Gastric ulcers reduce A-type potassium currents in rat gastric sensory ganglion neurons

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Submitted 12 June 2003; accepted in final form 1 October 2003

Dang, K., Bielefeldt K., and Gebhart G. F. Gastric ulcers reduce A-type potassium currents in rat gastric sensory ganglion neurons. Am J Physiol Gastrointest Liver Physiol 286: G573–G579, 2004. First published October 2, 2003; 10.1152/ajpgi.00258.2003.—Voltage-dependent potassium currents are important contributors to neuron excitability and thus also to hypersensitivity after tissue insult. We hypothesized that gastric ulcers would alter K+ current properties in primary sensory neurons. The rat stomach was surgically exposed, and a retrograde tracer (1,1'-dioctadecyl-3,3,3,3'-tetramethylindocarbocyanine methanesulfonate) was injected into multiple sites in the stomach wall. Inflammation and ulcers were produced by 10 injections of 20% acetic acid (HAc) in the gastric wall. saline (Sal) injections served as control. Nodose or T9–T10 dorsal root ganglia (DRG) cells were harvested and cultured 7 days later to record whole cell K+ currents. Gastric sensory neurons expressed transient and sustained outward currents. Gastric inflammation significantly decreased the A-type K+ current density in DRG and nodose neurons (Sal vs. HAc: 82.9 ± 7.9 vs. 46.5 ± 6.1 pA/pF; nodose: 149.2 ± 10.9 vs. 71.4 ± 11.8 pA/pF), whereas the sustained current was not altered. In addition, there was a significant shift in the steady-state inactivation to more hyperpolarized potentials in nodose neurons (Sal vs. HAc: −76.3 ± 1.0 vs. −83.6 ± 2.2 mV) associated with an acceleration of inactivation kinetics. These data suggest that a reduction in K+ currents contributes, in part, to increased neuron excitability that may lead to development of dyspeptic symptoms.

Male Sprague-Dawley rats (150–200 g; Harlan, Indianapolis, IN) were used for all experiments. Rats were housed under a 12:12-h light-dark cycle with free access to food and water and were handled following the guidelines of the American Physiological Society. The experimental protocol was approved by the Animal Care and Use Committee of The University of Iowa.

Cell labeling and induction of gastric ulcers. Under intraperitoneal pentobarbital sodium anesthesia (50 mg/kg), the rat stomach was surgically exposed and 1,1'-dioctadecyl-3,3,3,3'-tetramethylindocarbocyanine methanesulfonate (DiI; 100 mg in 2 ml DMSO; Molecular Probes, Eugene, OR) was injected into 10 sites in the stomach wall (4 ml/site). The wound was closed with 4.0 silk suture, and rats were allowed to recover for 7 days. Rats were again anesthetized with pentobarbital sodium (as above), the stomach was reexposed, and 20% acetic acid (HAc) or saline (sal; control) was injected into 10 sites in the rat stomach wall in a similar manner (4 μl/site). The previously labeled areas could be easily identified due to the presence of DiI, allowing us to selectively inject HAc or Sal into areas with labeled afferents (1). Nodose and DRG neurons were harvested 7 days later.

Cell dissociation and culture. Rats were anesthetized and decapitated, and the nodose ganglia or bilateral T9-T10 DRG was rapidly removed. The ganglia were minced and incubated at 37°C, 5% CO₂ for 45 min in low glucose DMEM (GIBCO, Invitrogen, Grand Island, NY) containing collagenase (type 4; 2 mg/ml; Worthington Biochemical, Lakewood, NJ), trypsin (1 mg/ml), and DNase (0.1 mg/ml; both from Worthington). Tissue fragments were gently triturated to encourage cell dissociation. The enzymatic digestion was terminated by adding soybean trypsin inhibitor (2 mg/ml; Sigma-Aldrich, St. Louis, MO), bovine serum albumin (2 mg/ml; Amresco, Solon, OH), and 5% rat serum (Atlanta Biologicals, Norcross, GA). Cells were collected by 5-min centrifugation at 150 g and resuspended in DMEM containing 5% rat serum and 2% chick embryo extract (GIBCO). The cells were plated on poly-d-lysine-coated coverslips and incubated at 37°C, 5% CO₂ for 2–3 h before electrophysiological studies. Acutely dissociated neurons were round and devoid of any processes, thus reducing space-clamp errors.

