Stimulatory and Inhibitory Properties of Aminoglycoside Antibiotics at N-Methyl-D-Aspartate Receptors

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Accepted for publication May 11, 1999 This paper is available online at http://www.jpet.org

ABSTRACT

The effects of aminoglycoside antibiotics on N-methyl-D-aspartate (NMDA) receptors were studied using voltage-clamp recording of recombinant NMDA receptors expressed in Xenopus oocytes. A number of aminoglycosides were found to potentiate macroscopic currents at heteromeric NR1A/NR2B receptors, but not at NR1A/NR2A, NR1A/NR2C, NR1A/NR2D, or NR1B/NR2B receptors. The degree of potentiation had a rank order neomycin B > paromomycin > gentamicin C > gentamicin A > streptomycin. Potentiation was not seen with kasugamycin and spectinomycin. The degree of stimulation paralleled the number of the amino groups in the aminoglycosides. The stimulatory effects of aminoglycosides were more pronounced at subsaturating concentrations of glycine and at acidic pH, similar to the stimulatory effects of spermine. We measured the effects of aminoglycosides at mutant NMDA receptors to determine which amino acid residues in NMDA receptor subunits are involved in stimulation. Mutations that reduced or abolished spermine stimulation also reduced stimulation by aminoglycosides. Several aminoglycosides produced a weak voltage-dependent block of NMDA receptors, but the degree of inhibition did not appear to correlate with the number of amino groups in the molecule. The results suggest that aminoglycosides having more than three amino groups have stimulatory effects that are mediated through the spermine-binding site on NMDA receptors.

Aminoglycoside antibiotics are useful in the treatment of serious infections caused by Gram-negative bacilli (Begg and Barclay, 1995), although the aminoglycosides can induce ototoxicity and subsequent hearing impairment (Brummett and Morrison, 1990). The rate of onset and the extent of hearing loss in patients receiving aminoglycosides are dose-dependent and usually irreversible (Stringer et al., 1991). To develop aminoglycosides that do not induce hearing loss, it is important to clarify the molecular mechanisms responsible for aminoglycoside-induced ototoxicity. In this regard, it has been reported that neomycin and kanamycin are agonists at a polyamine site on the N-methyl-D-aspartate (NMDA) receptor based on their effects in ligand-binding assays with NMDA receptors on synaptic membranes (Pullan et al., 1992; Segal and Skolnick, 1998). Neomycin and kanamycin, like polyamines, can increase the binding of radiolabeled 1-(1-(2-thienyl)cyclohexyl)piperidine and dizocilpine (MK-801). Furthermore, neomycin was found to enhance NMDA-activated currents in rat hippocampal pyramidal neurons with a mechanism similar to that of spermine (Lu et al., 1998). There is also a report that ifenprodil, a novel NMDA receptor antagonist (Carter et al., 1990; Williams, 1993), limits aminoglycoside-induced hearing loss (Basile et al., 1996).

A number of modulators, including spermine and protons, influence NMDA receptors, and there are complex interactions between these modulators (McBain and Mayer, 1994; Williams, 1997). Spermine has several macroscopic effects on NMDA receptors, including glycine-independent stimulation (seen with saturating concentrations of glycine) and voltage-dependent block (Durand et al., 1993; Williams et al., 1994). Protons inhibit NMDA receptors with a tonic inhibition of ~50% at physiological pH (Tang et al., 1990; Traynelis and Cull-Candy, 1990). The glycine-independent form of spermine stimulation may involve relief of proton inhibition, and both processes are influenced by the alternatively spliced insert encoded by exon 5 in the NR1 subunit (Zheng et al., 1994; Traynelis et al., 1995). NMDA receptors are heterooligomers composed of combinations of NR1 and NR2 subunits. Glycine-independent spermine stimulation is seen at receptors containing NR1 variants, such as NR1A, that lack the proline at position 109, which is believed to form a hydrogen bond with the P-12 proline of glycine.

Received for publication February 23, 1999.

ABBREVIATIONS: NMDA, N-methyl-D-aspartate; BAPTA, 1,2-bis(2-aminophenoxy)ethane-N,N,N′,N′-tetraacetic acid; MK-801, dizocilpine.
exon 5 insert, together with NR2B, but not at receptors containing NR2A, NR2C, or NR2D. Voltage-dependent block is seen at both NR1/NR2A and NR1/NR2B receptors but is weak or absent at NR1/NR2C and NR1/NR2D receptors (Williams, 1997).

