Voltage-gated sodium channels isolated from mammalian brain are composed of $\alpha$, $\beta_1$, and $\beta_2$ subunits. The $\alpha$ subunit forms the ion conducting pore of the channel, whereas the $\beta_1$ and $\beta_2$ subunits modulate channel function, as well as channel plasma membrane expression levels. $\beta_1$ and $\beta_2$ each contain a single, extracellular Ig-like domain with structural similarity to the neural cell adhesion molecule (CAM), myelin Po. $\beta_2$ contains strong amino acid homology to the third Ig domain and to the juxtamembrane region of F3/contactin. Many CAMs of the Ig superfamily have been shown to interact with extracellular matrix molecules. We hypothesized that $\beta_2$ may interact with tenascin-R (TN-R), an extracellular matrix molecule that is secreted by oligodendrocytes during myelination and that binds F3/contactin. We show here that cells expressing sodium channel $\beta_1$ or $\beta_2$ subunits are functionally modulated by TN-R. Transfected cells stably expressing $\beta_1$ or $\beta_2$ subunits initially recognized and then were repelled from TN-R substrates. The cysteine-rich amino-terminal domain of TN-R expressed as a recombinant peptide, termed EGF-L, appears to be responsible for the repellent effect on $\beta$ subunit-expressing cells. The epidermal growth factor-like repeats and fibronectin-like repeats 6–8 are most effective in the initial adhesion of $\beta$ subunit-expressing cells. Application of EGF-L to $\alpha II\Delta 1/\beta_2$ channels expressed in Xenopus oocytes potentiated expressed sodium currents without significantly altering current time course or the voltage dependence of current activation or inactivation. Thus, sodium channel $\beta$ subunits appear to function as CAMs, and TN-R may be an important regulator of sodium channel localization and function in neurons.

Sodium channels from brain are heterotrimeric structures composed of a central, pore-containing $\alpha$ subunit and two auxiliary subunits, $\beta_1$ (or its splice variant $\beta_1A$) and $\beta_2$. The $\beta$ subunits do not form the pore but play critical roles in channel gating, voltage dependence of activation and inactivation, and expression levels (1–3). $\beta_1$ and $\beta_2$ subunits contain Ig-like extracellular domains and are members of the $V$-set of the Ig superfamily that includes CAMs (3, 4). $\beta_2$ exhibits strong amino acid homology to F3/contactin, a CAM that interacts with the extracellular matrix molecule TN-R as well as with the Ig superfamily adhesion molecules L1 and TAG-1 in rodents and NgCAM and NrCAM in chicken. This homology is most striking in the third Ig-like domain and to the region just proximal to the transmembrane segment of F3/contactin. Two members of the tenasin family bind directly to purified rat brain sodium channels (5). Using immobilized GST fusion proteins, it was shown that purified, heterotrimetric brain sodium channels, as well as a recombinant $\beta_2$ extracellular domain, bind specifically to the fibronectin repeat regions of TN-R and TN-C.

Tenascin molecules play important roles in cellular interactions in the developing nervous system, such as neuronal migration, neuritogenesis, and neuronal regeneration (6–9). TN-R is expressed predominantly by oligodendrocytes during the onset and early phases of myelination and remains expressed by some oligodendrocytes in the adult (10–14). It is also expressed in some neurons and interneurons in the spinal cord, retina, cerebellum, and hippocampus (10, 12, 14). TN-R co-localizes with other glial-derived molecules (i.e. myelin-associated glycoprotein and a phosphacan-related molecule) at high density in central nervous system myelinated axons (15). TN-R has been shown to have disparate effects resulting from interaction with one of its neuronal receptors, F3/contactin: promotion of neurite outgrowth when presented as a uniform substrate for some neuronal cell types and inhibition of growth cone advance and axonal outgrowth from retinal ganglion cells when offered as a sharp substrate boundary. TN-R also induces axonal defasciculation in vivo (15–21).

