I_{\text{Gly}} \) by increasing desensitization of the receptor, this is unlikely because ondansetron actually decreased the rate of desensitization of current activated by a submaximal concentration of glycine. Finally, ondansetron did not alter the desensitization rate of current activated by a saturating concentration (1 mM) of glycine.

The suppression of peak \( I_{\text{Gly}} \) by the ++ paradigm is much larger than the –+ paradigm. Because ondansetron has a molecular weight of 365.9, much greater than glycine (75.1), it will take much longer for ondansetron to reach its site of action than glycine. In the –+ paradigm, ondansetron has not been allowed to pre-equilibrate with the GlyR before the presentation of the agonist. The onset time constant of 1790 ms supports this hypothesis, explaining why ondansetron suppressed \( I_{\text{Gly}} \) less when applied with a short pulse as shown in Fig. 4A, a (see below for details).

The fact that both the onset and offset of ondansetron action could be fit by a simple exponential suggests that the ondansetron-glycine receptor interaction can be modeled as a simple bimolecular reaction and expressed as:

\[
R + D \rightleftharpoons RD
\]

\[
\frac{k_1}{k_{-1}} = \frac{R}{D}
\]

where \( R \) and \( D \) are glycine receptor and ondansetron, respectively; \( k_1 \) and \( k_{-1} \) are the forward and backward rate constants, respectively. The time constant for the onset and offset could be expressed as \( 1/(k_1[D] + k_{-1}) \) and \( 1/k_{-1} \), respectively, where \( [D] \) is the concentration of ondansetron. The experiments of Fig. 4A, d give time constants for onset and offset of 1790 ms and 397 ms in the presence of 54 \( \mu \)M ondansetron. These values result in \( k_1 = 18.0 \text{ M}^{-1} \text{s}^{-1} \) and \( k_{-1} = 2.52 \text{ s}^{-1} \). Thus, the apparent dissociation constant \( K_D \) is 69 \( \mu \)M. This value is much higher than 25 \( \mu \)M ondansetron required to inhibit 50% \( I_{\text{Gly}} \) activated by 30 \( \mu \)M glycine. This difference is consistent with the observation that ondansetron had a stronger effect when applied with pretreatment (++) paradigm and the peak \( I_{\text{Gly}} \) was more sensitive to ondansetron than the steady state \( I_{\text{Gly}} \). An alternative interpretation is that, because glycine has a considerably faster “on” rate (\( \tau_{\text{on}} = 284 \text{ ms} \)) than ondansetron (1790 ms), ondansetron applied in the middle of a longer lasting pulse of glycine would only partially inhibit \( I_{\text{Gly}} \), thus increasing the IC\(_{50}\) value for ondansetron. Because the forward rate constant \( k_1 \) (18.0 \text{ M}^{-1} \text{s}^{-1}) is much slower than free diffusion in solution, the binding site for ondansetron is not freely accessible.

There are several differences between ondansetron effects on \( I_{\text{Gly}} \) and current induced by GABA (\( I_{\text{GABA}} \)). First, peak \( I_{\text{Gly}} \) is more sensitive to ondansetron than the steady-state current. This is just the opposite of \( I_{\text{GABA}} \), where the steady-state, rather than peak current was more sensitive to ondansetron. Secondly, although ondansetron inhibition of steady-state \( I_{\text{GABA}} \) is noncompetitive, the effect on peak \( I_{\text{Gly}} \) is competitive. Furthermore, in contrast to the observation that ondansetron had an effect on the resting state of the GABA\(_A\) receptor, ondansetron had no effect on the GlyR in its resting state. Finally, ondansetron had a faster onset than offset of effect on \( I_{\text{GABA}} \); the converse was observed for \( I_{\text{Gly}} \).

Glycine and GABA are the principal inhibitory neurotransmitters in the adult mammalian CNS. Several studies show that glycine receptor activation depolarizes embryonic and neonatal neurons but hyperpolarizes mature neurons (Abe et al., 1994; Chen et al., 1996; Ito and Cherubini, 1991). In this study, we demonstrated that glycine depolarized and hyperpolarized neurons of neonatal and mature rats, respectively. Ondansetron suppressed both effects of glycine. Thus, it is possible that ondansetron inhibition of the glycine response can have different effects on the CNS of neonates and adults.

That is, by suppressing the glycine and GABA response, ondansetron decreases and increases the excitability of the CNS of neonates and adults, respectively.

The clinical significance of ondansetron’s effect on \( I_{\text{Gly}} \) is obvious. Despite the fact that the effects of ondansetron observed here were obtained with concentrations that are relatively high compared with those expected to arise from clinically safe doses, ondansetron could be much more potent when applied in vivo. Studies have shown that in the intact brain, whenever the potency of GABAergic and/or glycinernergic inhibition is diminished, epileptiform activity appears (Krnjević, 1983). It is possible that in vivo synaptic inhibition is reduced at ondansetron concentrations much lower than the IC\(_{50}\) for in vitro suppresses GABA or glycine responses. The loss of inhibitory restraint thereby permits unopposed excitatory drive, leading to hyperexcitation and convulsions. In view of the critical importance of the glycinernergic system in the central nervous system, the antiglycine action of ondansetron may result in behavioral changes after repeated use. Thus, in addition to producing an antiemetic effect by blocking 5-HT\(_3\) receptors, ondansetron can also produce CNS disinhibition by blocking glycine receptors. The later action is likely to play a significant role in the ondansetron-induced seizures observed in vivo.

Acknowledgments

We thank Glaxo Wellcome, Inc. for the donation of ondansetron.

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