PAIN AND DISCOMFORT ARE PROMINENT SYMPTOMS OF MANY CHRONIC DISEASES OF THE GASTROINTESTINAL TRACT AND ARE CONSIDERED TO REFLECT VISCERAL HYPERSENSITIVITY. CHANGES IN THE EXCITABILITY OF PRIMARY AFFERENT NEURONS (PERIPHERAL SENSITIZATION) AND/OR ALTERED INFORMATION PROCESSING IN THE SPINAL CORD OR HIGHER CENTERS (CENTRAL SENSITIZATION) ARE PRINCIPAL REASONS FOR DEVELOPMENT OF SUCH HYPERSENSITIVITY. WE RECENTLY DEVELOPED ANIMAL MODELS TO STUDY THE RELATIVE ROLE OF PERIPHERAL SENSITIZATION IN GASTRIC HYPERSENSITIVITY (32). BECAUSE VOLTAGE-SENSITIVE ION CURRENTS ARE CRITICAL FOR ACTION POTENTIAL GENERATION AND NEURON EXCITABILITY (26), WE EXAMINED IN THESE MODELS PROPERTIES OF VOLTAGE-SENSITIVE SODIUM CURRENTS IN DISSOCIATED PRIMARY GASTRIC SENSORY NEURONS HARVESTED FROM THE NODOSE AND DORSAL ROOT GANGLION (DRG) (1). WE FOUND SIGNIFICANT CHANGES IN PEAK SODIUM CURRENT, CONTRIBUTED ALMOST EXCLUSIVELY BY THE TTX-RESISTANT CURRENT, AND IN ACTIVATION AND INACTIVATION KINETICS AFTER GASTRIC INSULT, CONSISTENT WITH AN IMPORTANT ROLE OF PERIPHERAL SENSITIZATION IN VISCERAL HYPERSENSITIVITY TRIGGERED BY GASTRIC INFLAMMATION.

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Solutions and electrophysiological recordings. Cells were rinsed and transferred to a recording chamber (1 ml) filled with external solution (in mM): 150 N-methyl-D-glucamine (NMDG), 5 KCl, 4 MgCl₂, 0.03 CdCl₂, 10 HEPES, 10 glucose, and 0.1 TTX. pH was adjusted to 7.4 with HCl with an osmolarity of 295 mosM. Neurons that innervated the stomach were identified by Dil content using a rhodamine filter (excitation wavelength ~546 nm, barrier filter at 580 nm). Consistent with our previous studies, only one to five cells per coverslip (<2% of the total cells) were unambiguously labeled (1). Fire-polished micropipettes with tip resistances of 2–3 MΩ were used for voltage-clamp recordings. The pipette was filled with internal solution (in mM): 100 NMDG, 40 KCl, 1 CaCl₂, 2 MgCl₂, 10 EGTA, 4 Na₂ATP, and 0.5 Tris-GTP. pH was adjusted to 7.2 using HCl with an osmolarity of 295 mosM. After gigaseal formation, the membrane patch was ruptured by slight suction. The voltage was clamped at −70 mV by an Axopatch 200B amplifier (Axon Instruments, Union City, CA), digitized at 10 kHz (Digidata 1350, Axon Instruments), and controlled by Clampex software (Axon Instruments). Series resistance was compensated by >60%. Considering the peak transient outward current of <4 nA, the maximal voltage error after electronic correction would be <9 mV, assuming a doubling of the access resistance after establishing the whole cell configuration. Cells that had <60% series resistance compensation were discarded from the study. The leak current and residual capacitative transients were digitally subtracted using a Pn protocol, with P being the test pulse and n being the number of hyperpolarizing voltage steps used for digital subtraction (n = 6 unless stated otherwise). To isolate transient outward currents, we employed a previously described electrophysiological protocol (11, 27). Cells were held for 500 ms at −110 mV before stepping them to various test potentials between −30 and 50 mV. To inactivate the transient outward current, the sequence was repeated from a prepotential of −30 mV. The digital subtraction of current traces from those triggered from a holding potential of −110 mV isolated the transient component of the outward current. To ensure that slow inactivation of the delayed rectifier did not significantly confound the results, we inhibited the transient outward current and fitted the decay of the sustained current with a single exponential. The time constant of 2.7 ± 0.1 s at a test potential of 50 mV (n = 3) is consistent with prior data on the C-type inactivation and argues against a distortion of our results due to slow inactivation of the delayed rectifier. All experiments were performed at room temperature (21–23°C).