As a strategy to search for residues in the NMDA receptor that are involved in modulation by spermine, we compared the amino acid sequence of NR1 with the sequences of PotD, a polyamine-binding protein from *Escherichia coli* (Sugiyama et al., 1996; Kashiwagi et al., 1996b), and the *E. coli* spermidine acetyltransferase (Fukuchi et al., 1994). Several regions in the extracellular domains of NR1 show weak homology with PotD and spermidine acetyltransferase, and we studied the effects of point mutations in those regions. We identified E342 and D669 in NR1A as residues that are important for glycine-independent spermine stimulation. We also found that residues in the M2 pore-forming region of NR1, including W608 and N616, and in the proximal N terminus, including E181 and E185, affect spermine stimulation. All of the residues that control spermine stimulation also affect pH sensitivity of NMDA receptors (Williams et al., 1995; Kashiwagi et al., 1996a, 1997; Masuko et al., 1999). Mutants that affect spermine stimulation and pH sensitivity also produce small decreases in ifenprodil inhibition. These effects are likely to be secondary to the change in pH sensitivity, because ifenprodil inhibition is pH-sensitive (Pahk and Williams, 1997). Recently, we have identified residues in NR1 that form part of the ifenprodil-binding site. Mutations at these residues drastically reduce the inhibitory effects of ifenprodil but have little or no effect on sensitivity to spermine and pH (Masuko et al., 1999).

In this study, we have determined whether aminoglycoside antibiotics share common structural determinants with spermine for potentiation of NMDA receptors. We measured the effects of aminoglycosides at wild-type and mutant NMDA receptors expressed in *Xenopus* oocytes. We found that several aminoglycosides have effects similar to spermine. Furthermore, the degree of potentiation of NMDA receptors by aminoglycosides was nearly parallel with their relative potencies to induce hearing loss (Frost et al., 1960; Begg and Barclay, 1995). The results are consistent with the idea that aminoglycoside antibiotics cause hearing loss through binding to a polyamine site on NMDA receptors.

**Experimental Procedures**

**cDNA Clones and Site-Directed Mutagenesis.** The wild-type NR1A and NR1B clones and the W608L and N616Q mutants (Moriyoshi et al., 1991; Sugihara et al., 1992; Sakurada et al., 1993) were gifts from Dr. S. Nakanishi (Kyoto University, Faculty of Medicine, Kyoto, Japan). The NR1A variant lacks the 21-amino acid encoded by exon 5, whereas NR1B contains the insert. The wild-type NR2A and NR2B clones (Monyer et al., 1992) were gifts from Dr. P. H. Seeburg (Center for Molecular Biology, University of Heidelberg, Heidelberg, Germany). The mouse NR2C and NR2D clones (e3 and e4) (Ikeda et al., 1992; Kutsuwada et al., 1992; Williams, 1995) were gifts from Dr. M. Mishina (Faculty of Medicine, University of Tokyo, Tokyo, Japan).

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**Fig. 1.** Structures of aminoglycoside antibiotics.
The NR1A mutants Y109L, Y114L, E181Q/E185Q, E342Q, W563L, E621Q, and D669N were prepared as described previously (Williams et al., 1995; Kashiwagi et al., 1996a, 1997; Masuko et al., 1999). Amino acids are numbered from the initiator methionine in NR1A (Moriyoshi et al., 1991).