We postulated that $\beta$ subunits might function as CAMs in terms of interaction with extracellular matrix molecules. To determine whether sodium channel $\beta$ subunits are functionally modulated by TN-R, we used stably transfected fibroblasts expressing $\beta_1$ or $\beta_2$ subunits plated on substrates that contained TN-R or recombinant TN-R domains synthesized as

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* This work was supported by a Neuroscience Network of Canada grant (to P. E. B.), NMSS Grant RG-2882-A1 and a Johnson & Johnson Focused Giving Award (to L. L. I.), Medical Research Council Grant MT-13485 (to D. S. R.), and a grant from the German Research Society (to M. S.). The costs of publication of this article were defrayed in part by the payment of page charges. This article therefore must be hereby indicated "advertisement" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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† K. Kazen-Gillespie, D. S. Ragsdale, and L. L. Isom, unpublished results.

‡ The abbreviations used are: EGF, epidermal growth factor; EGF-L, fragment containing the cysteine-rich amino terminus and the EGF-like repeats; EGF-S, fragment containing the EGF-like repeats; FG, fibrinogen-like; FN, fibronectin; FN 6–8, fragment containing FN type III homologous repeats 6–8; GST, glutathione S-transferase; PO, poly-L-ornithine; TN, tenasin; CAM, cell adhesion molecule; CHL, Chinese hamster lung; CMF-HBSS, Ca$^{2+}$- and Mg$^{2+}$-free Hanks’ balanced salt solution.

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GST fusion proteins. We show that cells expressing β1 or β2 subunits initially recognize TN-R plated on a nitrocellulose substrate. This event is then followed by repulsion. Application of a recombinant pepptide domain of TN-R, EGF-L, resulted in the rapid and specific potentiation of sodium currents expressed by co-injection of α, β1, and β2 subunits in Xenopus oocytes. We hypothesize that functional interactions between sodium channel β subunits and TN-R may be important for neuronal desialcification or growth cone guidance during central nervous system development and may represent a critical communication link between the axon and the node of Ranvier.

**EXPERIMENTAL PROCEDURES**

**Materials**—Purification of TN-R from adult mouse brains by immuno-affinity chromatography was performed as described (13). Generation and purification of the recombinant TN-R domain of TN as fusion proteins with GST were performed as described (21). Chinese hamster lung (CHL) 1610 cells were obtained from the American Type Culture Collection. Nitrocellulose used in the cell repulsion assays was obtained from Schleicher & Schuell (catalog no. 401188, BA55, 0.45 μm).

**Construction of Mammalian Expression Vectors**—A mammalian expression vector containing the coding sequence of the rat brain sodium channel β2 subunit was constructed by subcloning a restriction fragment from pβ2LSP64T-BXN (3) into the Asp718 and NotI restriction endonuclease sites of pcDNA3.1Zeo (+) (Invitrogen, Carlsbad, CA), a vector that also contains the gene for zeocin resistance. The resulting plasmid (pcDNA3.1Zeo-β2L) was then sequenced completely with Thermo Sequenase (Amersham Pharmacia Biotech). A mammalian expression vector for β1, pcDNA3β1, was developed previously (3).