Drugs were dissolved in water and added to the recording chamber and allowed to equilibrate for 5 min before recordings began. Unless stated otherwise, all chemicals were purchased from Sigma-Aldrich.

Statistical analysis. All data are given as means ± SE. Comparisons were made using Student’s unpaired t-test. Results were considered to be statistically significant when P < 0.05.

RESULTS

Electrophysiological characterization of K⁺ currents. Consistent with prior reports, depolarization from −110 mV to various test potentials triggered rapidly activating and partially inactivating outward currents in both nodose and DRG neurons (Fig. 1). Changes in the extracellular potassium concentration shifted the reversal potential as predicted by the Nernst equation, confirming that potassium was the primary charge carrier (reversal potential at [K⁺]ₑ = 5 mM: −48 mV; reversal potential at [K⁺]ₑ = 20 mM: −17 mV).

To further characterize the transient current, we used the electrophysiological approach to separate inactivating from sustained currents described above (see MATERIALS AND METHODS). Gastric nodose neurons expressed inactivating outward currents that could be differentiated based on their voltage dependence and kinetics. A rapidly activating and inactivating current was present in 14 of 20 cells examined. The current reached its peak amplitude within 3.9 ± 0.4 ms and decayed with a time constant of 5.6 ± 0.8 ms after a depolarization to +50 mV. As shown in Fig. 2, A and B, the time course of activation and inactivation was voltage dependent. A second inactivating component became obvious at more depolarized potentials in the same 14 of these 20 cells. At steps to +50 mV, the current reached its peak within 28 ± 7.4 ms and inactivated with a time constant of 136 ± 8 ms. In contrast to the rapidly decaying current, the time course of inactivation did not depend on voltage within the voltage range tested (Fig. 2). Similarly, we identified rapidly and slowly activating and inactivating outward currents in 14 and 19 of 30 DRG neurons, respectively. The time constants at 50 mV were 6.1 ± 1 and 125.1 ± 10.9 ms, respectively (Fig. 2, C and D).

Fig. 1. Representative outward currents obtained in gastric sensory neurons evoked in dorsal root ganglia (DRG; A) and nodose ganglia (NG) neurons (B). DRG and nodose neurons had a cell capacitance of ~75 and 50 pF, respectively. Outward currents elicited by a 300-ms depolarization to +50 mV from a holding potential (Vₑ) of −110 or −30 mV are superimposed. The A current (I_A; asterisk) was isolated by digitally subtracting the current obtained after depolarization from −30 mV from the current triggered after depolarization from −110 mV. Gastric ulceration decreased the A current in DRG (C) and NG (D) neurons. HAc, acetic acid.
To further characterize the transient outward currents, we determined the voltage dependence of inactivation by changing the voltage from prepotentials between −110 and 0 mV for 500 ms to a test potential of +10 mV. All results were normalized to the peak current at −110 mV. As shown in Fig. 3, the inactivating current in both nodose and DRG neurons could be dissected into two components based on its voltage dependence of inactivation. Approximately 35% of the peak current inactivated at hyperpolarized potentials, with an additional 15–20% inactivating at steps to −20 mV or more depolarized potentials. We fitted the decrease in peak currents at voltages negative to −40 mV to a Boltzmann equation. The voltage of half-inactivation was −78.9 ± 1.2 mV (slope factor: −7.7 ± 0.5) for DRG neurons (n = 11) and −76.3 ± 1.0 mV (slope factor: −9.6 ± 0.6) for nodose neurons (n = 12; not significant compared with DRG neurons). The second inactivating component could not be properly fit to a Boltzmann equation due to its relatively small amplitude.

