

functional plasticity in neurons modulation of sodium −**channel expression as a basis for The neuron as a dynamic electrogenic machine:**

Stephen G. Waxman

doi: 10.1098/rstb.2000.0559 Phil. Trans. R. Soc. Lond. B 2000 **355**, 199-213

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 The neuron as a dynamic electrogenic
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machine: modulation of sodium-channel The neuron as a dynamic electrogenic
machine: modulation of sodium-channel
expression as a basis for functional plasticity **in the South South**
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in neurons
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Stephen G. Waxman

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Neurons signal each other via regenerative electrical impulses (action potentials) and thus can be thought
 Neurons signal each other via regenerative electrical impulses (action potentials) and thus can be thought
of as electrogenic machines. Voltage-gated sodium channels produce the depolarizations necessary for
action potenti Neurons signal each other via regenerative electrical impulses (action potentials) and thus can be thought
of as electrogenic machines. Voltage-gated sodium channels produce the depolarizations necessary for
action potenti of as electrogenic machines. Voltage-gated sodium channels produce the depolarizations necessary for action potential activity in most neurons and, in this respect, lie close to the heart of the electrogenic machinery. Alt electrogenesis, it is now clear that nearly a dozen genes encode distinct sodium channels with different machinery. Although classical neurophysiological doctrine accorded 'the' sodium channel a crucial role in
electrogenesis, it is now clear that nearly a dozen genes encode distinct sodium channels with different
molecular s electrogenesis, it is now clear that nearly a dozen genes encode distinct sodium channels with different
molecular structures and functional properties, and the majority of these channels are expressed within
the mammalian molecular structures and functional properties, and the majority of these channels are expressed within
the mammalian nervous system. The transcription of these sodium-channel genes, and the deployment of
the channels that the mammalian nervous system. The transcription of these sodium-channel genes, and the deployment of
the channels that they encode, can change significantly within neurons following various injuries.
Moreover, the transcri the channels that they encode, can change significantly within neurons following various injuries.
Moreover, the transcription of these genes and the deployment of various types of sodium channels
within neurons of the nor Moreover, the transcription of these genes and the deployment of various types of sodium channels
within neurons of the normal nervous system can change markedly as neurons respond to changing
milieus or physiological inpu within neurons of the normal nervous system can change markedly as neurons respond to changing milieus or physiological inputs. As a result of these changes in sodium-channel expression, the membranes of neurons may be ret milieus or physiological inputs. As a result of these changes in sodium-channel expression, the membranes of neurons may be retuned so as to alter their transductive and/or encoding properties. Neurons within
the normal and injured nervous system can thus function as dynamic electrogenic machines with electro-
responsive prope the normal and injured ner
responsive properties that
shifting functional needs. **Keywords:** action potential; electrogenesis; ion channel; sodium channel; neural plasticity

1. INTRODUCTION

1. **INTRODUCTION**
In the many decades since Sherrington (1906) described
are central nervous system as an 'enchanted loom', we 1. **INTRODUCTION**
the many decades since Sherrington (1906) described
the central nervous system as an 'enchanted loom', we
are learned much about the ways in which the ten In the many decades since Sherrington (1906) described

in exercit about the ways in which the ten

illion neurons within the brain and spinal cord commuhe central nervous system as an 'enchanted loom', we ave learned much about the ways in which the ten illion neurons within the brain and spinal cord commuicate with each other, in the aggregate forming a illion neurons within the brain and spinal cord commu-
icate with each other, in the aggregate forming a
omputer that is more complex and flexible than any
evice produced by man. Each neuron functions relatively icate with each other, in the aggregate forming a
omputer that is more complex and flexible than any
evice produced by man. Each neuron functions relatively
dependently in integrating incoming information so as evice produced by man. Each neuron functions relatively idependently in integrating incoming information, so as evice produced by man. Each neuron functions relatively
dependently in integrating incoming information, so as
a sequence of regenerative electrical impulses
action potentials) that conveys its message to other (action potentials) in integrating incoming information, so as

action potentials) that conveys its message to other

action potentials) that conveys its message to other

action potentials have been been been been been be neurons. In this regard, neurons can be thought of as
action potentials) that conveys its message to other
between the regard, neurons can be thought of as
a lectrogenic machines. According to the Sherringtonian action potentials) that conveys its message to other
determines. According to the Sherringtonian
determines. According to the Sherringtonian
iew the richness of function of the enchanted loom rests For the regard, neurons can be thought of as
lectrogenic machines. According to the Sherringtonian
iew, the richness of function of the enchanted loom rests
in the changing and complex patterns of action potentials lectrogenic machines. According to the Sherringtonian
iew, the richness of function of the enchanted loom rests
n the changing and complex patterns of action potentials iew, the richness of function of the enchanted loom rests
in the changing and complex patterns of action potentials
enerated by these neuronal electrogenic machines in
spaces to activity at synapses some having excitatory In the changing and complex patterns of action potentials
enerated by these neuronal electrogenic machines in
esponse to activity at synapses, some having excitatory
fects and others having inhibitory ones which impinge esponse to activity at synapses, some having excitatory ffects and others having inhibitory ones, which impinge exponse to activity at synapses, some having excitatory
ffects and others having inhibitory ones, which impinge
pon them. The synaptic mechanisms responsible for
generalization and inhibitory effects have been a tonic of ffects and others having inhibitory ones, which impinge
pon them. The synaptic mechanisms responsible for
 Ω are excitatory and inhibitory effects have been a topic of
etailed study and we now understand not only the pon them. The synaptic mechanisms responsible for
 \overline{O} rese excitatory and inhibitory effects have been a topic of
etailed study, and we now understand not only the
reductate behaviour of synapses, but also appreciate rese excitatory and inhibitory effects have been a topic of etailed study, and we now understand not only the eady-state behaviour of synapses, but also appreciate at synaptic activity is a dynamic process that can etailed study, and we now understand not only the

Ranvier, which serve as way-stations for saltatory

eady-state behaviour of synapses, but also appreciate

nat synaptic activity is a dynamic processs that can

1977; Waxm exady-state behaviour of synapses, but also appreciate
at synaptic activity is a dynamic processs that can
e altered by mechanisms that include both sprouting
nd pruning and also facilitation potentiation and and synaptic activity is a dynamic processs that can
e altered by mechanisms that include both sprouting
nd pruning, and also facilitation, potentiation and

depression. Indeed, synaptic plasticity is increasingly well
understood and is considered to be an important depression. Indeed, synaptic plasticity is increasingly well
understood, and is considered to be an important
substrate for the adaptive mutability that characterizes depression. Indeed, synaptic plasticity is increasingly well
understood, and is considered to be an important
substrate for the adaptive mutability that characterizes
the nervous system's actions understood, and is considered to be an important substrate for the adaptive mutability that characterizes the nervous system's actions. bstrate for the adaptive mutability that characterizes
enervous system's actions.
The unique and important capability of neurons to
mmunicate via series of action notentials suggests that

the nervous system's actions.
The unique and important capability of neurons to
communicate via series of action potentials suggests that,
as we think about these cells as electrogenic machines The unique and important capability of neurons to
communicate via series of action potentials suggests that,
as we think about these cells as electrogenic machines
and consider their information-processing capabilities we communicate via series of action potentials suggests that,
as we think about these cells as electrogenic machines
and consider their information-processing capabilities, we
must not neglect the molecules necessary for a fu as we think about these cells as electrogenic machines
and consider their information-processing capabilities, we
must not neglect the molecules necessary for a funda-
mental aspect of their electrogenicity, the ability to must not neglect the molecules necessary for a funda-
mental aspect of their electrogenicity, the ability to must not neglect the molecules necessary for a funda-
mental aspect of their electrogenicity, the ability to
generate action potentials. The pivotal studies of Hodgkin
& Huyley (1952) taught us that in most neurons mental aspect of their electrogenicity, the ability to
generate action potentials. The pivotal studies of Hodgkin
& Huxley (1952) taught us that, in most neurons,
voltage-gated sodium channels are responsible for the generate action potentials. The pivotal studies of Hodgkin & Huxley (1952) taught us that, in most neurons, voltage-gated sodium channels are responsible for the regenerative depolarization, that underlies the action & Huxley (1952) taught us that, in most neurons,
voltage-gated sodium channels are responsible for the
regenerative depolarization that underlies the action
potential. This crucial role of sodium channels is voltage-gated sodium channels are responsible for the
regenerative depolarization that underlies the action
potential. This crucial role of sodium channels is
reflected for example, by their aggregation in bigh regenerative depolarization that underlies the action
potential. This crucial role of sodium channels is
reflected, for example, by their aggregation in high
density within the cell membrane at the initial segment of potential. This crucial role of sodium channels is motor neurons, where the axon takes its origin from the density within the cell membrane at the initial segment of
motor neurons, where the axon takes its origin from the
neuronal cell body (Waxman & Quick 1978), and is also
annarent in the clustering of sodium channels in high motor neurons, where the axon takes its origin from the
neuronal cell body (Waxman & Quick 1978), and is also
apparent in the clustering of sodium channels in high
densities within the axon membrane, at the nodes of neuronal cell body (Waxman & Quick 1978), and is also
apparent in the clustering of sodium channels in high
densities within the axon membrane, at the nodes of
Ranvier, which, serve as way-stations for saltatory apparent in the clustering of sodium channels in high
densities within the axon membrane, at the nodes of
Ranvier, which serve as way-stations for saltatory
conduction along myelinated axons (Ritchie & Rogart densities within the axon membrane, at the nodes of
Ranvier, which serve as way-stations for saltatory
conduction along myelinated axons (Ritchie & Rogart
1977: Waxman 1977: Shrager 1989) Electronbysiological Ranvier, which serve as way-stations for saltatory conduction along myelinated axons (Ritchie & Rogart
1977; Waxman 1977; Shrager 1989). Electrophysiological
evidence indicates that, in at least some types of neurons,
action potentials, are initiated by the sodium channels 1977; Waxman 1977; Shrager 1989). Electrophysiological
evidence indicates that, in at least some types of neurons,
action potentials are initiated by the sodium channels

that are clustered at the initial segment and secondarily
and the sometodendritic component of the neuron and hat are clustered at the initial segment and secondarily
vade the somatodendritic component of the neuron and
he axon trunk (Coombs et al. 1957: Fatt 1957: Fuortes et al. hat are clustered at the initial segment and secondarily
wade the somatodendritic component of the neuron and
he axon trunk (Coombs *et al.* 1957; Fatt 1957; Fuortes *et al.*
957: Dodge & Cooley 1973) wade the somatodendritic component of the neuron and
he axon trunk (Coombs *et al.* 1957; Fatt 1957; Fuortes *et al.*
957; Dodge & Cooley 1973).

The heroic epoch of electrophysiology that was ushered 957; Dodge & Cooley 1973).
The heroic epoch of electrophysiology that was ushered
in by Hodgkin & Huxley's (1952) discoveries has been
allowed by an equally enlightening era of molecular The heroic epoch of electrophysiology that was ushered
1 by Hodgkin & Huxley's (1952) discoveries has been
plowed by an equally enlightening era of molecular
5 euroscience Much has been learned over the past few n by Hodgkin & Huxley's (1952) discoveries has been the played by an equally enlightening era of molecular p
euroscience. Much has been learned, over the past few in
lears about the molecular structure and function of si position of molecular structure and function of euroscience. Much has been learned, over the past few ears, about the molecular structure and function of euronal sodium channels. Although students of euroscience. Much has been learned, over the past few

ears, about the molecular structure and function of

euronal sodium channels. Although students of

euroscience have traditionally been taught about 'the' ears, about the molecular structure and function of
euronal sodium channels. Although students of
euroscience have traditionally been taught about 'the'
dium channel it is now clear that a repertoire of multiple euronal sodium channels. Although students of
euroscience have traditionally been taught about 'the'
odium channel, it is now clear that a repertoire of multiple
odium channels with different molecular properties is euroscience have traditionally been taught about 'the'

bidium channel, it is now clear that a repertoire of multiple

bidium channels with different molecular properties is

straightfor deployment within neurons. Moreover between that a repertoire of multiple

Solium channels with different molecular properties is

Solitable for deployment within neurons. Moreover, it is

decoming increasingly clear that the expression of sodium becoming increased numbers of sodium channels
 \Box becoming increased numbers of sodium channels
 \Box expression of sodium
 \Box expression of sodium
 \Box expression of sodium
 \Box hannels within some types of neurons vailable for deployment within neurons. Moreover, it is
decoming increasingly clear that the expression of sodium
hannels within some types of neurons is state dependent
and dynamic and that because sodium channels are decoming increasingly clear that the expression of sodium
hannels within some types of neurons is state dependent
and dynamic, and that, because sodium channels are
desertial players in electrogenesis, this molecular plast Fhannels within some types of neurons is state dependent

and dynamic, and that, because sodium channels are
 $\sum_{n=1}^{\infty}$ sential players in electrogenesis, this molecular plasticity
 $\sum_{n=1}^{\infty}$ and endow neurons w nd dynamic, and that, because sodium channels are

desired players in electrogenesis, this molecular plasticity.

The player of significant functional plasticity.

The urban modulation of sodium-channel expression is only Seential players in electrogenesis, this molecular plasticity
Can endow neurons with significant functional plasticity.
Ithough modulation of sodium-channel expression is only
equining to be understood the available eviden I am endow neurons with significant functional plasticity.

Ithough modulation of sodium-channel expression is only

eginning to be understood, the available evidence

rovides hints suggesting that it may represent a widedithough modulation of sodium-channel expression is only eginning to be understood, the available evidence rovides hints suggesting that it may represent a widepread motif. This paper reviews current progress in this rovides hints suggesting that it may represent a wide-
pread motif. This paper reviews current progress in this
celd and suggests that, as a result of plasticity of sodium-
hannel expression neurons can functionally remode pread motif. This paper reviews current progress in this

celd and suggests that, as a result of plasticity of sodium-

hannel expression, neurons can functionally remodel their

cion-potential generating apparatus so that action-potential-generation-potential-generating apparatus, so that we can hink of them as dynamic electrogenic machines hannel expression, neurons can functionally remodel their
ction-potential-generating apparatus, so that we can
hink of them as dynamic electrogenic machines.