**Transfection and Characterization of Cell Lines**—1610 cells were transfected with 10 μg of cDNA using DOTAP as described previously (22). The following transfections were performed: 1610 + pcDNA3 (mock transfection), 1610 + β1, and 1610 + β2. Following drug selection with G418 (Life Technologies, Inc.) or Zeocin (Invitrogen), surviving cell clones were expanded and analyzed by Northern and Western blots for β subunit expression. Northern blot analysis was performed as described previously (3) using Trizol reagent-purified total RNA (Life Technologies, Inc.) and digoxigenin-labeled RNA probes for β1 (22) or β2 (3). Chemiluminescent labeling and detection were performed using Genius reagents (Roche Molecular Biochemicals). For Western blot analysis, confluent T-225 cell culture flasks of 1610 were harvested by scraping, completely with ThermoSequenase (Amersham Pharmacia Biotech). A aliquots of TN-R (15 μg) or GST fusion domains of TN-R (25 μg) were applied to the nitrocellulose-coated surfaces of the dishes and incubated for 2 h at 37 °C in a humidified atmosphere. The dried spots were washed with PBS and then flooded with CMF-HBSS containing 2% heat-inactivated fatty acid-free BSA (Sigma) and incubated for 2 h to block residual nonspecific protein binding sites. The dishes were then washed with PBS, and cells from the various cell lines were plated at a density of 10^5 cells/ml in 0.5 ml of growth medium containing 10% BSA. After 20 h of growth (5% CO2 at 37 °C), cultures were fixed with CMF-HBSS containing 2.5% glutaraldehyde. For adhesion blocking assays, a mixture of EGF-L, EGF-S, and FN 6–8 was added to the culture medium at the concentrations indicated in Table II. After fixation, cultures were stained with 0.5% toluidine blue in 2.5% sodium carbonate. Cells adhering to the various spots of TN-R fragments were photographed and counted. All experiments were performed at least five times.

**Electrophysiological Analysis of the Effects of the EGF-L Domains of TN-R on Sodium Channels**—Xenopus oocytes were isolated by collagenase treatment of pieces of ovary, as described previously (24). On the day after isolation, oocytes were microinjected with 50 μl of RNA encoding the α1A β1, and β2 subunits. The concentration of α1A subunit RNA was 20–50 ng/μl, and the concentration of β1 and β2 subunit RNA was 100–200 ng/μl.

Two-electrode voltage clamp recording was performed 2–5 days after injection, using a Turbo TEC 10C amplifier (Adams & List, Westbury, NY) and pCLAMP software (Axon Instruments, Foster City, CA). Electrodes were filled with 3 M KCl and had resistances of <0.3 MΩ. Data were acquired at 2.5 kHz. Capacity transients, as well as leak currents, were subtracted using the P4 procedure (25). Recordings were performed at room temperature in a 200-μl chamber filled with frog Ringer solution (115 mM NaCl, 2.5 mM KCl, 1.8 mM CaCl2, 10 mM HEPES, pH 7.2). Fusion proteins were added directly to the bath and subsequently washed out by superfusion. As controls for the electrophysiological effects of the recombinant EGF-L domain of TN-R, the fusion protein was treated with protease K (100 μg/ml) overnight at 56 °C. The enzyme was then inactivated by heating at 90 °C for 15 min. This procedure digested the fusion protein such that no silver-stained bands were visible after SDS-polyacrylamide gel electrophoresis on 15% acrylamide gels.

**RESULTS**

**Reversal Interactions between TN-R and Transfected Cells Expressing Sodium Channel β Subunits**—To determine whether sodium channel β subunits are modulated by TN-R, we examined the growth behavior of transfected 1610 cells (26). We created stable cell lines that express β1 alone (1610β1, clone 4), and β2 alone (1610β2, clone 1). We also created mock-transfected 1610 cells that contained pcDNA3 alone. Characterization of β1 or β2 expression in these cell lines by Northern and Western blot analyses is shown in Fig. 1.