Effects of 4-aminopyridine and α-dendrotoxin. To determine the pharmacological properties of outward currents, we used 4-aminopyridine (4-AP) and α-dendrotoxin (DTX). 4-AP inhibited the fast and slow transient outward currents in both nodose and DRG neurons (Fig. 4). In the presence of 5 mM 4-AP, the peak inactivating component decreased by 65 ± 7% in nodose neurons (n = 6) and 50 ± 6% in DRG neurons (n = 5). In cells with slowly inactivating outward currents, 4-AP significantly decreased the current at the end of the depolarizing pulse, which may be at least partly due to the slow inactivation kinetics. However, as shown in Fig. 4A, 4-AP did not only block the transient outward current but also affected the sustained component, albeit to a lesser degree. These results are consistent with prior reports, demonstrating that 4-AP can inhibit the delayed rectifier in some cells (24, 35).

Application of DTX (1 μM, 5 min) reduced the peak and the sustained currents in both groups of neurons studied (Fig. 5). DTX inhibited 35 ± 8 and 20 ± 4% of the A current in nodose (n = 4) and DRG (n = 5) neurons, respectively. Similarly, the sustained current at the end of a 300-ms step to 50 mV was decreased by 25 ± 7 and 11 ± 4% in nodose and DRG neurons, respectively.

Effects of gastric ulceration on K⁺ currents. HAc-induced gastric ulcers were confirmed macroscopically by the presence of ulcerations or wall thickening due to inflammation, consis-
tent with previous report (2). Gastric ulceration significantly increased nodose (n = 18) cell capacitance to 57.1 ± 3.1 pF compared with 43.1 ± 2.8 pF from Sal-treated controls (P < 0.05). In contrast, DRG (n = 18) cell capacitance remained unchanged (62.3 ± 2.5 vs. 68.1 ± 3.5 pF; not significant). To determine the effect of gastric injury on K⁺ currents, we measured the outward currents triggered by a depolarization to 50 mV. To control for changes in cell size, we divided the results by cell capacitance (current density). As shown in Fig. 5, gastric ulceration caused a significant decrease in density of the peak current from 276 ± 11 to 205 ± 11 pA/pF (n = 18; P < 0.001, Sal vs. HAc) in nodose neurons and from 266 ± 9 pA/pF to 209 ± 11 pA/pF in DRG neurons (n = 24; P < 0.01, Sal vs. HAc). In contrast, the density of the sustained outward current did not change significantly (nodose neurons: 154 ± 10 vs. 144 ± 13 pA/pF; DRG neurons: 192 ± 12 vs. 215 ± 14 pA/pF; Sal vs. HAc, respectively). Consistent with these results, digital subtraction revealed that there was a significant decrease in the peak A current from 149 ± 11 to 71 ± 12 pA/pF (n = 18; P < 0.001) in nodose neurons and from 83 ± 8 to 47 ± 6 pA/pF in DRG neurons (n = 24; P < 0.01).

To examine whether gastric ulceration altered properties of the transient outward current, we determined kinetics and the voltage dependence of activation and inactivation as described above. Because we noted a decrease in the peak current, we analyzed the voltage dependence of activation of the electrophysiologically isolated A current. We expressed the results as normalized conductance determined by dividing the current by cell capacitance.

Fig. 4. Effects of 4-aminopyridine (4-AP) and α-dendrotoxin (DTX) on the outward currents. Outward currents were evoked by depolarization to test potential of +50 mV from a holding potential of −110 mV (500 ms) in the presence and 5 min after the application of the 4-AP (A and B) and DTX (C and D), respectively. To demonstrate the effect of these agents on outward currents, the trace obtained after drug administration was digitally subtracted from the control trace (∗).

Fig. 5. Effects of gastric ulcers on outward current density in sensory neurons. Total outward current was reduced in DRG (A) and NG (B) of rats with gastric ulcers compared with controls. Digital isolation of the Iₐ, showed ~40 and 60% reductions of Iₐ in DRG and NG neurons of HAc-treated rats compared with controls. C and D: normalized conductance of the Iₐ for DRG and NG neurons, respectively. In NG neurons, the voltage dependence of activation was shifted significantly to more positive potentials following gastric ulceration (filled symbols) compared with saline-treated controls (open symbols) but remained unchanged in both groups of DRG neurons.
half-activation was significantly shifted from −26.6 ± 1.8 to −14.3 ± 4.0 mV (P < 0.05; Fig. 5). The significant decrease in transient outward current only allowed a detailed analysis in some cells. In contrast to the results obtained in nodose neurons, we did not see a significant change in the voltage dependence of activation after induction of gastric ulcerations (Fig. 5; −4.5 ± 3.5 vs. −12.7 ± 2.7 mV; Sal vs. HAc; not significant). Thirteen nodose neurons exhibited sufficient current density to allow determination of kinetics; eight primarily expressed rapidly inactivating currents, and five predominantly expressed slowly inactivating currents. Whereas the fast inactivation was not changed, the time constants of the more slowly decaying component were significantly shorter in cells from animals with gastric ulcers (Fig. 6). Of 13 DRG neurons examined, a rapidly inactivating current sufficient in amplitude to allow determination of current kinetics was present in only one cell. Two neurons expressed slowly decaying currents with time-to-peak and inactivation time constants within the range recorded under control conditions.