2. PLASTICITY IN THE LOCALIZATION OF NEURONAL I THE LOCALIZATION OF
SODIUM CHANNELS

SODIUM CHANNELS
SODIUM CHANNELS
The complex and non-uniform pattern of distribution
sodium channels within the mature neuron is perhans SODIUM CHANNELS

The complex and non-uniform pattern of distribution

f sodium channels within the mature neuron is perhaps

est exemplified by the myelinated axon where there are The complex and non-uniform pattern of distribution
f sodium channels within the mature neuron is perhaps
est exemplified by the myelinated axon where there are
are are are are are distributed at the myelinated density. Wi f sodium channels within the mature neuron is perhaps
est exemplified by the myelinated axon where there are
narp gradients of sodium-channel density. Within the
xon membrane, the distribution of sodium channels is est exemplified by the myelinated axon where there are
arp gradients of sodium-channel density. Within the
xon membrane, the distribution of sodium channels is
on-homogeneous Sodium channels are clustered in high narp gradients of sodium-channel density. Within the
son membrane, the distribution of sodium channels is
on-homogeneous. Sodium channels are clustered in high
ensities (210^3 nm^{-2}) in the axon membrane at the node xon membrane, the distribution of sodium channels is
on-homogeneous. Sodium channels are clustered in high
ensities $(>10^3 \mu m^{-2})$ in the axon membrane at the node on-homogeneous. Sodium channels are clustered in high
ensities $(>10^3 \,\mu\text{m}^{-2})$ in the axon membrane at the node
f Ranvier, where they are required for the generation of
ction potentials. In contrast, the number of sod ensities $(>10^3 \,\mu\text{m}^{-2})$ in the axon membrane at the node
f Ranvier, where they are required for the generation of
ction potentials. In contrast, the number of sodium (I
hannels falls rapidly in extrapodal regions and f Ranvier, where they are required for the generation of
ction potentials. In contrast, the number of sodium
hannels falls rapidly in extranodal regions and there is a
such lower density of sodium channels ($\leq 25 \text{ nm}^{-2$ ction potentials. In contrast, the number of sodium
hannels falls rapidly in extranodal regions and there is a
uch lower density of sodium channels $(<25 \,\mu\text{m}^{-2})$ in
he internodal axon membrane, beneath the myelin hannels falls rapidly in extranodal regions and there is a

uch lower density of sodium channels $(<25 \,\mu\text{m}^{-2})$ in

he internodal axon membrane, beneath the myelin

aeath (Ritchie & Rogart 1977; Waxman 1977; Shrager uch lower density of sodium channels $(<25 \mu m^{-2})$ in

he internodal axon membrane, beneath the myelin

acath (Ritchie & Rogart 1977; Waxman 1977; Shrager

989) Figure 1 demonstrates this non-uniform distribuhe internodal axon membrane, beneath the myelin
1989). Figure 1 demonstrates this non-uniform distribu-
1989). Figure 1 demonstrates this non-uniform distribu-
100 of sodium channels. heath (Ritchie & Rogart 1977; Waxman 1977; Shrager

Although sodium channels are deployed within the ion of sodium channels.
Although sodium channels are deployed within the
euronal membrane in a highly non-uniform manner,
ith relatively sharp borders between channel-rich and Although sodium channels are deployed within the
peuronal membrane in a highly non-uniform manner,
ith relatively sharp borders between channel-rich and
looor domains the pattern of sodium-channel distribution euronal membrane in a highly non-uniform manner,
ith relatively sharp borders between channel-rich and
poor domains, the pattern of sodium-channel distribution
in the pattern of sodium-channel distribution The relatively sharp borders between channel-rich and
 χ) poor domains, the pattern of sodium-channel distribution
 χ) in timmutable. It changes markedly, in fact, both during
 χ evelopment and in response to som $\begin{minipage}{.4\linewidth} \textbf{log} \textbf{log$ In the development and in response to some pathological insults.

Unring the development of the myelinated axons, for
 \vert xample, there is a distinct phylogenetic sequence, evelopment and in response to some pathological insults. Juring the development of the myelinated axons, for
xample, there is a distinct phylogenetic sequence,
hereby the premyelinated axon initially displays a
niform membrane structure and subsequently clusters of xample, there is a distinct phylogenetic sequence,

thereby the premyelinated axon initially displays a

niform membrane structure and, subsequently, clusters of

origin channels develop close to the time when myelin is thereby the premyelinated axon initially displays a niform membrane structure and, subsequently, clusters of origin channels develop close to the time when myelin is Ω rst laid down (Waxman & Esster 1980; Wiley-I iving niform membrane structure and, subsequently, clusters of
 Ω rst laid down (Waxman & Foster 1980; Wiley-Livingston
 Ω rst laid down (Waxman & Foster 1980; Wiley-Livingston
 Ω Ellisman 1980; Waxman et al. 1982; Dug ordium channels develop close to the time when myelin is

Figure 1980; Wiley-Livingston

Ellisman 1980; Waxman *et al.* 1982; Dugandzija-

Jovakavic *et al.* 1995; Vabnik *et al.* 1996). Later in It is a laid down (Waxman & Foster 1980; Wiley-Livingston

Lellisman 1980; Waxman *et al.* 1982; Dugandzija-

lovakavic *et al.* 1995; Vabnik *et al.* 1996). Later in

welination the internodal part of the axon membrane t Ellisman 1980; Waxman *et al.* 1982; Dugandzija-
Jovakavic *et al.* 1995; Vabnik *et al.* 1996). Later in nyelination, the internodal part of the axon membrane
Iso matures. Sodium-channel expression is maintained at a nearly constant level until the formation of compact

myelin, which provides capacitative and resistive myelin, which provides capacitative and resistive
shielding and is accompanied by a suppression of sodium-
channel expression in the underlying internodal axon myelin, which provides capacitative and resistive
shielding and is accompanied by a suppression of sodium-
channel expression in the underlying internodal axon
membrane (Waxman 1987) shielding and is accompanied
channel expression in the unembrane (Waxman 1987).
The highly differentiated channel expression in the underlying internodal axon
membrane (Waxman 1987).
The highly differentiated membrane organization of

membrane (Waxman 1987).
The highly differentiated membrane organization of
the mature axon is not fixed or invariant. Figure 2
presents an electron micrograph, which shows that the The highly differentiated membrane organization of
the mature axon is not fixed or invariant. Figure 2
presents an electron micrograph, which shows that the
internodal axon membrane retains the canability for the mature axon is not fixed or invariant. Figure 2
presents an electron micrograph, which shows that the
internodal axon membrane retains the capability for
significant molecular plasticity Following loss of the overpresents an electron micrograph, which shows that the
internodal axon membrane retains the capability for
significant molecular plasticity. Following loss of the over-
wing myelin, the formerly internodal axon membrane internodal axon membrane retains the capability for
significant molecular plasticity. Following loss of the over-
lying myelin, the formerly internodal axon membrane
can reorganize so as to acquire a density of sodium chan significant molecular plasticity. Following loss of the over-
lying myelin, the formerly internodal axon membrane
can reorganize, so as to acquire a density of sodium chan-
nels that is much higher than normal (Foster et lying myelin, the formerly internodal axon membrane
can reorganize, so as to acquire a density of sodium chan-
nels that is much higher than normal (Foster *et al.* 1980). can reorganize, so as to acquire a density of sodium channels that is much higher than normal (Foster *et al.* 1980).
The acquisition of increased numbers of sodium channels
within the demyelinated axon membrane has functional
significance, since it endows the bared membrane wit The acquisition of increased numbers of sodium channels
within the demyelinated axon membrane has functional
significance, since it endows the bared membrane with
the canability to conduct action potentials, even in the within the demyelinated axon membrane has functional
significance, since it endows the bared membrane with
the capability to conduct action potentials, even in the
absence of myelin (Bostock & Sears 1976, 1978; Waxman significance, since it endows the bared membrane with
the capability to conduct action potentials, even in the
absence of myelin (Bostock & Sears 1976, 1978; Waxman
& Brill 1978). This plasticity of the axon membrane, and the capability to conduct action potentials, even in the absence of myelin (Bostock & Sears 1976, 1978; Waxman & Brill 1978). This plasticity of the axon membrane, and the resultant recovery of axon potential conduction in absence of myelin (Bostock & Sears 1976, 1978; Waxman & Brill 1978). This plasticity of the axon membrane, and the resultant recovery of axon potential conduction in chronically demyelinated axons, appear to contribute to & Brill 1978). This plasticity of the axon membrane, and
the resultant recovery of axon potential conduction in
chronically demyelinated axons, appear to contribute to
the clinical recovery that occurs, for example, during the resultant recovery of axon potential conduction in
chronically demyelinated axons, appear to contribute to
the clinical recovery that occurs, for example, during
remissions in disorders such as multiple sclerosis chronically demyelinated axons, appear to contribute to
the clinical recovery that occurs, for example, during
remissions in disorders such as multiple sclerosis
(Waxman 1998) the clinical recovery that occurs, for example, during
remissions in disorders such as multiple sclerosis
(Waxman 1998).

3. MULTIPLE SODIUM CHANNEL GENES ARE TIPLE SODIUM CHANNEL GENES A
EXPRESSED WITHIN NEURONS

Iovakavic et al. 1995; Vabnik et al. 1996). Later in oocytes (Akopian et al. 1996; Sangameswaran et al. 1996); velination, the internodal part of the axon membrane (iii) NaN, expressed preferentially in C-type and trigem-S. MULTIPLE SUDIOM CHANNEL GENES ARE
EXPRESSED WITHIN NEURONS
Following the molecular cloning of the first three
dium channels from the brain by Numa and bis EXPRESSED WITHIN NEURONS
Solid and the molecular cloning of the first three
sodium channels from the brain by Numa and his
colleagues (Noda et al. 1986a) it has become apparent Following the molecular cloning of the first three
sodium channels from the brain by Numa and his
colleagues (Noda *et al.* 1986*a*), it has become apparent
that nearly a dozen molecularly distinct voltage-gated sodium channels from the brain by Numa and his colleagues (Noda *et al.* 1986*a*), it has become apparent that nearly a dozen, molecularly distinct voltage-gated colleagues (Noda *et al.* 1986*a*), it has become apparent that nearly a dozen, molecularly distinct voltage-gated sodium channels are encoded by different genes within mammals (see for example Noda *et al.* 1986*b*: K ay that nearly a dozen, molecularly distinct voltage-gated
sodium channels are encoded by different genes within
mammals (see, for example, Noda *et al.* 1986*b*; Kayano *et*
al. 1988: Auld *et al.* 1988: Suzuki *et al.* 1988 *al.* 1988; Auld *et al.* 1988; Audd *et al.* 1986*b*; Kayano *et al.* 1988; Auld *et al.* 1988; Suzuki *et al.* 1988; Schaller *et al.* 1985. At least eight puttive sodium-channel genes mammals (see, for example, Noda et al. 1986b; Kayano et al. 1988; Auld et al. 1988; Suzuki et al. 1988; Schaller et al. 1995). At least eight putative sodium-channel genes al. 1988; Auld et al. 1988; Suzuki et al. 1988; Schaller et al. 1995). At least eight putative sodium-channel genes
are expressed within neurons. Notably, multiple sodium-
channel genes are expressed within even reasonably al. 1995). At least eight putative sodium-channel genes
are expressed within neurons. Notably, multiple sodium-
channel genes are expressed within even reasonably
well-defined groups of neurons. One of the best-studied are expressed within neurons. Notably, multiple sodium-
channel genes are expressed within even reasonably
well-defined groups of neurons. One of the best-studied
examples of this is provided by dorsal root ganglion channel genes are expressed within even reasonably
well-defined groups of neurons. One of the best-studied
examples of this is provided by dorsal root ganglion well-defined groups of neurons. One of the best-studied
examples of this is provided by dorsal root ganglion
(DRG) neurons (figure 3). These primary sensory
neurons express the messenger RNA_{S} (mRNAs) for at examples of this is provided by dorsal root ganglion
(DRG) neurons (figure 3). These primary sensory
neurons express the messenger RNAs (mRNAs) for at
least six presumed sodium channels The sodium-channel (DRG) neurons (figure 3). These primary sensory
neurons express the messenger RNAs $(mRNAs)$ for at
least six presumed sodium-channels. The sodium-channel
 $mRNAs$ expressed within DRG neurons include high neurons express the messenger RNAs $(mRNAs)$ for at least six presumed sodium channels. The sodium-channel mRNAs expressed within DRG neurons include high levels of transcripts for the α -I and Na6 sodium chanleast six presumed sodium channels. The sodium-channel
mRNAs expressed within DRG neurons include high
levels of transcripts for the α -I and Na6 sodium chan-
nels which are also present at high levels within many mRNAs expressed within DRG neurons include high levels of transcripts for the α -I and Na6 sodium channels, which are also present at high levels within many other neuronal cell types within the central nervous nels, which are also present at high levels within many
other neuronal cell types within the central nervous
system (Black *et al.* 1996). In addition, DRG neurons
express high levels of four additional presumed sodiumother neuronal cell types within the central nervous
system (Black *et al.* 1996). In addition, DRG neurons
express high levels of four additional presumed sodium-
channel mRNAs, which are not detectable at significant system (Black *et al.* 1996). In addition, DRG neurons express high levels of four additional presumed sodium-
channel mRNAs, which are not detectable at significant
levels or are present at only low levels in other neuro express high levels of four additional presumed sodium-
channel mRNAs, which are not detectable at significant
levels, or are present at only low levels, in other neuronal
cell types: (i) PNL-bNF a sodium channel that is channel mRNAs, which are not detectable at significant
levels, or are present at only low levels, in other neuronal
cell types: (i) PN1-hNE, a sodium channel that is
expressed preferentially in DBG neurons (Toledo-Aral *et* levels, or are present at only low levels, in other neuronal
cell types: (i) PNI–hNE, a sodium channel that is
expressed preferentially in DRG neurons (Toledo-Aral *et*
 e^{t} 1997) produces a fast transient tetrodotoxin (cell types: (i) PNI-hNE, a sodium channel that is expressed preferentially in DRG neurons (Toledo-Aral *et al.* 1997), produces a fast transient tetrodotoxin (TTX)-sensitive current in response to sudden depolarizations expressed preferentially in DRG neurons (Toledo-Aral et al. 1997), produces a fast transient tetrodotoxin (TTX)-
sensitive current in response to sudden depolarizations
and a persistent current that is evoked by slow depolar-
izations close to resting potential (Cummins et al. sensitive current in response to sudden depolarizations
and a persistent current that is evoked by slow depolar-
izations close to resting potential (Cummins *et al.* 1998);
(ii) SNS-PN3 which is expressed preferentially i and a persistent current that is evoked by slow depolarizations close to resting potential (Cummins *et al.* 1998);
(ii) SNS–PN3, which is expressed preferentially in small
DRG and trigeminal neurons encodes a slowly inac izations close to resting potential (Cummins *et al.* 1998); (ii) SNS-PN3, which is expressed preferentially in small DRG and trigeminal neurons, encodes a slowly inacti-(ii) SNS–PN3, which is expressed preferentially in small
DRG and trigeminal neurons, encodes a slowly inactivating TTX-resistant sodium current when expressed in
operator (Akopian et al. 1996: Sangameswaran et al. 1996) DRG and trigeminal neurons, encodes a slowly inactivating TTX-resistant sodium current when expressed in oocytes (Akopian *et al.* 1996; Sangameswaran *et al.* 1996); (iii) N₂N expressed preferentially in C-type and trig vating TTX-resistant sodium current when expressed in oocytes (Akopian *et al.* 1996; Sangameswaran *et al.* 1996); (iii) NaN, expressed preferentially in C-type and trigem-
inal neurons exhibits an amino-acid sequence th inal neurons, exhibits an amino-acid sequence that, while only 47% similar to SNS^PN3, predicts that it