Because 1610 cells do not express endogenous sodium channel α, β1, or β2 subunits (22) (Fig. 1) or F3/contactin (data not shown), we were able to examine the effects of TN-R on sodium channel β subunits in isolation. We predicted that β2 subunits may interact with TN-R because of their homology to F3/contactin. β1 also contains an extracellular CAM domain and is structurally homologous to β2 (4). We observed that CHL cells transfected with β2 (1610β2) or β1 (1610β1) subunits were strongly repelled by TN-R substrate coated on top of PO on nitrocellulose when allowed to settle in culture for 20 h (Fig. 2). Parental 1610 cells adhered well to TN-R during this time. These results are similar to observations in which cerebellar neurons expressing F3/contactin were repelled from a TN-R substrate (15, 18, 19, 21). One or both of the auxiliary β subunits may elicit signaling events similar to those described for F3/contactin upon interaction with TN-R (15). Parental 1610 cells and cells transfected with β1 or β2 subunits were not repelled from NCAM or laminin (data not shown). Thus, β1 and β2 subunits appear to be modulated specifically by TN-R to produce a repellent effect of the transfected cells away from the TN-R substrate. This effect could be the result of other processes (for example, apoptosis or anti-adhesion), although previous studies describing the repulsion of cerebellar neurons from a TN-R substrate excluded cell death as a reason for detachment (18).
Repulsive Effects of Different Domains of TN-R on Sodium Channel β Subunits Transfected in CHL Cells—We used recombinant peptides of TN-R (summarized in Fig. 3) along with 1610β1 and 1610β2 cells to determine which domains are responsible for the observed repulsive effects. TN-R has a modular structure containing a cysteine-rich amino-terminal domain followed by EGF-like repeats, fibronectin type III (FN III) domains, and a fibronogen-like knob at the carboxyl terminus (6–9, 12, 27–30). The fusion protein EGF-L contains the amino-terminal cysteine-rich domain plus the EGF-like repeats. EGF-S contains only the EGF-like repeats. FN 6–8 contains the sixth through the eighth fibronectin domains. FG contains the carboxyl-terminal fibrogen-like knob. CHL cells were plated onto nitrocellulose that had been coated with PO and the carboxyl-terminal fibrinogen-like knob. CHL cells were transfected with subunit-transfected Chinese hamster lung (1610) fibroblast cells. Left panel, bright-field micrographs of 1610 and β subunit-transfected 1610 cells plated on spots of TN-R coated onto PO-treated four-well dishes. Cells were maintained for 20 h at 37 °C before fixation and staining with Coomassie Blue. Coating concentration was 15 μM for TN-R. Values are reported as the mean ± S.E. visual field. CHL, (parental 1610 cells) 280 ± 42 cells/visual field; β1, (1610β1) 34 ± 6 cells/visual field, p = 0.017; β2, (1610β2) 17 ± 4 cells/visual field, p = 0.014. The value of adherent CHL cells on TN-R is shown as a control (100%). Asterisks indicate significant values, with p < 0.05.

The EGF-L Domain of TN-R Potentiates Sodium Currents—Our results from the adhesion and repulsion assays suggested an interaction between TN-R and sodium channel β subunits. This interaction, direct or indirect, might be expected to alter the functional properties of the ion channel as well. To test this hypothesis, we examined the effects of EGF-L and FN 6–8 fusion proteins on whole cell sodium currents recorded by voltage-clamp. Initially, we assessed sodium currents in SNaIIA subunits expressed in CHL cells may initially recognize TN-R as adhesive, prior to repulsion, similar to the situation with F3/contactin. Using a cell-substrate assay described previously to detect cell adhesion, we have found that cells expressing β1 subunits adhere to TN-R recombinant domains. As summarized in Table I, β1-expressing cells adhere to FN 6–8 and to EGF-S. Table II shows that a mixture of EGF-L, EGF-S, and FN 6–8 fusion proteins added to the cell culture medium blocks the adhesion of β1-expressing CHL cells to the EGF-like or fibronogen-like domains of TN-R in a concentration-dependent manner. As in the situation for F3-contactin interactions with TN-R, our results suggest that sodium channel β1 subunits initially recognize TN-R substrates with an adhesive response. Following that recognition, cells expressing β1 subunits are repelled by TN-R, as we show using cell-substrate assays to designed to detect repulsion. Similar experiments were attempted for β2-expressing cells. Unfortunately, our results were uninterpretable due to nonspecific interactions with GST alone. Other methods must be explored to answer this question in the future.
from the cell migration assays suggested that protein phosphorylation may modulate EGF-L-mediated effects on cell migration (data not shown). However, in the whole cell recording configuration used to record sodium currents in SNaIA + β1 + β2 cells, the cell cytoplasm was dialyzed into the patch pipette, which may have resulted in loss of intracellular constituents necessary for EGF-L- or FN-dependent modulation of sodium channel function. Therefore, as an alternative approach, we expressed sodium channels in Xenopus oocytes and examined whole cell sodium currents by two-electrode voltage clamp. In two-electrode recordings, EGF-L fusion protein produced a rapid increase in the amplitude of sodium currents (Fig. 6). EGF-L-mediated potentiation was observed in oocytes coexpressing the type IIA α subunit along with β1 and β2 (Fig. 6A), as well as in oocytes coexpressing αIA alone (Fig. 6B). In contrast, neither FN 6–8 fusion protein nor GST affected sodium currents in oocytes (Fig. 6E), suggesting that potentiation is a specific effect of the EGF-L domain of TN-R. EGF-L-mediated potentiation was not accompanied by any detectable changes in the voltage dependence of current activation (Fig. 6C) or inactivation (Fig. 6D) or in any obvious effects on current time course (Fig. 6, A and B). The concentration of 50 ng/μl was chosen in the experiments shown in Fig. 6 because it elicited a maximal potentiation response. However, clear potentiation was also observed with concentrations as low as 5 ng/μl. The potentiating activity was not inactivated by heating EGF samples to 100 °C for 10 min, suggesting that a highly stable protein domain is responsible for potentiation. In contrast, potentiation was greatly reduced by pretreatment of the fusion protein with proteinase K (Fig. 6F).