Because the reduction in A current density may be partly due to a change in the voltage dependence of inactivation, we examined this property in sensory neurons from HAc-treated animals following the protocol described above. As shown in Fig. 3, the two distinct components could still be separated with an apparent shift of the steady-state inactivation to more hyperpolarized potentials in nodose neurons. By fitting values obtained with prepulse potentials negative of −40 mV with the Boltzmann equation (see above), we obtained voltages for half-inactivation of −83.6 ± 2.2 mV (slope factor: 9.0 ± 0.6; n = 9; P < 0.05 compared with Sal) for nodose neurons and −79.7 ± 1.2 mV (slope factor 9.2 ± 0.5; n = 13; not significant compared with Sal) for DRG neurons.

**DISCUSSION**

With the use of a previously established animal model of gastric ulceration, we have recently shown behavioral changes consistent with the development of gastric hypersensitivity (32). To better understand peripheral mechanisms contributing to these behavioral effects, we examined the properties of primary afferent neurons innervating the stomach. The key results of the present study are I) gastric afferent neurons in the nodose and DRG ganglion express potassium currents that can be distinguished based on their electrophysiological and pharmacological properties; II) gastric ulceration decreases the transient outward current; and III) gastric ulceration changes the electrophysiological properties of the transient outward current in nodose neurons. In the aggregate, these results suggest that hypersensitivity following gastric insult is contributed to, in part, by changes in K+ currents that increase excitability of gastric sensory neurons.

Consistent with previously published reports (11, 17, 43), we identified three electrophysiologically distinct components of the total outward currents in DRG and nodose ganglion neurons. In addition to the sustained potassium current, gastric sensory neurons express two inactivating outward currents that can be distinguished based on their kinetics of activation and inactivation and their voltage dependence of inactivation. The time course of activation was strongly voltage dependent for both components. Similarly, the decay of the rapidly inactivating current accelerated with stronger depolarization, a characteristic property of the rapidly inactivating potassium current in mammalian neurons (5, 11, 27). In contrast, the more slowly inactivating component decayed at rates that did not vary consistently over the voltage range tested. Similar results have been reported for brain stem neurons and the heterologously expressed human Kv4.3 channel (9, 14), whereas others (5, 11) have described a voltage-dependent acceleration of current decay in the slowly inactivating outward current as well. These apparent discrepancies may be, at least in part, due to different recording conditions, because calcium buffering can affect inactivation kinetics (7).

We used pharmacological approaches to further characterize the transient potassium currents. Prior studies (15, 17, 41) demonstrated that 4-AP inhibits both the fast and slowly inactivating potassium currents with increasing concentrations over a range from 0.1 to 5 mM, thus limiting its use to separate these components. The onset and recovery of this block are time dependent, with prolonged inhibition even at hyperpolarized voltages, thereby compromising cell viability (39). Therefore, a single high concentration of 4-AP was selected to test whether the pharmacological characteristics are consistent with prior reports. The reduction of both the fast and slow components of the transient outward current by 4-AP confirms that this current has the typical pharmacological properties of an A current (11, 12, 27, 43). Whereas some investigators (11, 41) have reported an inhibition of transient outward currents by...
DTX, we and others (16) did not observe such a selective effect on A currents in visceral sensory neurons. This difference between neurons innervating the skin (11) and the generally unmyelinated visceral sensory neurons may be due to differential expression of potassium channel subunits (13, 19). Such a differential expression of potassium channel subunits has been documented for DRG neurons (34).