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Figure 1. Electron micrograph Figure 1. Electron micrograph
showing cytochemical staining of a
normal myelinated fibre from Figure 1. Electron micrograph
showing cytochemical staining of a
normal myelinated fibre from
guinea-pig sciatic nerve with ferric showing cytochemical staining of a
normal myelinated fibre from
guinea-pig sciatic nerve with ferric
ion and ferrocyanide. There is selecnormal myelinated fibre from
guinea-pig sciatic nerve with ferric
ion and ferrocyanide. There is selec-
tive staining of the axon membrane guinea-pig sciatic nerve with ferric
ion and ferrocyanide. There is selective staining of the axon membrane
at a node of Ranvier (arrows), while ion and ferrocyanide. There is selective staining of the axon membrane
at a node of Ranvier (arrows), while
the internodal axon membrane tive staining of the axon membrane
at a node of Ranvier (arrows), while
the internodal axon membrane
remains unstained. This stain at a node of Ranvier (arrows), which
the internodal axon membrane
remains unstained. This stain
provides a marker for regions of t provides a marker for regions of the remains unstained. This stain
provides a marker for regions of the
axon membrane expressing a high
density of sodium channels. A provides a marker for regions of
axon membrane expressing a high
density of sodium channels. A,
axonlasm: M, myelin: $\times 16000$ axon membrane expressing a high
density of sodium channels. A,
axoplasm; M, myelin; ×16 000.
Modified from Quick & Waxman density of sodium channels. A,
axoplasm; M, myelin; $\times 16000$.
Modified from Quick & Waxman (1976).

encodes a distinct TTX-resistant sodium channel (Dib-
prodes a distinct TTX-resistant sodium channel (Dib-
tail et al. 1998a), its sequence has been confirmed by ncodes a distinct TTX-resistant sodium channel (Dib-
Hajj *et al.* 1998*a*), its sequence has been confirmed by
liste *et al.* (1998), patch-clamp studies in transgenic mice The results a distinct TTX-resistant sodium channel (Dib-

Iajj *et al.* (1998), patch-clamp studies in transgenic mice

that which SNS-PN3 has been knocked out indicate that Iajj *et al.* 1998a), its sequence has been confirmed by

discriming that e and e al. (1998), patch-clamp studies in transgenic mice

that SNS-PN3 has been knocked out indicate that
 $\frac{1}{2}$ N channels produce a pers The *et al.* (1998), patch-clamp studies in transgenic mice

It which SNS-PN3 has been knocked out indicate that
 $\begin{bmatrix} \text{la}N & \text{channels} \\ \text{d}N & \text{channels} \end{bmatrix}$ produce a persistent TTX-resistant

adjum current with substantia I which SNS–PN3 has been knocked out indicate that
laN channels produce a persistent TTX-resistant
dium current with substantial overlap between activa-
lon and steady-state inactivation curves, suggesting that laN channels produce a persistent TTX-resistant It is active near resting potential overlap between activation and steady-state inactivation curves, suggesting that
is active near resting potential (Cummins *et al.* 1999);
iv) N₂G originally cloned from astrocytes and % on and steady-state inactivation curves, suggesting that

is active near resting potential (Cummins *et al.* 1999);

iv) NaG, originally cloned from astrocytes and at first

pought to be a glial cell-specific sodium cha is active near resting potential (Cummins *et al.* 1999);
iv) NaG, originally cloned from astrocytes and at first
nought to be a glial cell-specific sodium channel
 Ω Gautron *et al.* 1999) is also expressed at high leve iv) NaG, originally cloned from astrocytes and at first

nought to be a glial cell-specific sodium channel

DGautron *et al.* 1992), is also expressed at high levels

ithin DBG neurons (Black *et al.* 1996) and at low leve ought to be a glial cell-specific sodium channel

Gautron *et al.* 1992), is also expressed at high levels
 *i*thin DRG neurons (Black *et al.* 1996) and at low levels
 *i*thin other neurons of neural crest origin but not Gautron *et al.* 1992), is also expressed at high levels *ithin* DRG neurons (Black *et al.* 1996) and at low levels *ithin* other neurons of neural crest origin but not *ithin* other types of neurons (Felts *et al.* 1997 *i*thin DRG neurons (Black *et al.* 1996) and at low levels *i*thin other neurons of neural crest origin but not *i*thin other types of neurons (Felts *et al.* 1997*a*), some uthorities have noted that NaG mRNA is also pr ithin other neurons of neural crest origin but not

positively charged amino-acid residues in the putative
voltage sensor region, and have expressed doubt as to positively charged amino-acid residues in the putative
voltage sensor region, and have expressed doubt as to
whether NaG functions as a voltage-dependent sodium positively charged amino-acid residues in the putative
voltage sensor region, and have expressed doubt as to
whether NaG functions as a voltage-dependent sodium
channel (Akonian et al. 1997) voltage sensor region, and have expressed doubt as to whether NaG functions as a voltage-dependent sodium channel (Akopian *et al.* 1997). whether NaG functions as a voltage-dependent sodium
channel (Akopian *et al.* 1997).
The physiological signatures of only a few of these
sodium-channel subtypes within DRG neurons have been

in other types of neurons (Felts *et al.* 1997*a*), some sodium channels are functionally important. For example, uthorities have noted that NaG mRNA is also present the available evidence from a 'top-down' approach a lun The physiological signatures of only a few of these determined. Analysis of the function of each of these sodium-channel subtypes within DRG neurons have been
determined. Analysis of the function of each of these
channels is complicated by results that suggest their
currents interact in a complex manner during electrodetermined. Analysis of the function of each of these
channels is complicated by results that suggest their
currents interact in a complex manner during electro-
genesis (see for example Rizzo et al. 1996; Cummins & channels is complicated by results that suggest their
currents interact in a complex manner during electro-
genesis (see, for example, Rizzo *et al.* 1996; Cummins &
Waxman 1997: Schild & Kunze 1997) Nevertheless there currents interact in a complex manner during electrogenesis (see, for example, Rizzo et al. 1996; Cummins & Waxman 1997; Schild & Kunze 1997). Nevertheless, there genesis (see, for example, Rizzo *et al.* 1996; Cummins & Waxman 1997; Schild & Kunze 1997). Nevertheless, there is electrophysiological evidence that indicates that differences in the currents produced by the different ty Waxman 1997; Schild & Kunze 1997). Nevertheless, there is electrophysiological evidence that indicates that differences in the currents produced by the different types of sodium channels are functionally important. For exa is electrophysiological evidence that indicates that differences in the currents produced by the different types of sodium channels are functionally important. For example, the available evidence from a "top-down" approach ences in the currents produced by the different types of indicates that selective expression of different channel

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Figure 2. Molecular plasticity of the axon Figure 2. Molecular plasticity of the axon
membrane. These micrographs illustrate the
acquisition, by chronically demyelinated Figure 2. Molecular plasticity of the axon
membrane. These micrographs illustrate the
acquisition, by chronically demyelinated
(formerly internodal) axon membrane, of membrane. These micrographs illustrate th
acquisition, by chronically demyelinated
(formerly internodal) axon membrane, of
node-like staining with ferric ion and acquisition, by chronically demyelinated
(formerly internodal) axon membrane, of
node-like staining with ferric ion and (formerly internodal) axon membrane, of
node-like staining with ferric ion and
ferrocyanide (compare to figure 1). The
development of higher-than-normal node-like staining with ferric ion and
ferrocyanide (compare to figure 1). T
development of higher-than-normal
sodium-channel densities in the demy ferrocyanide (compare to figure 1). The
development of higher-than-normal
sodium-channel densities in the demyelinated
axon membrane permits it to support action development of higher-than-normal
sodium-channel densities in the demyelinated
axon membrane permits it to support action sodium-channel densities in the demyelinated
axon membrane permits it to support action
potential conduction in the absence of myelin,
thus providing a basis for restoration of impulse thus providing a basis for restoration of impulse potential conduction in the absence of m
thus providing a basis for restoration of i
conduction that contributes to clinical
remissions in disorders such as multiple s remissions in disorders such as multiple sclerosis. A, demyelinated axon; S, Schwann cell; e, remissions in disorders such as multiple sclerosis.
A, demyelinated axon; S, Schwann cell; e,
extracellular space; $\times 65 000$. Modified from
Foster et al. (1980) A, demyelinated axor
extracellular space; >
Foster *et al.* (1980).

subtypes, in groups of DRG neurons with different subtypes, in groups of DRG neurons with different
ensory functions, endows them with different trans-
uctive and/or encoding properties. Figure 4 displays abtypes, in groups of DRG neurons with different
ensory functions, endows them with different trans-
uctive and/or encoding properties. Figure 4 displays
thele-cell natch-clamp recordings of sodium current ensory functions, endows them with different trans-
uctive and/or encoding properties. Figure 4 displays
hole-cell patch-clamp recordings of sodium current,
.om a cutaneous afferent DRG neuron and a muscle uctive and/or encoding properties. Figure 4 displays

thole-cell patch-clamp recordings of sodium current,

om a cutaneous afferent DRG neuron and a muscle

fferent DRG neuron (Honmou et al. 1994). The sodium com a cutaneous afferent DRG neuron and a muscle
fferent DRG neuron (Honmou *et al.* 1994). The sodium
urrents in these two subtypes of DRG neurons differ in
erms of kinetics and voltage dependence (figure 4c d): fferent DRG neuron (Honmou *et al.* 1994). The sodium
urrents in these two subtypes of DRG neurons differ in
erms of kinetics and voltage dependence (figure $4c$,*d*);
his appears to provide at least a partial basis for t erms of kinetics and voltage dependence (figure $4c$, d); his appears to provide at least a partial basis for the erms of kinetics and voltage dependence (figure $4c,d$);
his appears to provide at least a partial basis for the
ifferent action potential characteristics that are
isolayed by these cells (figure $4e f$). his appears to provide at least a pa
ifferent action potential charact
isplayed by these cells (figure $4e, f$).
Physiological signatures have also b Frem action potential characteristics that are
splayed by these cells (figure $4e, f$).
Physiological signatures have also been established by
bottom-un' approach for some of the sodium-channel

isplayed by these cells (figure $4e$, f).
Physiological signatures have also been established by
'bottom-up' approach for some of the sodium-channel
cancerints that are expressed in DRG peurops, such as Physiological signatures have also been established by

'bottom-up' approach for some of the sodium-channel

canscripts that are expressed in DRG neurons, such as

be PNI-bNE channel When expressed in mammalian 'bottom-up' approach for some of the sodium-channel
canscripts that are expressed in DRG neurons, such as
he PN1-hNE channel. When expressed in mammalian
ell lines that lack other ion channels, the properties of ranscripts that are expressed in DRG neurons, such as
he PNI–hNE channel. When expressed in mammalian
ell lines that lack other ion channels, the properties of
'NI–hNE can be examined in isolation. In the expreshe PN1-hNE channel. When expressed in mammalian ell lines that lack other ion channels, the properties of
N1-hNE can be examined in isolation. In the expres-
ion system provided by HEK 293 cells, PN1-hNE is PNI-hNE can be examined in isolation. In the expression system provided by HEK 293 cells, PNI -hNE needes a sodium channel characterized by slow closed-
at inactivation. As a result of this PNI -hNE channels ion system provided by HEK 293 cells, PNI-hNE
ncodes a sodium channel characterized by slow closed-
ate inactivation. As a result of this, PNI-hNE channels
an be activated by slow depolarizations close to resting ncodes a sodium channel characterized by slow closed-
ate inactivation. As a result of this, PNI-hNE channels
an be activated by slow depolarizations close to resting ate inactivation. As a result of this, PNI-hNE channels
an be activated by slow depolarizations close to resting
otential, a property that poises them to amplify depo-
rizing signals such as generator potentials (Cummins e an be activated by slow depolarizations close to resting otential, a property that poises them to amplify depo-
arizing signals such as generator potentials (Cummins *et*¹/ 1998) It seems likely that PNI-bNE channels do arizing signals such as generator potentials (Cummins et l. 1998). It seems likely that PN1-hNE channels do, in Factor and Such as generator potentials (Cummins *et*
 μ . 1998). It seems likely that PNI-hNE channels do, in

act, subserve this function within DRG neurons

acsibly together with Na6 channels which as (b. 1998). It seems likely that PNI-hNE channels do, in μ ct, subserve this function within DRG neurons possibly together with Na6 channels, which, as a seribed below can also activate in response to slow Let, subserve this function within DRG neurons
possibly together with Na6 channels, which, as
pescribed below, can also activate in response to slow,
and denolarizations: Vexa-Saenz DeMiera et al. 1997. possibly together with Na6 channels, which, as

) escribed below, can also activate in response to slow,

) nall depolarizations; Vega-Saenz DeMiera *et al.* 1997;

; aman *et al.* 1997; Tanaka *et al.* 1999) PNI–bNE chanexcribed below, can also activate in response to slow,
and depolarizations; Vega-Saenz DeMiera *et al.* 1997;
laman *et al.* 1997; Tanaka *et al.* 1999). PNI-hNE channall depolarizations; Vega-Saenz DeMiera *et al.* 1997;

daman *et al.* 1997; Tanaka *et al.* 1999). PNI-hNE chan-

els are localized at the distal tips of neurites arising

om sensory neurons *in nitre* (Toledo-Aral *et* taman *et al.* 1997; Tanaka *et al.* 1999). PNI-hNE chan-
els are localized at the distal tips of neurites arising
rom sensory neurons *in vitro* (Toledo-Aral *et al.* 1997). els are localized at the distal tips of neurites arising

om sensory neurons *in vitro* (Toledo-Aral *et al.* 1997).