Preparation of Oocytes and Voltage-Clamp Recording. Adult female *Xenopus laevis* (Saitama Experimental Animals Supply Co. Ltd., Saitama, Japan) were chilled on ice, and the preparation and maintenance of oocytes were carried out using methods similar to those described (Williams et al., 1993). Capped cRNAs were prepared from linearized cDNA templates using mMessage mMachine kits (Ambion, Austin, TX). Oocytes were injected with NR1A and NR2 cRNAs at a ratio of 1:5 (0.2–4 ng of NR1A plus 1–20 ng of NR2). Macroscopic currents were recorded with a two-electrode voltage-clamp using Dual Electrode Voltage Clamp Amplifier CEZ-1250 (Nihon Koden, Tokyo, Japan). Electrodes were filled with 3 M KCl. Oocytes were continuously superfused (ca. 5 ml/min) with a Mg$^{2+}$-free saline solution (96 mM NaCl, 2 mM KCl, 1.8 mM BaCl$_2$, 10 mM HEPES, pH 7.5). This solution contained BaCl$_2$ rather than CaCl$_2$, and, in most experiments, oocytes were injected with K$^+$-1,2-bis(2-aminophenoxy)ethane-$N,N',N''$N''-tetraacetic acid (BAPTA; 100 nM 40 mM, pH 7.4) on the day of recording to eliminate Ca$^{2+}$-activated Cl$^{-}$ currents (Leonard and Kolso, 1990; Williams, 1993). To study the pH sensitivity of NMDA receptors, glutamate was applied in buffer at a given pH with a 30- to 40-s wash at that pH before and after application of glutamate. Concentration-response curves for glutamate and glycine were determined by using five to seven different concentrations of glutamate or glycine in the presence of a saturating concentration of coagonist. Data were recorded by using a MacLab/200 interface with MacLab Chart V3.5 software (AD Instruments, Tokyo, Japan).

**Materials.** Glutamate, glycine, neomycin B, paromomycin, gentamicin C, kanamycin A, geneticin, streptomycin, and kasugamycin, and pu-trescine.

<table>
<thead>
<tr>
<th>Compound</th>
<th>No. of Amino Groups</th>
<th>Enhancement of NMDA Receptor Activity</th>
<th>Hearing Loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neomycin B</td>
<td>6</td>
<td>61%</td>
<td>42 µM</td>
</tr>
<tr>
<td>Paromomycin</td>
<td>5</td>
<td>38%</td>
<td>97 µM</td>
</tr>
<tr>
<td>Gentamicin C</td>
<td>5</td>
<td>32%</td>
<td>38 µM</td>
</tr>
<tr>
<td>Kanamycin A</td>
<td>4</td>
<td>24%</td>
<td>134 µM</td>
</tr>
<tr>
<td>Geneticin</td>
<td>4</td>
<td>31%</td>
<td>129 µM</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>3</td>
<td>16%</td>
<td>67 µM</td>
</tr>
<tr>
<td>Kasugamycin</td>
<td>2</td>
<td>0%</td>
<td>—</td>
</tr>
<tr>
<td>Pu-trescine</td>
<td>2</td>
<td>0%</td>
<td>—</td>
</tr>
</tbody>
</table>

*TABLE 1* Relationship between enhancement of NMDA receptor activity and hearing loss

Values of maximal enhancement (%) and EC$_{50}$ were determined from the data shown in Fig. 2, in which the concentrations of aminoglycosides and polyamines were varied from 0 to 300 µM. The degree of hearing loss was estimated from the data obtained by Frost et al. (1960) and Begg and Barclay (1995).

**Fig. 2.** Effects of aminoglycoside antibiotics and polyamines at NMDA receptors. A, the effects of 100 µM spermine and 200 µM neomycin B, kanamycin A, or streptomycin on inward currents induced by glutamate (Glu, 10 µM; with 10 µM glycine) were measured in oocytes expressing NR1A/NR2B receptors and voltage-clamped at −20 mV. B, the effects of various concentrations of aminoglycosides and polyamines at NR1A/NR2B are shown. ○, spermine; △, neomycin B; ■, paromomycin; ●, gentamicin C; ○, geneticin; ◆, spermidine; △, kanamycin A; □, streptomycin; ■, kasugamycin; ◆, pu-trescine. Values are means ± S.E. from four oocytes.
Stimulatory Effects of Aminoglycoside Antibiotics at NMDA Receptors. We first carried out experiments to look for stimulatory effects of aminoglycoside antibiotics at NR1A/NR2B receptors. The structures of the aminoglycosides used in this study are shown in Fig. 1. To look for stimulation, we measured the effects of aminoglycosides on responses to glutamate (10 μM, with 10 μM glycine) at NR1A/NR2B receptors in oocytes voltage-clamped at −20 mV. For comparison, we also measured the effects of spermine (Fig. 2). Kasugamycin and spectinomycin, containing two amino groups like putrescine, did not show any stimulation (Fig. 2 and Table 1). Neomycin B, which contains six amino groups, showed the greatest degree of stimulation, similar to that seen with spermine. Paromomycin and gentamicin C, containing five amino groups, also markedly potentiated NMDA receptor activity, whereas a weaker stimulation was seen with kanamycin A, genetin, and streptomycin, each having four or three amino groups. The aminoglycosides by themselves did not induce currents (illustrated for neomycin in Fig. 2A). The polyamines and aminoglycosides had similar potencies, with EC50 values ranging from 40 to 130 μM, but with markedly different degrees of potentiation (Fig. 2 and Table 1). The

