action potential–linked calcium channels, since early ototoxicity is reversed by calcium.[1,2]

We suggest that the screening of potential aminoglycoside antibiotics at N-channels may identify the agents that are less toxic.

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AMINOGLYCOSIDE EFFECTS ON VOLTAGE-SENSITIVE CALCIUM CHANNELS AND NEUROTOXICITY

To the Editor: Since ototoxicity and neuromuscular toxicity of aminoglycoside antibiotics are reversed by calcium,[1,2] and presynaptic events appear to be involved in aminoglycoside-induced neuromuscular blockade,[3,4] we suspected a role for voltage-sensitive calcium channels in aminoglycoside neurotoxicity. Among the several subtypes of those channels, the N-channel is predominantly involved in neurotransmitter release.[5-7] We investigated the influences of therapeutic concentrations of aminoglycosides on N-channels monitored by either $^{45}Ca^{2+}$ uptake or binding of the calcium-channel toxin [^{125}I]omega-conotoxin GV IA, which predominantly labels N-channels in neuronal membranes.[8]

Aminoglycosides inhibit brain neuronal and sympathetic-ganglia–membrane binding of [^{125}I]conotoxin, and relative potencies correlate closely with neuromuscular toxicity ($r = 0.69$, $P<0.02$ for brain; $r = 0.70$, $P<0.01$ for ganglia) (Table 1). By contrast, the aminoglycosides are much weaker or totally inactive at L-channels labeled with [^{3}H]nitrendipine. Both the absolute and relative drug potencies are similar in blocking [^{125}I]conotoxin binding and $^{45}Ca^{2+}$ uptake into rat-brain synaptosomes under conditions in which calcium accumulation selectively involves N-channels ($r = 0.94$, $P<0.001$).[7] Aminoglycoside inhibition of $^{45}Ca^{2+}$ uptake also correlates well with neuromuscular toxicity ($r = 0.71$, $P<0.001$). Moreover, the drugs inhibit $^{45}Ca^{2+}$ uptake and [^{125}I] conotoxin by 50 percent at therapeutic plasma and tissue concentrations.[1,2]

Our data suggesting a role for N-type calcium channels in aminoglycoside neurotoxicity are in accord with the reversal of toxic effects by calcium treatment. Other calcium-dependent events may also be relevant, especially in renal toxicity, as is suggested by aminoglycoside inhibition of renal phosphatidylinositol phospholipase.[9] Ototoxicity derived from initial impairment of cochlear action potentials by aminoglycosides may reflect an influence on

Table 1. Aminoglycoside Potencies at Calcium-Channel Binding Sites and Calcium Flux through N-Channels.

Aminoglycoside	Presynaptic Neurotoxicity*	[^{3}H]Nitrendipine Binding to Brain Membranes† (N = 12)	[^{125}I]Conotoxin Binding to Brain Membranes‡ (N = 11)	$^{45}Ca^{2+}$ Uptake§ (N = 17)	[^{125}I]Conotoxin Binding to Sympathetic Ganglia‡ (N = 11)
		median inhibitory concentration (μM)			
Neomycin	++++	>1000	3	5	7
Amikacin	+++	>1000	10	10	15
Gentamicin	++	>1000	10	20	20
Tobramycin	++	>1000	20	50	28
Streptomycin	++	330	50	150	60
Kanamycin	+	>1000	200	500	250

*Presynaptic neuromuscular toxicity levels were derived from experimental studies.[3]

†[^{3}H]Nitrendipine binding was assayed in whole rat-brain homogenates as previously described.[6] Median inhibitory concentrations were derived from single experiments performed in duplicate and repeated twice.

‡[^{125}I]Omega-conotoxin binding was assayed in whole rat-brain homogenates and rabbit sympathetic-ganglion homogenates as previously described.[8] Median inhibitory concentrations were derived from single experiments performed in duplicate and repeated twice.

§Synaptosomal $^{45}Ca^{2+}$ flux was assayed as previously described.[7] Median inhibitory concentrations were derived from individual experiments performed in triplicate and repeated three times and represent the concentration of drug inhibiting ligand binding by 50 percent. Correlations (see text) were computed from all repetitions of experiments.