Ithough their localization *in situ* has not yet been deter-

ined a distal localization at the sensory om sensory neurons *in vitro* (Toledo-Aral *et al.* 1997).

Ithough their localization *in situ* has not yet been deter-

ined, a distal localization at the sensory terminals

could place PNI-bNE channels close to the tri Ithough their localization *in situ* has not yet been deter-
ined, a distal localization at the sensory terminals
vould place PN1^{-h}NE channels close to the trigger
lones which produce trains of action potentials in ined, a distal localization at the sensory terminals

vould place PNI – NNE channels close to the trigger

dones which produce trains of action potentials in

sponse to generator potentials Such a spatial localizarould place PNI-hNE channels close to the trigger
Dones which produce trains of action potentials in
esponse to generator potentials. Such a spatial localiza-
ion close to sensory transduction zones, would meet Oones which produce trains of action potentials in
esponse to generator potentials. Such a spatial localiza-
ion, close to sensory transduction zones, would meet
unctional needs since it would take advantage of the functional separation potentials. Such a spatial localiza-
ion, close to sensory transduction zones, would meet
inctional needs since it would take advantage of the ion, close to sensory transduction zones, would meet inctional needs since it would take advantage of the ining of these channels, to amplify slow depolarizing pputs (Cummins $et al.$ 1998). μ ining of these channels, to amplify slow depolarizing

hole-cell patch-clamp recordings of sodium current, channels may not be unique to DRG neurons. Indeed, om a cutaneous afferent DRG neuron and a muscle current interest in these sensory neurons, and their fferent DRG neuron There are four putative sodium-channel transcripts There are four putative sodium-channel transcripts
that appear to be selectively distributed in DRG
neurons. The presence of neuronal type-specific sodium There are four putative sodium-channel transcripts
that appear to be selectively distributed in DRG
neurons. The presence of neuronal type-specific sodium
channels may not be unique to DRG neurons. Indeed neurons. The presence of neuronal type-specific sodium neurons. The presence of neuronal type-specific sodium
channels may not be unique to DRG neurons. Indeed,
current interest in these sensory neurons, and their
accessibility for experimental study outside of the spinal channels may not be unique to DRG neurons. Indeed,
current interest in these sensory neurons, and their
accessibility for experimental study outside of the spinal
cord in isolation from other neuronal cell types have current interest in these sensory neurons, and their
accessibility for experimental study outside of the spinal
cord in isolation from other neuronal cell types, have
facilitated the cloning of SNS–PN3 and NaN and the accessibility for experimental study outside of the spinal
cord in isolation from other neuronal cell types, have
facilitated the cloning of SNS-PN3 and NaN, and the identification of PN1 and NaG, as sodium channels that facilitated the cloning of SNS–PN3 and NaN, and the
identification of PN1 and NaG, as sodium channels that
are preferentially expressed within them. It is an intri-
guing possibility, that, other, neuron-specific, sodium identification of PNI and NaG, as sodium channels that
are preferentially expressed within them. It is an intri-
guing possibility that other, neuron-specific, sodium
channels are expressed preferentially within other nucl are preferentially expressed within them. It is an intriguing possibility that other, neuron-specific, sodium
channels are expressed preferentially within other nuclei
or neuronal cell groups within the brain and spinal co guing possibility that other, neuron-specific, sodium
channels are expressed preferentially within other nuclei
or neuronal cell groups within the brain and spinal cord.
This together with alternative splicing (Sarao et al channels are expressed preferentially within other nuclei
or neuronal cell groups within the brain and spinal cord.
This, together with alternative splicing (Sarao *et al.* 1991;
Gustafson *et al.* 1993; Schaller *et al.* or neuronal cell groups within the brain and spinal cord.
This, together with alternative splicing (Sarao *et al.* 1991;
Gustafson *et al.* 1993; Schaller *et al.* 1992) and RNA
editing could confer unique electrophysiolog This, together with alternative splicing (Sarao *et al.* 1991; Gustafson *et al.* 1993; Schaller *et al.* 1992) and RNA editing, could confer unique electrophysiological proper-
ties on various types of neurons, and would Gustafson et al. 1993; Schaller et al. 1992) and RNA editing, could confer unique electrophysiological proper-
ties on various types of neurons, and would further
increase the complexity that sodium-channel diversity
endows on the nervous system ties on various types of neuro
increase the complexity that s
endows on the nervous system.

**4. SODIUM-CHANNEL GENE EXPRESSION IS A HANNEL GENE EXPRESS
DYNAMIC PROCESS**

DYNAMIC PROCESS
It is now well established that sodium-channel expres-**STINANIL PROCESS**
It is now well established that sodium-channel expres-
sion in neurons is not static. On the contrary, it is a
highly dynamic process. During the course of develop-It is now well established that sodium-channel expression in neurons is not static. On the contrary, it is a highly dynamic process. During the course of develop-
ment the level of expression of some sodium channels sion in neurons is not static. On the contrary, it is a
highly dynamic process. During the course of develop-
ment, the level of expression of some sodium channels
increases while expression of others (e.g. α -III) conc highly dynamic process. During the course of development, the level of expression of some sodium channels increases, while expression of others (e.g. α -III) concomiment, the level of expression of some sodium channels
increases, while expression of others (e.g. α -III) concomi-
tantly decreases in most parts of the nervous system
(Beckh et al. 1989; Brysch et al. 1991; Waxman et a increases, while expression of others (e.g. α -III) concomitantly decreases in most parts of the nervous system (Beckh *et al.* 1989; Brysch *et al.* 1991; Waxman *et al.* 1994; Felts *et al.* 1997*h*) tantly decreases i
(Beckh *et al.* 1989;
Felts *et al.* 1997*b*). eckh *et al.* 1989; Brysch *et al.* 1991; Waxman *et al.* 1994;
Its *et al.* 1997*b*).
At least some of these developmental changes appear
reflect the regulatory effects of neurotrophins and

Felts *et al.* 1997*b*).
At least some of these developmental changes appear
to reflect the regulatory effects of neurotrophins and
other growth factors on the transcription of various At least some of these developmental changes appear
to reflect the regulatory effects of neurotrophins and
other growth factors on the transcription of various
sodium-channel genes. These effects are complex. For to reflect the regulatory effects of neurotrophins and other growth factors on the transcription of various sodium-channel genes. These effects are complex. For other growth factors on the transcription of various
sodium-channel genes. These effects are complex. For
example, nerve growth factor (NGF) has opposing
actions on expression of the α -SNS and α -III sodiumsodium-channel genes. These effects are complex. For
example, nerve growth factor (NGF) has opposing
actions on expression of the α -SNS and α -III sodium-
channel genes, unregulating the former and downexample, nerve growth factor (NGF) has opposing
actions on expression of the α -SNS and α -III sodium-
channel genes, upregulating the former and down-
regulating the latter in mature DBG neurons in with actions on expression of the α -SNS and α -III sodium-
channel genes, upregulating the former and down-
regulating the latter in mature DRG neurons *in vitro* (Black *et al*. 1997) and *in vivo* (Dib-Hajj *et al.* ¹⁹⁹⁸*^b*). At

Example 19 and 20 a igure 3. (a) Dorsal root ganglion neurons express multiple sodium channels. The micrographs illustrate sodium-channel
-subunit mRNAs visualized in sections from adult rat DRG by *in situ* hybridization with subtype-specif -subunit mRNAs visualized in sections from adult rat DRG by *in situ* hybridization with subtype-specific antisense riboprobes.
1RNAs for α-I, Na6, hNE–PN1, SNS, NaN and NaG are present at moderate-to-high levels in DRG iRNAs for α -I, Na6, hNE-PN1, SNS, NaN and NaG are present at moderate-to-high levels in DRG neurons. Hybridization ontain 100-bp ladder marker. Lane 1 contains amplification products (bands a-d) from domain 1 in DRG cDNA. Lanes 2-9

now the result of cutting this DNA with EcoRV, EcoN1, Aval, Sphl, BamH1, AflII, Xbal and EcoR1, which are specific to subunits -I, -III, -III, Na6, PN1, SNS, NaG and NaN, respectively. Reproduced with permission from Dib-H

heast some of the effects of NGF on sodium-channel expression are mediated by pathways involving protein
insee Δ (Kalman *et al.* 1990) but there is evidence the effects of NGF on sodium-channel
xpression are mediated by pathways involving protein
inase A (Kalman *et al.* 1990), but there is evidence
valicating that NGF regulates the expression of different xpression are mediated by pathways involving protein
inase A (Kalman *et al.* 1990), but there is evidence
adicating that NGF regulates the expression of different
graphs wind the expression of different
graphs wind the e inase A (Kalman *et al.* 1990), but there is evidence

dicating that NGF regulates the expression of different

ypes of sodium channels via different signal trans-

uction pathways some of which are protein kinase A dicating that NGF regulates the expression of different

ypes of sodium channels via different signal trans-

uction pathways, some of which are protein kinase A (

dependent (D'Arcangelo *et al*, 1993) ypes of sodium channels via different signal trans-
uction pathways, some of which are protein kinase A
idependent (D'Arcangelo *et al.* 1993).

b stimulate sodium-channel expression in PCl2 cells Basic fibroblast growth factor (bFGF) has been found
a stimulate sodium-channel expression in PCl2 cells
Pollack *et al.* 1990). Brain-derived growth factor (BDNF)
ces not alter sodium current expression to a significant So stimulate sodium-channel expression in PC12 cells
Pollack *et al.* 1990). Brain-derived growth factor (BDNF)
oes not alter sodium current expression to a significant
legree in DBG peurons although it has significant ef Pollack *et al.* 1990). Brain-derived growth factor (BDNF)

oes not alter sodium current expression to a significant

egree in DRG neurons, although it has significant effects

an GABA receptor expression in these cells (or a alter sodium current expression to a significant

) egree in DRG neurons, although it has significant effects

) n GABA receptor expression in these cells (Oyelese *et al.*

997) and increases sodium-channel mRNA and) egree in DRG neurons, although it has significant effects

) n GABA receptor expression in these cells (Oyelese *et al.*
 $\binom{997}{2}$ and increases sodium-channel mRNA and sodium-

urrent expression in PCl₂ sublines In GABA receptor expression in these cells (Oyelese *et al.* 997) and increases sodium-channel mRNA and sodium-
urrent expression in PCl2 sublines engineered to express
 $\cdot kC$ receptors (Fanger *et al.* 1995) Glial-derive 997) and increases sodium-channel mRNA and sodium-
urrent expression in PCl2 sublines engineered to express
 $\cdot kC$ receptors (Fanger *et al.* 1995). Glial-derived growth
uctor (GDNF) strongly modulates the expression of N Factor (Factor in PCl2 sublines engineered to express
 \cdot kC receptors (Fanger *et al.* 1995). Glial-derived growth
 \cdot ctor (GDNF) strongly modulates the expression of NaN
 \cdot IB4⁺ DBG neurons which are known to e ²: **EXECUTE:** EXECUTE: **EXECUTE:** THE REFERENCE CONSTRUCT THE PROPERTY 1124⁺ DRG neurons, which are known to express the ret
 EXECUTE: $\frac{dI}{dr}$ al. 1999). Consistent, with this rector (GDNF) strongly modulates the expression of NaN

1 IB4⁺ DRG neurons, which are known to express the ret

expector (Fjell *et al.* 1999). Consistent with this,

2) trathecal administration of GNDF partially protect ¹ IB4⁺ DRG neurons, which are known to express the ret experted that ℓ and ℓ added administration of GNDF partially protects required the decrease in conduction velocity that is explore (Fiell *et al.* 1999). Consistent with this,

itrathecal administration of GNDF partially protects

gainst the decrease in conduction velocity that is

beeved in c-fibres following axotomy (Bennett *et al.* Intrathecal administration of GNDF partially protects
gainst the decrease in conduction velocity that is
bserved in c-fibres following axotomy (Bennett *et al.*
008) Multiple neurotrophins and growth factors thus gainst the decrease in conduction velocity that is bserved in c-fibres following axotomy (Bennett *et al.* 998). Multiple neurotrophins and growth factors thus bserved in c-fibres following axotomy (Bennett *et al.* 998). Multiple neurotrophins and growth factors thus ppear to have effects on DRG neurons, probably via ultiple signalling pathways, and it is possible that 998). Multiple neurotrophins and growth factors thus
ppear to have effects on DRG neurons, probably via
ultiple signalling pathways, and it is possible that *Phil. Trans. R. Soc. Lond.* B (2000) *Phil. Trans. R. Soc. Lond.* B (2000)

sodium-channel expression in these cells reflects combinasodium-channel expression in the
torial effects of multiple factors.
Interestingly, the effects of ne Interestingly, the effects of multiple factors.
Interestingly, the effects of neurotrophins on expres-
Interestingly, the effects of neurotrophins on expres-
and of sodium channels may be time dependent and

action pathways, some of which are protein kinase A (1995) have demonstrated, for example, that pulsed
dependent (D'Arcangelo *et al.* 1993).
Basic fibroblast growth factor (bFGF) has been found can induce the selective ex torial effects of multiple factors.
Interestingly, the effects of neurotrophins on expres-
sion of sodium channels may be time dependent and
thus could be activity dependent. Toledo-Aral et al. Interestingly, the effects of neurotrophins on expression of sodium channels may be time dependent and thus could be activity dependent. Toledo-Aral *et al.* (1995) have demonstrated for example, that pulsed sion of sodium channels may be time dependent and
thus could be activity dependent. Toledo-Aral *et al.*
(1995) have demonstrated, for example, that pulsed
administration of NGF (for periods as short as 1 min) thus could be activity dependent. Toledo-Aral et al. can induce the selective expression of the PN1 sodiumadministration of NGF (for periods as short as 1 min)
can induce the selective expression of the PNI sodium-
channel subunit (but not the α -II subunit) in PCl2 cells
via a signalling pathway requiring immediate earl can induce the selective expression of the PNI sodium-
channel subunit (but not the α -II subunit) in PCl2 cells
via a signalling pathway requiring immediate early
genes. It is not yet known whether the precise pattern channel subunit (but not the α -II subunit) in PCl2 cells
via a signalling pathway requiring immediate early
genes. It is not yet known whether the precise pattern of
episodic exposure to peurotrophins has an effect on via a signalling pathway requiring immediate early
genes. It is not yet known whether the precise pattern of
episodic exposure to neurotrophins has an effect on
channel expression genes. It is not yet ki
episodic exposure to
channel expression. isodic exposure to neurotrophins has an effect on
annel expression.
Electrical activity itself may modulate the expression of
dium channels within excitable cells. Catterall and