Results

Stimulatory Effects of Aminoglycoside Antibiotics at NMDA Receptors. We first carried out experiments to look for stimulatory effects of aminoglycoside antibiotics at NR1A/NR2B receptors. The structures of the aminoglycosides used in this study are shown in Fig. 1. To look for stimulation, we measured the effects of aminoglycosides on responses to glutamate (10 μM, with 10 μM glycine) at NR1A/NR2B receptors in oocytes voltage-clamped at −20 mV. For comparison, we also measured the effects of spermine (Fig. 2). Kasugamycin and spectinomycin, containing two amino groups like putrescine, did not show any stimulation (Fig. 2 and Table 1). Neomycin B, which contains six amino groups, showed the greatest degree of stimulation, similar to that seen with spermine. Paromomycin and gentamicin C, containing five amino groups, also markedly potentiated NMDA receptor activity, whereas a weaker stimulation was seen with kanamycin A, genetin, and streptomycin, each having four or three amino groups. The aminoglycosides by themselves did not induce currents (illustrated for neomycin in Fig. 2A). The polyamines and aminoglycosides had similar potencies, with EC50 values ranging from 40 to 130 μM, but with markedly different degrees of potentiation (Fig. 2 and Table 1). The

Fig. 3. Subunit specificity of aminoglycoside stimulation. The effects of 100 μM spermine and 200 μM aminoglycoside antibiotics were determined in oocytes expressing NR1A/NR2A, NR1A/NR2B, and NR1B/NR2B receptors and voltage-clamped at −20 mV, and NR1A/NR2C and NR1A/NR2D receptors were voltage-clamped at −30 mV. Values are means ± S.E. from four oocytes.
stimulatory effects of aminoglycoside antibiotics were almost parallel with the number of amino groups and, interestingly, with their ability to induce hearing loss (Frost et al., 1960; Begg and Barclay, 1995) (Table 1).

To determine the subunit-specificity of stimulation by aminoglycosides, we studied their effects at NR1A/NR2 receptors containing different NR2 subunits: NR2A, NR2B, NR2C, and NR2D. We also studied NR1/NR2B receptors containing the NR1s variant, which includes the exon 5 insert, because receptors containing NR1s do not show spermine stimulation (Zheng et al., 1994; Traynelis et al., 1995). Aminoglycoside antibiotics did not potentiate responses at receptors containing NR2A, NR2C, NR2D, or NR1s (Fig. 3), supporting the idea that aminoglycosides may act at the spermine-binding site or share structural and mechanistic properties in common with spermine. Neomycin B slightly decreased the response at NR1A/NR2A receptors, but we have not studied this effect in detail.

Spermine can increase the affinity of NMDA receptors for glycine and decrease the affinity for glutamate. Aminoglycoside antibiotics had effects similar to spermine (Fig. 4). We calculated the EC50 for glycine and glutamate measured in the absence and presence of aminoglycosides (Fig. 4D). Neomycin B had the most pronounced effect on the affinity of NMDA receptors for glycine and glutamate, and kanamycin A and streptomycin also increased glycine sensitivity (Fig. 4). Spermine stimulation is influenced by extracellular pH and may involve relief of tonic proton inhibition at NR1A/NR2B receptors (Traynelis et al., 1995). Stimulation by aminoglycosides also was influenced by extracellular pH (Fig. 4), with a larger stimulation at more acidic pH. The pH IC50 was shifted to more acidic values in the presence of neomycin B, kanamycin A, and streptomycin, similar to effects seen with spermine (Fig. 4D).