**DISCUSSION**

The extracellular matrix protein TN-R modulates cells expressing sodium channel β1 or β2 subunits. Using a combination of adhesion and repulsion assays, we describe events beginning with an initial recognition of the FN 6–8 and EGF-like repeats of TN-R followed by a repellent effect on transfected four-well dishes. Cells were maintained for 20 h at 37 °C before fixation and staining with Coomassie Blue. Coating concentration was 25 μM for different domains of TN-R. The identities of the cell lines are indicated. Scale bar, 50 μm.
with high affinity to recombinant fibronectin-like fusion protein domains of TN-R or TN-C immobilized on microtitre plates and display a low affinity for the EGF-like repeats (5).

It is interesting to consider the developmental time course of β1 and β2 subunit expression in brain (3, 31) compared with the development of oligodendrocytes. Over 90% of sodium channels in the rat brain during early postnatal development are thought to contain a disulfide-linked β2 subunit as well as a non-covalently linked β1 subunit (32). Most oligodendrocytes develop after postnatal day 7 in rat brain (33). Thus, β1 and β2 subunits would be expected to be present in the neuronal plasma membrane during the early stages of myelination, when TN-R is secreted. It may be possible that β1 and β2 subunits function as CAMs apart from α and play roles in neuronal development other than channel modification. It is also possible that β1, which is noncovalently bound to α, can dissociate and reassociate with the channel complex, such that the channel is dimeric or trimeric, depending on the particular needs of the cell. Thus, the presence or absence of β1 in the channel complex may determine the level of responsiveness of the sodium channel to TN-R.

The interaction of TN-R with the CAMs β1 and β2 in the central nervous system may lead to neuronal defasciculation (20). Central nervous system axons have been shown to form fascicles via homophilic or heterophilic binding of CAMs between axons. Preliminary results from our laboratory show that β1 and β2 exhibit homophilic binding when expressed individually in Drosophila S2 cells, leading to cell aggregation (5). Through binding to β subunits or other CAMs on adjacent axons, β subunits may contribute to axonal fasciculation. Interaction of TN-R with β1 or β2 may then serve to disrupt this interaction, initiating the process of defasciculation.

TN-R has been shown previously to inhibit growth cone advance as well as neurite outgrowth when presented as a sharp substrate boundary (16–19). The repulsion of β subunit-expressing fibroblasts from TN-R substrates in our hands may occur through a similar mechanism. It is possible that growth cone repulsion, and thus axon guidance, is facilitated through the interaction of TN-R with sodium channel β subunits present at the growth cones, resulting in cell repulsion.