channel expression.
Electrical activity itself may modulate the expression of
sodium channels within excitable cells. Catterall and
colleagaues (Sherman *et al.* 1985: Offord & Catterall sodium channels within excitable cells. Catterall and colleagaues (Sherman *et al.* 1985; Offord & Catterall sodium channels within excitable cells. Catterall and colleagaues (Sherman *et al.* 1985; Offord & Catterall 1989) have shown that electrical activity, cAMP levels and intracellular calcum all modulate the expression of colleagaues (Sherman *et al.* 1985; Offord & Catterall 1989) have shown that electrical activity, cAMP levels and intracellular calcium all modulate the expression of sodium channels in muscle cells. And elevation of intr 1989) have shown that electrical activity, cAMP levels
and intracellular calcium all modulate the expression of
sodium channels in muscle cells. And elevation of intra-
cellular calcium by exposure to the calcium ionophore and intracellular calcium all modulate the expression of
sodium channels in muscle cells. And elevation of intra-
cellular calcium by exposure to the calcium ionophore
 $\triangle 23187$ has been shown to modulate sodium-channel sodium channels in muscle cells. And elevation of intra-
cellular calcium by exposure to the calcium ionophore
A23187 has been shown to modulate sodium-channel
mRNA and sodium-current expression in neuroblastoma cellular calcium by exposure to the calcium ionophore
A23187 has been shown to modulate sodium-channel
mRNA and sodium-current expression in neuroblastoma
cells (Hirsh & Quandt 1996) Sashibara et al. (1996) bave A23187 has been shown to modulate sodium-channel
mRNA and sodium-current expression in neuroblastoma
cells (Hirsh & Quandt 1996). Sashihara *et al.* (1996) have mRNA and sodium-current expression in neuroblastoma
cells (Hirsh & Quandt 1996). Sashihara *et al.* (1996) have
demonstrated that deafferentation of the olfactory bulb,
via surgical transection of the olfactory nerve, resu cells (Hirsh & Quandt 1996). Sashihara *et al.* (1996) have
demonstrated that deafferentation of the olfactory bulb,
via surgical transection of the olfactory nerve, results in a

Figure 4. Different sodium currents are expressed in functionally different types of DRG neurons. (*a*) DRG neurons in cell
where (*b*) Eluoreccence microscopy following introduceous injection of Eluorecold focilitates ide igure 4. Different sodium currents are expressed in functionally different types of DRG neurons. (*a*) DRG neurons in cell
ulture. (*b*) Fluorescence microscopy following intracutaneous injection of Fluorogold facilitates igure 4. Different sodium currents are expressed in functionally different types of DRG neurons. (*a*) DRG neurons in cell
ulture. (*b*) Fluorescence microscopy following intracutaneous injection of Fluorogold facilitates ulture. (*b*) Fluorescence microscopy following intracutaneous injection of Fluorogold facilitates identification of cutaneous
ferent neurons which are brightly labelled. (*c*, *d*) Whole-cell patch-clamp records demonstr fferent neurons which are brightly labelled. (c, d) Whole-cell patch-clamp records demonstrate kinetically different Na⁺
urrents in muscle (c) as compared to cutaneous afferent (d) DRG neurons. Deployment of different urrents in muscle (c) as compared to cutaneous afferent (d) DRG neurons. Deployment of different ensembles of sodium
hannels in these different types of neurons endows them with different electrogenic properties that can hannels in these different types of neurons endows them with different electrogenic properties that can be seen following
ackade of potassium channels with 4-aminopyridine; note the different action potential characterist

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> 1994).
ownregulation of α -II sodium-channel mRNA in tufted ownregulation of α -II sodium-channel mRNA in tufted
and mitral cells. This effect is not due to denervation *per*
by but rather appears to be due to a change in the level of ownregulation of α -II sodium-channel mRNA in tufted

> and mitral cells. This effect is not due to denervation *per*
 α , but rather appears to be due to a change in the level of

> anantic activity since similar changes Ind mitral cells. This effect is not due to denervation *per*
 α , but rather appears to be due to a change in the level of

> ynaptic activity since similar changes occur following

> suterization of the naris of newborn r cauterization of the naris of newborn rats, which) ynaptic activity since similar changes occur following
auterization of the naris of newborn rats, which
bolishes access to olfactory stimuli without denervating
be olfactory bulb (Sashihara et al. 1997) auterization of the naris of newborn rats, which
bolishes access to olfactory stimuli without denervating
he olfactory bulb (Sashihara *et al.* 1997).
Little is currently known about the control mechanisms bolishes access to olfactory stimuli without denervating

re offactory bulb (Sashihara *et al.* 1997).
Little is currently known about the control mechanisms
esponsible for modulation of sodium-channel expression.
Uternatively spliced sodium-channel mRNAs that encode Little is currently known about the control mechanisms
esponsible for modulation of sodium-channel expression.
determatively spliced sodium-channel mRNAs that encode
encated proteins have been found (Plummer et al. 1997exponsible for modulation of sodium-channel expression.

Iternatively spliced sodium-channel mRNAs that encode

runcated proteins have been found (Plummer *et al.* 1997;

The *S* Wayman 1998) and since they may encode non-Iternatively spliced sodium-channel mRNAs that encode
cuncated proteins have been found (Plummer *et al.* 1997;
Oh & Waxman 1998) and, since they may encode non-
protional channel fragments, might participate in the funcated proteins have been found (Plummer *et al.* 1997;

(D) h & Waxman 1998) and, since they may encode non-

inctional channel fragments, might participate in the

ortrol of channel expression. The selective expressio Oh & Waxman 1998) and, since they may encode non-
inctional channel fragments, might participate in the
ontrol of channel expression. The selective expression of
inctional sodium channels primarily in excitable cells inctional channel fragments, might participate in the
ontrol of channel expression. The selective expression of
inctional sodium channels, primarily in excitable cells,
interest the presence of mechanisms that can suppress ontrol of channel expression. The selective expression of
inctional sodium channels, primarily in excitable cells,
aggests the presence of mechanisms that can suppress
heir expression. Mane et al. (1990) and Kraper et al. Inctional sodium channels, primarily in excitable cells, aggests the presence of mechanisms that can suppress
heir expression. Maue *et al.* (1990) and Kraner *et al.*

(1992) have demonstrated the presence of a 28 base-(1992) have demonstrated the presence of a 28 base-
pair (bp) silencer element, located in the 5'-flanking
region of the α -II sodium-channel gene that is active (1992) have demonstrated the presence of a 28 base-
pair (bp) silencer element, located in the 5'-flanking
region of the α -II sodium-channel gene, that is active
only in cells that do not express this gene suggesting pair (bp) silencer element, located in the 5'-flanking
region of the α -II sodium-channel gene, that is active
only in cells that do not express this gene, suggesting
that it is responsible for restricting the expressio region of the α -II sodium-channel gene, that is active
only in cells that do not express this gene, suggesting
that it is responsible for restricting the expression of α -
II channels to specific cell types. The prec that it is responsible for restricting the expression of α -
II channels to specific cell types. The precise
mechanism of action of this putative silencer element is
not understood. It is not yet clear whether similar II channels to specific cell types. The precise
mechanism of action of this putative silencer element is
not understood. It is not yet clear whether similar
control mechanisms participate in the requlation of mechanism of action of this putative silencer element is
not understood. It is not yet clear whether similar
control mechanisms participate in the regulation of
expression of other sodium-channel genes not understood. It is not yet clear whether similar
control mechanisms participate in the regulation of
expression of other sodium-channel genes.

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**5. REBUILDING THE ELECTROGENIC MACHINE AFTER INJURY: SODIUM-CHANNEL EXPRESSION NG THE ELECTROGENIC M
RY: SODIUM-CHANNEL EXP
CAN BE MALADAPTIVE CAN BE MALADAPTIVE**
In some cases, plasticity of sodium-channel expression

can be maladaptive. In early studies on motor neurons,

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Eccles and his colleagues (Eccles *et al*. 1958) demonstrated the test and his colleagues (Eccles *et al.* 1958) demonstrated at, following axonal transection, there are changes in antiparatedendritic excitability which appear to represent iccles and his colleagues (Eccles *et al.* 1958) demonstrated at, following axonal transection, there are changes in protocomatodendritic excitability which appear to represent as deployment of increased numbers of sodium hat, following axonal transection, there are changes in
omatodendritic excitability which appear to represent
ne deployment of increased numbers of sodium channels
within the neuronal membrane. More recent electrobout into the neuronal membrane. The neuronal membrane. More recent electro-
ithin the neuronal membrane. More recent electrore deployment of increased numbers of sodium channels
ithin the neuronal membrane. More recent electro-
hysiological studies have confirmed these findings
 $Kuno & I\,lins 1970)$ and have firmly established that ithin the neuronal membrane. More recent electro-
hysiological studies have confirmed these findings
Kuno & Llinas 1970) and have firmly established that
case abnormal somatodendritic excitability is sodium hysiological studies have confirmed these findings
Kuno & Llinas 1970) and have firmly established that
the abnormal somatodendritic excitability is sodium
endent (Sernagor et al. 1986; Titmus & Faber 1986) Kuno & Llinas 1970) and have firmly established that

ie abnormal somatodendritic excitability is sodium

ependent (Sernagor *et al.* 1986; Titmus & Faber 1986),

rouiding additional evidence for a change in sodium providing a somatodendritic excitability is sodium

pendent (Sernagor *et al.* 1986; Titmus & Faber 1986),

providing additional evidence for a change in sodium-

hannel denlowment in neurons following axonal injury ependent (Sernagor *et al.* 1986; Titmus & Faber 1986), roviding additional evidence for a change in sodium-
hannel deployment in neurons following axonal injury.
there studies have demonstrated increased sodiumroviding additional evidence for a change in sodium-
hannel deployment in neurons following axonal injury.
Other studies have demonstrated increased sodium-
Ahannel immunoreactivity within the injured axonal tips hannel deployment in neurons following axonal injury.

Ther studies have demonstrated increased sodium-

Hannel immunoreactivity within the injured axonal tips

If neurons (Devor *et al.* 1989; England *et al.* 1994–1996) Other studies have demonstrated increased sodium-

Hannel immunoreactivity within the injured axonal tips

of neuromas (Devor *et al.* 1989; England *et al.* 1994, 1996).

all the mechanism that could account for these cha Annel immunoreactivity within the injured axonal tips
 Solution for these changes is a
 One mechanism that could account for these changes is a
 One mechanism that could account for these changes is a
 One of the s f neuromas (Devor *et al.* 1989; England *et al.* 1994, 1996).
The mechanism that could account for these changes is a inft, following axotomy, in the vectorial transport of diamond and continuous $\&$ Faber 1990; Devor 1 **□**)ne mechanism that could account for these changes is a nift, following axotomy, in the vectorial transport of bdium channels (Titmus & Faber 1990; Devor 1994).

■ Molecular techniques have recently allowed us to ask hift, following axotomy, in the vectorial transport of

Molecular techniques have recently allowed us to ask
 λ Molecular techniques have recently allowed us to ask
 λ hether, in addition to accumulation of abnormally large

umbers of sodium channels following injury dif In Molecular techniques have recently allowed us to ask

D'hether, in addition to accumulation of abnormally large

umbers of sodium channels following injury, different

rent cross of sodium channel are denloved within ne The State of sodium channels following injury, different
pess of sodium channels following injury, different
pess of sodium channel are deployed within neurons
plowing around transection. Our initial experiments umbers of sodium channels following injury, different
ypes of sodium channel are deployed within neurons
pllowing axonal transection. Our initial experiments emonstrated that, following axonal transection, there is beyond in the upper section. Our initial experiments
emonstrated that, following axonal transection, there is
a numerical sodium-channel genes in adult
 $\frac{1}{10}$
 $\frac{1}{10}$ emonstrated that, following axonal transection, there is

In upregulation of several sodium-channel genes in adult

DRG neurons, including a striking upregulation of the

reviously silent α -III sodium-channel gene (Wax previously silent a-III sodium-channel genes in adult
 \angle IRG neurons, including a striking upregulation of the

reviously silent α -III sodium-channel gene (Waxman *et*
 $\frac{1}{1994}$) These changes are not due to an o *a* 1994). These changes are not due to an overall increase *l*. 1994). These changes are not due to an overall increase reviously silent α -III sodium-channel gene (Waxman *et l.* 1994). These changes are not due to an overall increase
1 protein synthesis. Using *in situ* hybridization and RT-
CR we have more recently shown (Dib-Haij *e l.* 1994). These changes are not due to an overall increase

1 protein synthesis. Using *in situ* hybridization and RT-

CR, we have more recently shown (Dib-Hajj *et al.* 1996,

998*a*) that in addition there is a downr 1 protein synthesis. Using *in situ* hybridization and RT-