Because it has been reported that ifenprodil limits aminoglycoside-induced hearing loss (Basile et al., 1996), the effects of ifenprodil on NMDA receptors were examined in the presence and absence of aminoglycosides. Ifenprodil inhibited NMDA responses, and the aminoglycosides had little effect on ifenprodil inhibition (Fig. 5). The IC50 values for ifenprodil in the absence or presence of spermine, neomycin B, kanamycin A, and streptomycin were 0.24, 0.48, 1.10, 0.30, and 0.35 μM, respectively. Because ifenprodil is equally effective in the absence or presence of aminoglycosides, the data suggest that ifenprodil will function as an effective NMDA antagonist even in the presence of aminoglycoside stimulation, which is consistent with the ability of ifenprodil to limit aminoglycoside-induced hearing loss if that loss results from overactivation of NMDA receptors (Basile et al., 1996).

Effects of Aminoglycoside Antibiotics on Mutated NMDA Receptors. The stimulatory effects of several aminoglycoside antibiotics were measured at receptors containing NR1A mutants. These mutants affect the glycine-independent form of spermine stimulation, and some of the mutated residues may normally contribute to a spermine binding site (Williams et al., 1995; Kashiwagi et al., 1996a, 1997; Masuko et al. 1999). As shown in Fig. 6A, the stimu-
latory effects of aminoglycosides, as well as those of spermine, were abolished at receptors containing NR1A E181Q/E185Q, E342Q, W608L, N616Q and D669N. Neomycin B inhibited the response at receptor containing NR1A D669N. The results suggest that aminoglycoside antibiotics bind to the stimulatory spermine-binding site on NMDA receptors or share common structural and mechanistic determinants with spermine.

We have recently identified amino acid residues in the proximal N-terminal domain of NR1A that selectively influence inhibition by ifenprodil and that appear to form part of the ifenprodil-binding site (Masuko et al., 1999). These residues include NR1A Y109 and Y114. Inhibition by ifenprodil was reduced at NR1A Y109L and Y114L, but the mutants did not reduce the stimulatory effects of spermine and aminoglycosides (Fig. 6B). An unusual effect was seen with the Y109L mutant, at which neomycin B increased the response greatly, but we have not studied the mechanism of this effect. These results indicate that aminoglycoside antibiotics have stimulatory effects that may be mediated through the stimulatory spermine-binding site but that their effects are largely independent of the ifenprodil-binding site.

Voltage-Dependent Inhibition by Aminoglycoside Antibiotics at NMDA Receptor. We carried out experiments to determine whether aminoglycosides produce voltage-dependent inhibition of NMDA receptors, as has been described for spermine. These experiments were carried out with NR1A/NR2A receptors, which do not show stimulation by spermine or aminoglycosides. We studied the effects of aminoglycosides in oocytes voltage-clamped at -20 mV and -100 mV (Fig. 7A). All of the aminoglycosides (200 µM) produced a voltage-dependent inhibition of NR1A/NR2A receptors, but their effects were weaker than that of 100 µM spermine. Neomycin B, gentamicin C, and streptomycin are also shown. B, the effects of spermine and aminoglycoside antibiotics were determined at mutated NR1A/NR2A receptors at -100 mV. Values are means ± S.E. from four oocytes.

Voltage-dependent inhibition by neomycin B, gentamicin C, and streptomycin was measured at normal NR1A/NR2A receptors containing NR1 mutants that reduce voltage-dependent block by spermine (Fig. 7B). In general, the inhibition by these three aminoglycosides was reduced by the NR1A mutants W563L, N616Q, E621Q, and D669N.
tion by neomycin B was not significantly reduced by the NR1A mutants W563L and D669N.