Gastric ulceration altered the properties of potassium currents in both DRG and nodose ganglia by decreasing the fast and slow components of the transient outward current, whereas the sustained potassium current remained unchanged. We also noted a change in the voltage dependence of activation and inactivation of the rapidly inactivating current, with a shift to more hyperpolarized potentials in nodose neurons, which will further decrease the number of channels that can be activated on depolarization from the resting membrane potential. Similar results have previously been described in visceral sensory neurons studied during inflammation of the bladder (42), whereas axotomy decreased potassium channel expression (22) or current density without altering channel properties (10). Such differential effects of organ inflammation compared with nerve injury have also been reported for sodium currents (1, 8).

Ishikawa et al. (22) recently reported selective downregulation of Kv1.1–3 and Kv2.1 proteins after axotomy and suggested that the reduction in expression of these K⁺ channel proteins may be responsible for the reduction in A current observed in the same model of injury (11). Similarly, changes in the expression and distribution of sodium channels have been described in response to inflammation within the target organs or axotomy (3, 18). The sparse innervation of the gastrointestinal tract with <1% of DRG neurons projecting to the stomach did not allow us to examine the molecular changes that underlie the decrease in A current density in more detail. However, others (10) have attributed the reduction of A current in cutaneous neurons after axotomy to selective downregulation of potassium channel subunits. Furthermore, potassium channel Kv1.1–2 and 1.6 proteins have been reported to influence the excitability of rat visceral sensory neurons (16).

Interestingly, we also noted a change in the size of nodose neurons, assessed by measuring the whole cell capacitance. Although we did not systematically study this and cannot reach firm conclusions based on our data, the small number of labeled gastric neurons argues against a significant selection bias. Moreover, similar findings have previously been reported in response to inflammation (1, 29, 42). The changes in voltage-sensitive currents and cell size suggest that mediators affect the soma of afferent neurons projecting to the inflamed area. Neurotrophins have been identified as important target-derived factors involved in injury and tissue repair mechanisms. Functional receptors for neurotrophins have been identified in the endings of afferent and efferent nerves (21, 29). These factors play a critical role in maintaining or modulating the functions of neurons. This is consistent with reports demonstrating degenerative changes in effenter neurons after axonal injury (31). Conversely, inflammation is associated with increases in production and release of growth factors, which may alter the electrophysiological and neurochemical properties of neurons (2, 38, 40). Zhang et al. (45) recently demonstrated a rapid change in potassium current due to nerve growth factor (NGF)-induced generation of ceramide. However, this fast effect is reversible and should thus not persist 2–8 h after cell dissociation and culture. Others (4) have described NGF-dependent changes in potassium channel expression. However, the exact role of NGF in regulating the expression of ion channels and altering neuron excitability remains unclear.

With their rapid activation and inactivation kinetics, transient potassium currents regulate action potential duration and firing patterns in neurons (23, 37, 42). Repeated depolarizations will progressively inactivate the transient currents, thereby prolonging individual action potentials and increasing the number of spikes generated during longer lasting stimulations (25). Consistent with previous publications on altered excitability of sensory neurons innervating the ileum and bladder (30, 42), we observed a reduction in action potential threshold and an increase in the number of spike discharges to current injections in gastric sensory neurons from a similar rat model of gastric ulcers (K. Dang, K. Bielefeldt, and G. F. Gebhart, unpublished observations). Considering the steep relationship between intracellular calcium concentrations and transmitter release (23), prolongations of the action potential will prolong calcium inflow through voltage-dependent calcium channels and thereby facilitate signal transmission at the synapse.

The stomach receives dual innervation through vagal and spinal afferent neurons. Although it is generally accepted that spinal pathways mediate nociceptive signaling (36), vagal afferents may contribute to chemonociception, discomfort, and emotive components associated with aversive stimuli (28, 44). Although we did not observe changes in outward currents after induction of mild superficial gastritis with iodosacetamide (1), the present results document that a more severe form of gastric inflammation altered the properties of both vagal and spinal afferents, consistent with a sensitization of both sensory pathways. These results confirm prior in vivo experiments demonstrating that inflammatory mediators rapidly sensitized vagal and spinal afferent fibers (33), suggesting that sensitized vagal afferents may contribute to dyspeptic symptoms.

ACKNOWLEDGEMENTS

We thank M. Burcham for graphics assistance.

GRANTS

This work was supported by National Institutes of Health Grants DK-01548, NS-35790, and NS-19912.

REFERENCES