CR, we have more recently shown (Dib-Hajj *et al.* 1996,

998*a*) that, in addition, there is a downregulation of the

SNS and NaN sodium-channel genes (figure 5 CR, we have more recently shown (Dib-Hajj *et al.* 1996, 998*a*) that, in addition, there is a downregulation of the -SNS and NaN sodium-channel genes (figure 5). There 998*a*) that, in addition, there is a downregulation of the
-SNS and NaN sodium-channel genes (figure 5). There
i evidence that some of these changes in sodium-channel
xpression persist for months following injury (Dib-Ha -SNS and NaN sodium-channel genes (figure 5). There
i evidence that some of these changes in sodium-channel
xpression persist for months following injury (Dib-Hajj
 $\frac{1}{d}$ 1996: Cummins & Waxman 1997) *evidence that some of these changes in*
al. 1996; Cummins & Waxman 1997).
These changes in sodium-channel genue xpression persist for months following injury (Dib-Hajj : *al.* 1996; Cummins & Waxman 1997).
These changes in sodium-channel gene expression are

al. 1996; Cummins & Waxman 1997).
These changes in sodium-channel gene expression are aralleled by distinct changes in the voltage-sensitive dium currents that can be recorded in DRG neurons These changes in sodium-channel gene expression are
aralleled by distinct changes in the voltage-sensitive
origin currents that can be recorded in DRG neurons.
Allowing axonal transection, there is a change in the aralleled by distinct changes in the voltage-sensitive
political political transection, there is a change in the
poseties of the fast TTX-sensitive sodium current in properties of the fast, TTX-sensitive sodium current in reperties of the fast, TTX-sensitive sodium current in hese cells (figure 6). Specifically, there is a switch from a owly repriming current (i.e. a current that recovers lowly from inactivation; $\tau \approx 60 \text{ ms}$ to a more rapidly owly repriming current (i.e. a current that recovers
owly from inactivation; $\tau \approx 60 \text{ ms}$) to a more rapidly
epriming current ($\tau \approx 15 \text{ ms}$) (Cummins & Waxman
997) It has been suggested that the emergence of the owly from inactivation; $\tau \approx 60 \text{ ms}$ to a more rapidly
priming current ($\tau \approx 15 \text{ ms}$) (Cummins & Waxman
997). It has been suggested that the emergence of the
anidly repriming current is due to the upregulation of epriming current ($\tau \approx 15 \text{ ms}$) (Cummins & Waxman 997). It has been suggested that the emergence of the apidly repriming current is due to the upregulation of τ -III channels (Cummins & Waxman 1997) but this 997). It has been suggested that the emergence of the apidly repriming current is due to the upregulation of -III channels (Cummins & Waxman 1997), but this ypothesis has not yet been definitively tested. There is -III channels (Cummins & Waxman 1997), but this
pothesis has not yet been definitively tested. There is
lso a downregulation of TTX-resistant sodium current
these cells following axotomy (Rizzo *et al.* 1995ypothesis has not yet been definitively tested. There is
a lso a downregulation of TTX-resistant sodium current
these cells following axotomy (Rizzo *et al.* 1995;
l'ummins & Waxman 1997), consistent, with the 1so a downregulation of TTX-resistant sodium current

1 these cells following axotomy (Rizzo *et al.* 1995;

1997), consistent with the

2 ownregulation of SNS-PN3 and NaN sodium-channel It these cells following axotomy (Rizzo *et al.* 1995;

)'ummins & Waxman 1997), consistent with the

) ownregulation of SNS–PN3 and NaN sodium-channel

cancerints (figure 7) Tummins & Waxm
Solution of SN can be assembly canceled the $\frac{1}{2}$. ownregulation of SNS-PN3 and NaN sodium-channel

ranscripts (figure 7).

Several arguments suggest that these changes should

redispose DRG neurons to fire spontaneously, or at inap-Several arguments suggest that these changes should
redispose DRG neurons to fire spontaneously, or at inap-
ropriately high frequencies, following injury. First,
reased densities of sodium channels at sites of action redispose DRG neurons to fire spontaneously, or at inap-
ropriately high frequencies, following injury. First,
recased densities of sodium channels at sites of action
tential generation in themselves, should lower ropriately high frequencies, following injury. First,
creased densities of sodium channels at sites of action
otential generation, in themselves, should lower
 Ω reshold (Wayman & Brill 1978; Matzner & Devor there is a site of sodium channels at sites of action

tential generation, in themselves, should lower

lower are lower at the Devor

lower and the Devor

lower and the Devor

lower at the set of the set of the property

c otential generation, in themselves, should lower

Direshold (Waxman & Brill 1978; Matzner & Devor

992). Second, overlap between steady-state activation

nd inactivation curves of different types of sodium chanand incrediction curves of different types of sodium chan-
else together with weak voltage dependence of TTX-992). Second, overlap between steady-state activation
nd inactivation curves of different types of sodium chan-
els, together with weak voltage dependence of TTXresistant sodium channels, may confer instability on the euronal membrane. Coexpression of combinations of els, together with weak voltage dependence of TTX-
esistant sodium channels, may confer instability on the
euronal membrane. Coexpression of combinations of euronal membrane. Coexpression of combinations of *hil. Trans. R. Soc. Lond.* B (2000)

Figure 5. Sodium channels α -III (*a*) are upregulated, and SNS (b) and NaN (c) are downregulated, in DRG neurons Figure 5. Sodium channels α -III (*a*) are upregulated, and
SNS (*b*) and NaN (*c*) are downregulated, in DRG neurons
following transection of their axons within the sciatic nerve.
The *in situ* hybridizations (right-ha SNS (*b*) and NaN (*c*) are downregulated, in DRG neuron following transection of their axons within the sciatic ner The *in situ* hybridizations (right-hand side) show α -III, SNS–PN3, and NaN mRNA in control DRG, and following transection of their axons within the sciatic nerve.
The *in situ* hybridizations (right-hand side) show α -III,
SNS–PN3, and NaN mRNA in control DRG, and at five to
seven days post-axotomy, $R\text{T-PCR}$ (left-h The *in situ* hybridizations (right-hand side) show α -III,
SNS-PN3, and NaN mRNA in control DRG, and at five to
seven days post-axotomy. RT-PCR (left-hand side) shows SNS–PN3, and NaN mRNA in control DRG, and at five
seven days post-axotomy. RT-PCR (left-hand side) shows
products of co-amplification of α -III and SNS together
with B-actin transcripts in control (C) and axotomized (A seven days post-axotomy. RT - PCR (left-hand side) shows
products of co-amplification of α -III and SNS together
with β -actin transcripts in control (C) and axotomized (A)
 DRG (days post-axotomy indicated above gels) products of co-amplification of α -III and SNS together
with β -actin transcripts in control (C) and axotomized (A
DRG (days post-axotomy indicated above gels), with
computer-enhanced images of amplification products with β -actin transcripts in control (C) and axotomized (A)
DRG (days post-axotomy indicated above gels), with
computer-enhanced images of amplification products shown
below gels. Co-amplification of NaN (392 bp) and GA computer-enhanced images of amplification products shown computer-enhanced images of amplification products shown
below gels. Co-amplification of NaN (392 bp) and GAPDH
(6076 bp) shows decreased expression of NaN mRNA at seven
days post-axotomy (lanes 2–4–6) compared with contro below gels. Co-amplification of NaN (392 bp) and GAPDH (6076 bp) shows decreased expression of NaN mRNA at sev
days post-axotomy (lanes 2, 4, 6) compared with controls
(lanes 1, 3, 5), (a, b) Modified from Dib Haii at al. (6076bp) shows decreased expression of NaN mRNA at sev
days post-axotomy (lanes 2, 4, 6) compared with controls
(lanes 1, 3, 5). (a, b) Modified from Dib-Hajj *et al.* (1996);
(c) modified from Dib-Hajj *et al.* (1998*a*) days post-axotomy (lanes 2, 4, 6) compared with controls (lanes 1, 3, 5). (a, b) Modified from Dib-Hajj *et al.* (1996); (c) modified from Dib-Hajj *et al.* (1998*a*).

Figure 6. A rapidly repriming sodium current, not detectable Figure 6. A rapidly repriming sodium current, not detectably
in normal DRG neurons, emerges in these cells following
axotomy. The graph shows recovery of TTX-sensitive sodius Figure 6. A rapidly repriming sodium current, not detectable
in normal DRG neurons, emerges in these cells following
axotomy. The graph shows recovery of TTX-sensitive sodium
current from inactivation as a function of time in normal DRG neurons, emerges in these cells following
axotomy. The graph shows recovery of TTX-sensitive sodium
current from inactivation as a function of time, for DRG
neurons following axonal transection (six and 22 da axotomy. The graph shows recovery of TTX-sensitive sodii
current from inactivation as a function of time, for DRG
neurons following axonal transection (six and 22 days post-
axotomy (DPA), results pooled) and for control, current from inactivation as a function of time, for DRG
neurons following axonal transection (six and 22 days post-
axotomy (DPA), results pooled) and for control, uninjured controls. Note the leftward shift in the recovery curve, which axotomy (DPA), results pooled) and for control, uninjured
controls. Note the leftward shift in the recovery curve, which
is due to the emergence of a rapidly repriming sodium current
in the axotomized neurons. Modified fro controls. Note the leftward shift in the recovery curve, which
is due to the emergence of a rapidly repriming sodium curren
in the axotomized neurons. Modified from Cummins &
Waxman (1997) is due to the emerg
in the axotomized 1
Waxman (1997).

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figure 7. Slow, TTX-resistant sodium currents in small DRG neurons are downregulated following axotomy. (*a*, *b*, left-hand
de) Whole-cell patch-clamp recordings from representative control (*a*) and axotomized (*b*, 6 DP igure 7. Slow, TTX-resistant sodium currents in small DRG neurons are downregulated following axotomy. (*a*, *b*, left-hand
de) Whole-cell patch-clamp recordings from representative control (*a*) and axotomized (*b*, 6 DPA de) Whole-cell patch-clamp recordings from representative control (*a*) and axotomized (*b*, 6 DPA) DRG neurons. Note the pss of the TTX-resistant, slowly inactivating component of sodium current following axotomy. Steady (*a*) whole-cell patch-clamp recordings from representative control (*a*) and axotomized (*b*, 6 DPA) DRG neurons. Note the
so of the TTX-resistant, slowly inactivating component of sodium current following axotomy. Stea so of the TTX-resistant, slowly inactivating component of sodium current following axotomy. Steady-state inactivation cu

2, b, right-hand side) show loss of a component characteristic of TTX-resistant currents. (*c*) Att 1, b, right-hand side) show loss of a component characteristic of TTX-resistantly following axotomy (modified from Cummins & Waxman 1997).

similarity following allocally (instanted from claimings at walk
everal types of channels, whose window currents bracket
ach other would be predicted to permit subthreshold exeral types of channels, whose window currents bracket
ach other, would be predicted to permit subthreshold
scillations in voltage supported by TTX-resistant being types of channels, whose window currents bracket
ach other, would be predicted to permit subthreshold
scillations in voltage, supported by TTX-resistant
hannels to activate other sodium channels thus produach other, would be predicted to permit subthreshold
scillations in voltage, supported by TTX-resistant
hannels, to activate other sodium channels, thus produscillations in voltage, supported by TTX-resistant
hannels, to activate other sodium channels, thus produ-
ing spontaneous activity (Rizzo *et al.* 1996). Third,
ecause TTX-sensitive sodium current in DRG neurons hannels, to activate other sodium channels, thus produ-
ing spontaneous activity (Rizzo *et al.* 1996). Third,
ecause TTX-sensitive sodium current in DRG neurons
allowing axotomy recovers more rapidly from inactivaing spontaneous activity (Rizzo *et al.* 1996). Third, ecause TTX-sensitive sodium current in DRG neurons pllowing axotomy recovers more rapidly from inactiva-
on than normal TTX-sensitive sodium currents in these ecause TTX-sensitive sodium current in DRG neurons
pllowing axotomy recovers more rapidly from inactiva-
ion than normal TTX-sensitive sodium currents in these polynomial and the recovers more rapidly from inactivation than normal TTX-sensitive sodium currents in these ells (Cummins & Waxman 1997), injured DRG neurons could be expected to display a reduced refractory period ion than normal TTX-sensitive sodium currents in these
ells (Cummins & Waxman 1997), injured DRG neurons
vould be expected to display a reduced refractory period,
nd to fire at higher-than-normal frequencies. Fourth ells (Cummins & Waxman 1997), injured DRG neurons

vould be expected to display a reduced refractory period,

nd to fire at higher-than-normal frequencies. Fourth, a

w-threshold persistent sodium current, which appears low-threshold be expected to display a reduced refractory period, nd to fire at higher-than-normal frequencies. Fourth, a low-threshold, persistent sodium current, which appears b be partially activated close to resting po nd to fire at higher-than-normal frequencies. Fourth, a
bw-threshold, persistent sodium current, which appears
b be partially activated close to resting potential, is
resent in DRG neurons (Baker & Bostock 1997). Persispw-threshold, persistent sodium current, which appears be partially activated close to resting potential, is
resent in DRG neurons (Baker & Bostock 1997). Persis-
ant sodium channels are known to participate in setting
he resting potential in ontic nerve axons (Stys et al. 19 resent in DRG neurons (Baker & Bostock 1997). Persisting potential in optic nerve axons (Stys *et al.* 1993).

as of the channels responsible for the persistent current and the channels are known to participate in setting
the resting potential in optic nerve axons (Stys *et al.* 1993).

As of the channels responsible for the persistent current

which are likely to include TTX -resistant DRG neurons and their axons following axotomy could which are likely to include TTX-resistant channels) in
NG neurons and their axons following axotomy could
roduce a hyperpolarizing shift in resting potential
hich by relieving resting inactivation might increase NG neurons and their axons following axotomy could
roduce a hyperpolarizing shift in resting potential
hich, by relieving resting inactivation, might increase
he amount of TTX-sensitive sodium current available for roduce a hyperpolarizing shift in resting potential
the amount of TTX-sensitive sodium current available for
exponses in response to rapid depolarizations Figure 1.1 Thich, by relieving resting inactivation, might increase
the amount of TTX-sensitive sodium current available for
Clectrogenesis in response to rapid depolaraizations he amount of TTX-sensitive sodium current available for
(Cummins & Waxman 1997). Finally, changes in sodium-
hannel expression in injured DBG neurons may be Dectrogenesis in response to rapid depolaraizations
Cummins & Waxman 1997). Finally, changes in sodium-
hannel expression in injured DRG neurons may be
commanied by changes in the expression of other ion Cummins & Waxman 1997). Finally, changes in sodium-
hannel expression in injured DRG neurons may be
companied by changes in the expression of other ion
hannels that participate in shaping their excitability hannel expression in injured DRG neurons may be companied by changes in the expression of other ion hannels that participate in shaping their excitability. There is evidence for a downregulation of potassiumcompanied by changes in the expression of other ion
hannels that participate in shaping their excitability.
There is evidence for a downregulation of potassium-
hannel expression in DBG neurons following axotomy hannels that participate in shaping their excitability.

There is evidence for a downregulation of potassium-

hannel expression in DRG neurons following axotomy

Everill & Kocsis 1999: Jabikawa et al. 1999) and this There is evidence for a downregulation of potassium-
hannel expression in DRG neurons following axotomy
Everill & Kocsis 1999; Ishikawa *et al.* 1999) and this,
20 would be expected to produce hyperexitability hannel expression in DRG neurons following axote
Everill & Kocsis 1999; Ishikawa *et al.* 1999) and \geq
 \geq 0, would be expected to produce hyperexcitability.
Although most of the studies on plasticity in sodi verill & Kocsis 1999; Ishikawa *et al.* 1999) and this,
b, would be expected to produce hyperexcitability.
Although most of the studies on plasticity in sodium-
annel expression after neuronal injury to date have

the separate of the studies on plasticity.