Discussion

Because aminoglycoside antibiotics are useful in the treatment of serious infections caused by Gram-negative bacilli (Begg and Barclay, 1995), it is important to try to limit their ototoxic side effects. It has been suggested that hearing loss may be related to enhancement of NMDA-receptor activity through the binding of aminoglycosides to a spermine-binding site on NMDA receptors (Pullan et al., 1992; Basile et al., 1996; Lu et al., 1998; Segal and Skolnick, 1998). We have been studying the properties of spermine-binding sites on the NMDA receptor using recombinant NMDA receptors expressed in Xenopus oocytes (Williams et al., 1995; Kashwagi et al., 1996a, 1997; Masuko et al., 1999). Therefore, we used this system to study in detail the effects of several aminoglycoside antibiotics on NMDA receptors. We studied eight aminoglycosides (neomycin B, paromomycin, gentamicin C, kanamycin A, genixin, streptomycin, kasugamycin, and spectinomycin) and found that the degree of enhancement of NMDA receptor activity was nearly parallel with the degree of hearing loss (Frost et al., 1960; Begg and Barclay, 1995) (Table 1).

Aminoglycosides have stimulatory properties only at NR1A/NR2B receptors, and their subunit selectivity is thus similar to that of spermine. The spermine-binding site that is involved in potentiation of NMDA receptors appears to be distinct from that responsible for voltage-dependent block, although some amino acid residues in NMDA subunits can influence both potentiation and block by spermine (Williams et al., 1995; Kashwagi et al., 1996a, 1997). Furthermore, we have found that the ifenprodil-binding site is distinct from the sites that control sensitivity to spermine and pH (Masuko et al., 1999). The results of studies with mutant NMDA receptors support the idea that the hearing loss induced by aminoglycosides is due to an effect at the stimulatory polyamine site on NMDA receptors rather than to voltage-dependent block of the receptors. It is known that activation of glutamate receptors is involved in membrane depolarization in cochlear hair cells (Kataoka and Ohmori, 1994) and that ifenprodil markedly attenuates both the hearing loss and the destruction of cochlear hair cells produced by aminoglycosides (Basile et al., 1996). Thus, potentiation of NMDA receptors by aminoglycosides may lead to the death of hair cells and, subsequently, to hearing loss.

Basile et al. (1996) reported that the potencies of aminoglycosides to enhance [3H]MK-801 binding to NMDA receptors generally correlated well with their ability to produce hearing loss in humans, but streptomycin was a prominent outlier. In the present work, potentiation of NMDA receptors by aminoglycosides, including streptomycin, was correlated with their ability to induce hearing loss. Overall, the results of the present work are similar to those seen in studies of [3H]MK-801 binding (Basile et al., 1996), but there are some differences in the apparent activities of some aminoglycosides. This likely reflects the multiple mechanisms of action of these compounds and the complexities of both experimental systems.

Neomycin B had an unusual profile among the aminoglycosides in the following respects: 1) a small inhibition at NR1A/NR2A receptors at relatively depolarized membrane potentials; 2) a voltage-dependent inhibition unaffected by NR1A D669N and W563L mutants; and 3) a large potentiation of receptors containing the NR1A Y109L mutant. The small inhibition seen at relatively depolarized potentials may simply be due to a residual voltage-dependent channel block by neomycin. The lack of effect of mutations at D669 and W563 may mean that neomycin does not interact with these residues, whereas the other aminoglycosides and spermine do interact with those residues. D669 and W563 are located at the entrance or mouth of the NMDA channel. Because neomycin and the other aminoglycosides are larger molecules than spermine, it may be that the conformation rather than the size of these compounds is an important determinant of their blocking activity. The large potentiation of NR1A(Y109L)/NR2B receptors by neomycin is difficult to interpret. There are complex interactions between polyamines, protons, and ifenprodil at NMDA receptors. Some mutations at Y109, which is part of the ifenprodil site, can disrupt pH sensitivity, although Y109L has little effect on sensitivity to spermine and pHi (Masuko et al., 1999). It may be that this mutation disrupts the coupling of proton inhibition and aminoglycoside sensitivity in a way that is specific for neomycin, accounting for the large potentiation seen with neomycin at receptors containing Y109L.

Our results suggest that it may be difficult to look for aminoglycoside antibiotics that are not ototoxic, because all aminoglycosides that have several amino, imino, or guanidino groups showed a potentiation of NMDA receptors. Thus, the most effective method to prevent hearing loss induced by aminoglycosides may be by coadministration of drugs such as ifenprodil that reduce activation of NMDA receptors. However, it is still worthwhile to look for aminoglycosides that have fewer amino groups but retain strong antibiotic properties. Such aminoglycosides may not induce ototoxicity.

References

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