EGF-L-mediated potentiation of sodium currents may represent a novel mechanism for modulation of sodium channel activity. Potentiation could involve an increase in the probability of sodium channel opening, an increase in single channel conductance, or up-regulation of silent channels. Surprisingly, potentiation was observed not only in oocytes coexpressing αIIA, β1, and β2 but also in oocytes expressing αIIA alone. This observation suggests the possibility that EGF-L can interact directly with sodium channel α subunits. Alternatively, potentiation of sodium currents in oocytes may be an indirect effect of EGF-L, reflecting a second messenger-mediated signal initiated by EGF-L interaction with some other oocyte membrane protein.

Recent observations on the activity of voltage-dependent sodium channels in TN-R knockout mice are in agreement with the hypothesis that TN-R modulates the activity of sodium channels (34). In these mice, there is no apparent change in expression or distribution of sodium channels, but compound action potential recordings from the optic nerves of the mutant mice show a significant decrease in conduction velocity as compared with wild type controls. Thus, in the absence of TN-R, the observed decrease in the optic nerve conduction velocity may reflect altered channel function. A more thorough analysis of the properties of sodium channels in the TN-R knock-out mu-

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**TABLE I**

|       | EGF-L | EGF-S | FN1-2 | FN3  | FN6–8 | FG  |
|-------|-------|-------|-------|------|-------|-----|
| Mean  | 81    | 114   | 19    | 12   | 142   | 25  |
| S.D.  | 69    | 16    | 11    | 10   | 60    | 28  |
| Mock  | 4     | 6     | 6     | 6    | 4     | 4   |
| S.D.  | 2     | 12    | 4     | 5    | 3     | 3   |

**TABLE II**

| Cell line/substrate | No additions | 50 μM mixture | 100 μM mixture | 150 μM mixture | 200 μM mixture | 250 μM mixture |
|---------------------|--------------|---------------|----------------|----------------|----------------|----------------|
| CHL/EGF-S           | 80           | 15             | 25             | 12             | 16             | 5              |
| S.D.                | 69           | 36             | 8              | 16             | 5              | 3              |
| 1610β1/FGN6–8       | 44           | 20             | 4              | 5              | 2              | 1              |
| S.D.                | 26           | 53             | 6              | 9              | 5              | 2              |

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3. J. Malhotra, M. Hortsch, and L. Isom, unpublished results.
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Modulation of Sodium Channel β Subunits by Tenascin-R

cause changes in sodium channel conductance or gating properties to produce excitotoxicity. Alternatively, expression of β1 subunits that are incapable of functioning as CAMs may alter sodium channel density and localization in the neuronal plasma membrane or cause changes in axonal guidance events, such as fasciaclation or growth cone collapse during brain development.

An interesting parallel may be drawn from the present study to the adhesion molecule on glia (AMOG/β2), the β2 subunit of the murine Na⁺, K⁺-ATPase (42). This cell surface glycoprotein is expressed by glial cells during neuronal development, as well as in the adult. It can form a complex with the α subunit to yield a functionally active Na⁺, K⁺-ATPase enzyme when injected into Xenopus oocytes, indicating that it can act as an integral member of the ion transport complex. In addition, AMOG/β2 acts as a CAM involved in neuron-glial interactions, promoting neurite outgrowth from cerebellar and hippocampal neurons. It is thought to be unlikely that Na⁺, K⁺-ATPase activity is involved in neurite outgrowth. Instead, AMOG/β2 may function independently of α subunits to exert this effect. Evidence that AMOG/β2 may appear at the cell surface independent of an α subunit has been found in the distal colon (43). Like AMOG/β2, sodium channel β subunits are cell surface glycoproteins expressed during critical stages of neuronal development. β1 and β2 now appear to have dual functions: as modulators of ion channel activity and as CAMs. We do not yet know whether sodium channel β subunits can appear and function at the cell surface independently of α during brain development. The present study now provides a framework from which the physiological significance of sodium channel-extracellular matrix interactions can be investigated.

Acknowledgments—We thank Vicky Kottis (McGill University) and Hongli Li (Montreal Neurological Institute) for excellent technical assistance.

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