Although most of the studies on plasticity in sodium-

hannel expression after neuronal injury to date have

expressed on DBG neurons it is possible the hyper-Although most of the studies on plasticity in sodium-
hannel expression after neuronal injury to date have
ocused on DRG neurons, it is possible the hyperexcitability also develops as a result of altered sodium-

he resting potential in optic nerve axons (Stys *et al.* 1993). matly 24 h following kainate-induced seizures in a rat .oss of the channels responsible for the persistent current model of epilepsy, and suggested that these other types of neurons following injury. It is now clear
that sodium-channel densities can increase in DRG other types of neurons following injury. It is now clear
that sodium-channel densities can increase in DRG
neurons as a response to inflammation in their projection other types of neurons following injury. It is now clear
that sodium-channel densities can increase in DRG
neurons as a response to inflammation in their projection
fields (Tanaka et al. 1998: Gould et al. 1998) and it ha that sodium-channel densities can increase in DRG neurons as a response to inflammation in their projection fields (Tanaka *et al.* 1998; Gould *et al.* 1998), and it has neurons as a response to inflammation in their projection
fields (Tanaka *et al.* 1998; Gould *et al.* 1998), and it has
been demonstrated that this is due, at least in part, to
changes in sodium-channel gene expression (T fields (Tanaka *et al.* 1998; Gould *et al.* 1998), and it has been demonstrated that this is due, at least in part, to changes in sodium-channel gene expression (Tanaka *et al.* 1998). Changes in sodium-channel expression changes in sodium-channel gene expression (Tanaka et al. 1998). Changes in sodium-channel expression have been
observed within neurons whose axons have lost their 1998). Changes in sodium-channel expression have been
observed within neurons whose axons have lost their
myelin in the tiaep rat, a mutant in which oligodendro-
cytes degenerate (Black et al. 1999). Sashihara et al. (199 observed within neurons whose axons have lost their
myelin in the tiaep rat, a mutant in which oligodendro-
cytes degenerate (Black *et al.* 1999). Sashihara *et al.* (1992)
observed the production of larger-than-normal nu myelin in the tiaep rat, a mutant in which oligodendro-
cytes degenerate (Black *et al.* 1999). Sashihara *et al.* (1992)
observed the production of larger-than-normal numbers
of sodium channels in the brains of genetical cytes degenerate (Black *et al.* 1999). Sashihara *et al.* (1992) observed the production of larger-than-normal numbers of sodium channels in the brains of genetically seizureobserved the production of larger-than-normal numbers
of sodium channels in the brains of genetically seizure-
susceptible mice. Bartolomei *et al.* (1997) and Gastaldi *et*
 d . (1997) observed transient changes in neuron of sodium channels in the brains of genetically seizure-
susceptible mice. Bartolomei *et al.* (1997) and Gastaldi *et*
al. (1997) observed transient changes in neuronal sodium-
channel mRNA expression that persited for susceptible mice. Bartolomei *et al.* (1997) and Gastaldi *et al.* (1997) observed transient changes in neuronal sodium-
channel mRNA expression that persisted for approxi-
matly 24^h following kainate-induced seizures i al. (1997) observed transient changes in neuronal sodium-
channel mRNA expression that persisted for approxi-
matly 24 h following kainate-induced seizures in a rat
model of enjlepsy and suggested that these changes could channel mRNA expression that persisted for approximatly 24h following kainate-induced seizures in a rat model of epilepsy, and suggested that these changes could lead to alterations in excitability Vreugdenbil *et al.* (1 matly 24h following kainate-induced seizures in a rat observed a shift in voltage dependence in sodium currents lead to alterations in excitability. Vreugdenhil *et al.* (1998) observed a shift in voltage dependence in sodium currents within hippocampal neurons in a model of epileptic kind-
ling consistent with the idea that there i observed a shift in voltage dependence in sodium currents
within hippocampal neurons in a model of epileptic kind-
ling, consistent with the idea that there is a switch in the
pattern of expression of sodium-channel genes. within hippocampal neurons in a model of epileptic kind-
ling, consistent with the idea that there is a switch in the
pattern of expression of sodium-channel genes. There is
evidence that persistent sodium channels constit ling, consistent with the idea that there is a switch in the pattern of expression of sodium-channel genes. There is evidence that persistent sodium channels constitute a pattern of expression of sodium-channel genes. There is
evidence that persistent sodium channels constitute a
particularly important substrate for the sustained depo-
larizations associated with epileptiform activity (Seca evidence that persistent sodium channels constitute a
particularly important substrate for the sustained depo-
larizations associated with epileptiform activity (Segal
1994: Segal & Douglas 1995) Thus even in the absence particularly important substrate for the sustained depo-
larizations associated with epileptiform activity (Segal
1994; Segal & Douglas 1995). Thus, even in the absence
of a global unregulation of sodium channels, a select larizations associated with epileptiform activity (Segal 1994; Segal & Douglas 1995). Thus, even in the absence 1994; Segal & Douglas 1995). Thus, even in the absence
of a global upregulation of sodium channels, a selective
upregulation of sodium channels producing persistent
sodium currents could increase neuronal excitability and of a global upregulation of sodium channels, a selective
upregulation of sodium channels producing persistent
sodium currents could increase neuronal excitability and
contribute to epileptogenesis upregulation of sodium channels producing persistent
sodium currents could increase neuronal excitability and
contribute to epileptogenesis.

ocused on DRG neurons, it is possible the hyper-
scitability also develops as a result of altered sodium-
hannel expression following other types of insult, and in (Iwahashi et al. 1994). It thus seems reasonable to ask As noted above, it is well established that sodiumcontribute to epileptogenesis.
As noted above, it is well established that sodium-
channel gene expression changes in DRG neurons
following injury to their axons (Waxman et al. 1994: Dib-As noted above, it is well established that sodium-
channel gene expression changes in DRG neurons
following injury to their axons (Waxman *et al.* 1994; Dib-
Haij et al. 1996; 1998a) Similar changes have been observed channel gene expression changes in DRG neurons
following injury to their axons (Waxman *et al.* 1994; Dib-
Hajj *et al.* 1996, 1998*a*). Similar changes have been observed
in facial motor neurons following axonal transecti following injury to their axons (Waxman *et al.* 1994; Dib-Hajj *et al.* 1996, 1998*a*). Similar changes have been observed in facial motor neurons following axonal transection (Iwahashi *et al*. 1994). It thus seems reasonable to ask

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hether sodium-channel expression is altered in some the vector of corticospinal expression is altered in some roups of corticospinal neurons following injury to their vons If this hypothesis is correct excitability of these cells the constant the pression is altered in some
roups of corticospinal neurons following injury to their
xons. If this hypothesis is correct, excitability of these cells
aight be altered following spinal cord injury which can roups of corticospinal neurons following injury to their
xons. If this hypothesis is correct, excitability of these cells
night be altered following spinal cord injury, which can
cancer or otherwise injure corticospinal ax xons. If this hypothesis is correct, excitability of these cells
right be altered following spinal cord injury, which can
ransect or otherwise injure corticospinal axons as they hight be altered following spinal cord injury, which can ansect or otherwise injure corticospinal axons as they are downwards within the spinal cord. It has been emonstrated that there are changes in the relative ransect or otherwise injure corticospinal axons as they
ravel downwards within the spinal cord. It has been
emonstrated that there are changes in the relative
resisting of TTX-sensitive and TTX-resistant sodium ravel downwards within the spinal cord. It has been
emonstrated that there are changes in the relative
of TTX-sensitive and TTX-resistant sodium
of experience and TTX-resistant sodium
of the urinary emonstrated that there are changes in the relative
ensities of TTX-sensitive and TTX-resistant sodium
urrents in afferent neurons innervating the urinary $\begin{cases} \text{ensities of TTX-sensitive and TTX-resistant sodium} \\ \text{larges in afferent neurons innervating the urinary ladder following experimental spinal cord injury} \\ \text{Voshimura & deGroat 1997} \\ \end{cases}$ urrents in afferent neurons innervating the urinary
ladder following experimental spinal cord injury
Yoshimura & deGroat 1997). Changes of this type in
xotomized corticoshinal neurons could alter their excitaxotomized corticospinal spinal cordinative vehicles in the vehicles of this type in solomized corticospinal neurons could alter their excit-
 \bullet bility and might at least in part explain the post-traumatic Yoshimura & deGroat 1997). Changes of this type in
xotomized corticospinal neurons could alter their excit-
bility and might at least in part explain the post-traumatic
spilensy seen in some patients following spinal cord sotomized corticospinal neurons could alter their excitative individual matches following spinal cord injury.

6. REBUILDING THE ELECTROGENIC MACHINE TO
6. REBUILDING THE ELECTROGENIC MACHINE TO
MEET FUNCTIONAL NEEDS: STATE DEPENDENCE **MEET FUNCTION AND ELECTROGENIC MACHINE TO A SECOND ACT FUNCTIONAL NEEDS: STATE DEPENDENCE**
MEET FUNCTIONAL NEEDS: STATE DEPENDENCE **MEET FUNCTIONAL NEEDS: STATE DEPENDENCE
AND ELECTROGENIC RETUNING
IN NON-PATHOLOGICAL NEURONS AND ELECTROGENIC RETUNING**

Most of the developmental and pathological changes in sodium-channel expression described above occur over a elatively long time-scale (a few days to a few months). The odium-channel expression described above occur over a
elatively long time-scale (a few days to a few months). The
electrophysiological state of neurons, in contrast, changes
ver a shorter time-scale. This leads us to ask: elatively long time-scale (a few days to a few months). The
detrophysiological state of neurons, in contrast, changes
ver a shorter time-scale. This leads us to ask: When a
euron in the non-pathological nervous system pass exploring is a shorter time-scale. This leads us to ask: When a lower a shorter time-scale. This leads us to ask: When a low-
euron in the non-pathological nervous system passes from de
ne functional state to another for e ver a shorter time-scale. This leads us to ask: When a euron in the non-pathological nervous system passes from ne functional state to another, for example from a relaeuron in the non-pathological nervous system passes from
ne functional state to another, for example from a rela-
vely quiescent state (generating action potentials at low
requencies) to a bursting (high-frequency discharg ne functional state to another, for example from a rela-
vely quiescent state (generating action potentials at low
requencies) to a bursting (high-frequency discharge) state,
ose it use a fixed repetitive of pre-existing s vely quiescent state (generating action potentials at low
requencies) to a bursting (high-frequency discharge) state,
oes it use a fixed repertoire of pre-existing sodium chan-
els in different ways? Or does it rebuild its requencies) to a bursting (high-frequency discharge) state,
oes it use a fixed repertoire of pre-existing sodium chan-
els in different ways? Or does it rebuild itself by deploying
new and different ensemble of sodium chan oes it use a fixed repertoire of pre-existing sodium chan-
els in different ways? Or does it rebuild itself by deploying
new and different ensemble of sodium channels so as to
stune its electrogenic machinery? els in different ways? Or does it rebu
new and different ensemble of sodi
etune its electrogenic machinery?
One model for studying this que new and different ensemble of sodium channels so as to
etune its electrogenic machinery?
One model for studying this question is provided by

he magnocellular neurosecretory cells within the supraoptic nucleus of the hypothalamus. The supraoptic ne magnocellular neurosecretory cells within the
apraoptic nucleus of the hypothalamus. The supraoptic
nagnocellular neurons send their axons to the neural
she of the nituitary. In their basal state, these cells are praoptic nucleus of the hypothalamus. The supraoptic
agnocellular neurons send their axons to the neural
be of the pituitary. In their basal state, these cells are
elatively quiescent fring at low frequencies relatively alternatively and their axons to the neural
be of the pituitary. In their basal state, these cells are
elatively quiescent, firing at low frequencies
 ≤ 3 impulses s^{-1} and irrequiarly but they respond to be of the pituitary. In their basal state, these cells are elatively quiescent, firing at low frequencies $\lt 3$ impulses s^{-1}) and irregularly, but they respond to banges in comptic stimuli by generating bursts of acti elatively quiescent, firing at low frequencies $\langle 3 \text{ impulses } s^{-1} \rangle$ and irregularly, but they respond to hanges in osmotic stimuli by generating bursts of action of the release of vasor responsively \leq 3 impulses s⁻¹) and irregularly, but they respond to
hanges in osmotic stimuli by generating bursts of action
otentials which trigger the release of vasopressin
Walters & Hatton 1974: Mason 1980) Earlier studies hanges in osmotic stimuli by generating bursts of action
otentials which trigger the release of vasopressin
Walters & Hatton 1974; Mason 1980). Earlier studies
ad shown that the magnocellular neurons possess an otentials which trigger the release of vasopressin
Walters & Hatton 1974; Mason 1980). Earlier studies
ad shown that the magnocellular neurons possess an
atrinsic regenerative mechanism (Andrew & Dudek Walters & Hatton 1974; Mason 1980). Earlier studies
ad shown that the magnocellular neurons possess an
trinsic regenerative mechanism (Andrew & Dudek
983; Hatton 1990), which can be triggered by endo-1trinsic regenerative mechanism (Andrew & Dudek enous osmosensitivity mediated by mechanosensitive 983; Hatton 1990), which can be triggered by endo-
enous osmosensitivity mediated by mechanosensitive
hannels (Ollet & Borque 1993) and by synaptic inputs
component component controller neurons which are also osmosenenous osmosensitivity mediated by mechanosensitive
hannels (Ollet & Borque 1993) and by synaptic inputs
om circumventricular neurons which are also osmosen-
live (Richard & Borque 1992) Moreover action potenhannels (Ollet & Borque 1993) and by synaptic inputs
om circumventricular neurons which are also osmosen-
tive (Richard & Borque 1992). Moreover, action poten-
al activity in magnocellular neurons of the rat was The component contribution of the rate also composed
tive (Richard & Borque 1992). Moreover, action poten-
al activity in magnocellular neurons of the rat was tive (Richard & Borque 1992). Moreover, action poten-
al activity in magnocellular neurons of the rat was
nown to be sodium dependent and TTX sensitive, indi-
ating that it is mediated by sodium channels (Andrew al activity in magnocellular neurons of the rat was
nown to be sodium dependent and TTX sensitive, indi-
ating that it is mediated by sodium channels (Andrew
r. Dudek 1983: Inenanza et al. 1993: I i. & Hatton 1996)

nown to be sodium dependent and TTX sensitive, indiating that it is mediated by sodium channels (Andrew ϵ Dudek 1983; Inenaga *et al.* 1993; Li & Hatton 1996). ating that it is mediated by sodium channels (Andrew
 ϵ Dudek 1983; Inenaga *et al.* 1993; Li & Hatton 1996).

Thus, in generating action potentials, the magnocellular

eurons activate sodium channels in their membrane t Dudek 1983; Inenaga *et al.* 1993; Li & Hatton 1996).

Thus, in generating action potentials, the magnocellular

eurons activate sodium channels in their membranes.

Intrinsic the membrane of these cells contain the sam Thus, in generating action potentials, the magnocellular
eurons activate sodium channels in their membranes.
iut does the membrane of these cells contain the same,
 $\sum_{n=1}^{\infty}$ a different ensemble of channels in the qu eurons activate sodium channels in their membranes.
 α at does the membrane of these cells contain the same,
 α a different, ensemble of channels in the quiescent and

ursting states? My colleagues and I recently te but does the membrane of these cells contain the same,
 \overrightarrow{D} r a different, ensemble of channels in the quiescent and
ursting states? My colleagues and I recently tested the
voothesis that the transition from the quies) r a different, ensemble of channels in the quiescent and ursting states? My colleagues and I recently tested the ypothesis that the transition from the quiescent to the ursting state includes a rebuilding of these cells' ursting states? My colleagues and I recently tested the ypothesis that the transition from the quiescent to the ursting state includes a rebuilding of these cells' electroypothesis that the transition from the quiescent to the ursting state includes a rebuilding of these cells' electroenic membrane, so that it contains a different repertoire f sodium channels (Tanaka *et al.* 1999). To tes enic membrane, so that it contains a different repertoire

hypothesis, we studied magnocellular neurons under
normal conditions and following salt loading, which is
known (Jones & Pickering 1969: Balment et al. 1980) to hypothesis, we studied magnocellular neurons under
normal conditions and following salt loading, which is
known (Jones & Pickering 1969; Balment *et al.* 1980) to
expose supraoptic neurons to a milieu of elevated extranormal conditions and following salt loading, which is
known (Jones & Pickering 1969; Balment *et al.* 1980) to
expose supraoptic neurons to a milieu of elevated extra-
cellular osmolality which triggers bursting known (Jones & Pickering 1969; Balment *et al.* 1980) to
expose supraoptic neurons to a milieu of elevated extra-
cellular osmolality which triggers bursting.
In our first experiments (Tanaka *et al.* 1999), we studied
sod

cellular osmolality which triggers bursting.
In our first experiments (Tanaka *et al.* 1999), we studied
sodium-channel gene expression in the supraoptic nuclei
of adult rats using isoform-specific riboprobes for *in situ* In our first experiments (Tanaka *et al.* 1999), we studied sodium-channel gene expression in the supraoptic nuclei of adult rats using isoform-specific riboprobes for *in situ* hybridization. We first studied the control sodium-channel gene expression in the supraoptic nuclei
of adult rats using isoform-specific riboprobes for *in situ*
hybridization. We first studied the control supraoptic of adult rats using isoform-specific riboprobes for *in situ*
hybridization. We first studied the control supraoptic
nucleus (from rats that had not been salt loaded), and
observed that low levels of the mRNA for the α hybridization. We first studied the control supraoptic
nucleus (from rats that had not been salt loaded), and
observed that low levels of the mRNA for the α -II and
Na6 sodium-channel α subunits are present within nucleus (from rats that had not been salt loaded), and
observed that low levels of the mRNA for the α -II and
Na6 sodium-channel α subunits are present within
magnocellular neurons Significant levels of α -I and $\$ observed that low levels of the mRNA for the α -II and Na6 sodium-channel α subunits are present within magnocellular neurons. Significant levels of α -I and α -III Na6 sodium-channel α subunits are present within
magnocellular neurons. Significant levels of α -I and α -III
mRNA could not be detected in these cells. We next salt-
loaded animals, and observed a distinct unregul magnocellular neurons. Significant levels of α -I and α -III
mRNA could not be detected in these cells. We next salt-
loaded animals, and observed a distinct upregulation of
the α -II and Na6 mRNAs (figure 8) These mRNA could not be detected in these cells. We next salt-
loaded animals, and observed a distinct upregulation of
the α -II and Na6 mRNAs (figure 8). These observations
(Tanaka *et al.* 1999) showed that in response to s loaded animals, and observed a distinct upregulation of
the α -II and Na6 mRNAs (figure 8). These observations
(Tanaka *et al.* 1999) showed that in response to salt
loading, expression of α -II and Na6 sodium channel the α -II and Na6 mRNAs (figure 8). These observations (Tanaka *et al.* 1999) showed that in response to salt loading, expression of α -II and Na6 sodium channels is unregulated at the transcriptional level i.e. the e (Tanaka *et al.* 1999) showed that in response to salt loading, expression of α -II and Na6 sodium channels is upregulated at the transcriptional level, i.e. the expression of the α -II and Na6 sodium-channel genes is loading, expression of α -II and Na6 sodium-channels
upregulated at the transcriptional level, i.e. the expressio
of the α -II and Na6 sodium-channel genes is increased.
The expression of ion-channels and receptors wi regulated at the transcriptional level, i.e. the expression
the α -II and Na6 sodium-channel genes is increased.
The expression of ion channels and receptors within
e cell membrane is controlled at transcriptional trans

of the α -II and Na6 sodium-channel genes is increased.
The expression of ion channels and receptors within
the cell membrane is controlled at transcriptional, trans-
lational and nost-translational levels (Ginty *et al* The expression of ion channels and receptors within
the cell membrane is controlled at transcriptional, trans-
lational and post-translational levels (Ginty *et al.* 1992; Sharma *et al.* 1993; Sucher *et al.* 1993; Hales & Tyndale lational and post-translational levels (Ginty *et al.* 1992; Sharma *et al.* 1993; Sucher *et al.* 1993; Hales & Tyndale 1994; Black *et al.* 1998). As a next step we therefore had to determine whether changes in gene tran Sharma *et al.* 1993; Sucher *et al.* 1993; Hales & Tyndale 1994; Black *et al.* 1998). As a next step we therefore had to determine whether changes in gene transcription were paralleled by increases in sodium-channel pro 1994; Black *et al.* 1998). As a next step we therefore had to determine whether changes in gene transcription were paralleled by increases in sodium-channel protein. To do this we used immunocytochemical and immunolearit determine whether changes in gene transcription were
paralleled by increases in sodium-channel protein. To do
this we used immunocytochemical and immunoblotting
methods with antibody SP20 directed against a paralleled by increases in sodium-channel protein. To do
this we used immunocytochemical and immunoblotting
methods with antibody SP20, directed against a
conserved region of sodium channels (Westenbrock et al. this we used immunocytochemical and immunoblotting
methods with antibody SP20, directed against a
conserved region of sodium channels (Westenbroek *et al.*) 1989, 1992), to examine the expression of sodium-channel conserved region of sodium channels (Westenbroek *et al.* 1989, 1992), to examine the expression of sodium-channel protein in the magnocellular neurons (Tanaka *et al.* 1999).
As shown in figure 9*a b*, these studies sho 1989, 1992), to examine the expression of sodium-channel
protein in the magnocellular neurons (Tanaka *et al.* 1999).
As shown in figure 9*a*, b , these studies showed that,
following salt loading, there is a distinct inc protein in the magnocellular neurons (Tanaka *et al.* 1999).
As shown in figure $9a,b$, these studies showed that,
following salt loading, there is a distinct increase in
sodium-channel immunoreactivity within these neuron As shown in figure $9a, b$, these studies showed that, following salt loading, there is a distinct increase in sodium-channel immunoreactivity within these neurons.
Consistent with these results, there is an increase in the density of the 230 kDa immunoreactive band charactersodium-channel immunoreactivity within these neurons.
Consistent with these results, there is an increase in the density of the 230 kDa immunoreactive band character-
istic of sodium channels (see Westenbroek *et al.* Consistent with these results, there is an increase in the density of the 230 kDa immunoreactive band characteristic of sodium channels (see Westenbroek *et al.* 1989) in membrane preparations from the supraoptic nucleus of salt-loaded rats (figure $9c$) istic of sodium channels (seen membrane preparations from salt-loaded rats (figure 9*c*).
Salt-loaded rats (figure 9*c*). Embrane preparations from the supraoptic nucleus of
t-loaded rats (figure $9c$).
These observations demonstrated that the transcription
 α -II and Na6 sodium-channel mRNA in magno-

salt-loaded rats (figure 9c).
These observations demonstrated that the transcription
of α -II and Na6 sodium-channel mRNA in magno-
cellular neurons is unregulated in response to osmotic These observations demonstrated that the transcription
of α -II and Na6 sodium-channel mRNA in magno-
cellular neurons is upregulated in response to osmotic
changes and further showed that this results in an of α -II and Na6 sodium-channel mRNA in magno-
cellular neurons is upregulated in response to osmotic
changes, and further showed that this results in an
increased level of sodium-channel protein in these cells cellular neurons is upregulated in response to osmotic
changes, and further showed that this results in an
increased level of sodium-channel protein in these cells, a
change which could support a remodelling of their elecincreased level of sodium-channel protein in these cells, a
change which could support a remodelling of their elecincreased level of sodium-channel protein in these cells, a
change which could support a remodelling of their elec-
trogenic machinery. To demonstrate that there was,
indeed a functional change of these cells however it wa change which could support a remodelling of their electrogenic machinery. To demonstrate that there was, indeed, a functional change of these cells, however, it was necessary to further show that these channels were trogenic machinery. To demonstrate that there was,
indeed, a functional change of these cells, however, it was
necessary to further show that these channels were
inserted into the cell membrane where they could alter indeed, a functional change of these cells, however, it was
necessary to further show that these channels were
inserted into the cell membrane where they could alter necessary to further show that these channels were
inserted into the cell membrane where they could alter
the electrogenic properties of these cells. We therefore
used patch-clamp recording to study sodium currents in inserted into the cell membrane where they could alter
the electrogenic properties of these cells. We therefore
used patch-clamp recording to study sodium currents in
magnocellular neurons (Tanaka et al. 1999). These the electrogenic properties of these cells. We therefore
used patch-clamp recording to study sodium currents in
magnocellular neurons (Tanaka *et al.* 1999). These
recordings demonstrated the presence of two distinct used patch-clamp recording to study sodium currents in magnocellular neurons (Tanaka et al. 1999). These magnocellular neurons (Tanaka *et al.* 1999). These
recordings demonstrated the presence of two distinct
sodium currents in control magnocellular neurons. The
first was a fast transient sodium current, which contrirecordings demonstrated the presence of two distinct
sodium currents in control magnocellular neurons. The
first was a fast transient sodium current, which contri-
butes to the rapid upstroke of the action potential. In sodium currents in control magnocellular neurons. The
first was a fast transient sodium current, which contri-
butes to the rapid upstroke of the action potential. In addition, because slower sodium currents with thresholds butes to the rapid upstroke of the action potential. In addition, because slower sodium currents with thresholds
closer to resting potential are known to contribute to
burst activity in some types of neurons including addition, because slower sodium currents with thresholds
closer to resting potential are known to contribute to
burst activity in some types of neurons including
supraontic neurons (I, k, H, H, H) and $I(0, 6)$ we searched f closer to resting potential are known to contribute to
burst activity in some types of neurons including
supraoptic neurons (Li & Hatton 1996), we searched for
them by applying slow $(0.23 \text{ mV m s}^{-1})$ ramp depolarizaburst activity in some types of neurons including
supraoptic neurons (Li & Hatton 1996), we searched for
them by applying slow $(0.23 \text{ mV m s}^{-1})$ ramp depolarizations in magnocellular neurons. These experiments

igure 8. Upregulation of α -II and Na6 sodium channel $\begin{cases} \text{where 8. Upregulation of } \alpha\text{-II and Na6 sodium channel} \text{RNA in supraoptic magnocellular neurons following salt} \text{and} \text{The micrographs from control (left column) and} \end{cases}$ $\begin{array}{l} \begin{array}{l} \text{Figure 8. Upregulation of α-II and Na6 sodium channel} \\ \text{1RNA in supraoptic magnocellular neurons following salt} \end{array} \end{array} \end{array}$ \vert 1RNA in supraoptic magnocellular neurons following salt
ading. The micrographs, from control (left column) and
alt-loaded (right column) rats, were digitally enhanced to
above in situ bubridization with subtune speci pading. The micrographs, from control (left column) and
alt-loaded (right column) rats, were digitally enhanced to
now *in situ* hybridization with subtype-specific riboprobes for la channel subunits α -I, α -II, α -III and Na6. α -I and α -III now *in situ* hybridization with subtype-specific riboprobes for
a channel subunits α -I, α -II, α -III and Na6. α -I and α -III
iRNA are not detectable, and low levels of α -II and Na6
iRNA are present in the Ia channel subunits α-I, α-II, α-III and Na6. α-I and α-III

1RNA are not detectable, and low levels of α-II and Na6

1RNA are present in the control supraoptic nucleus (no aster-

ks) Expression of the α-II and Na6 tran \begin{cases} iRNA are not detectable, and low levels of α -II and λ iRNA are present in the control supraoptic nucleus λ
s). Expression of the α -II and Na6 transcript is up-
explated following salt loading (asterisk TRNA are present in the control supraoptic nucleus (no aster-
les). Expression of the α -II and Na6 transcript is up-
egulated following salt loading (asterisks). Optical densities
less un unenhanced micrographs (graph) ks). Expression of the α -II and Na6 transcript is up-

egulated following salt loading (asterisks). Optical densities

om unenhanced micrographs (graph) provide a quantitative

equantitative

equals and show a signific equlated following salt loading (asterisks). Optical densities

om unenhanced micrographs (graph) provide a quantitative

leasure of mRNA levels and show a significant increase in

-II and Na6 mRNA following salt loading. Speasure of mRNA levels and show a significant increase ⁻-II and Na6 mRNA following salt loading. * denotes *p* < cale bar, 100 μm. Modified from Tanaka *et al.* (1999).

cale bar, $100 \mu m$. Modified from Tanaka *et al.* (1999).
emonstrated the presence of TTX-sensitive 'ramp' emonstrated the presence of TTX-sensitive 'ramp'
adium currents which were activated by slow depolariemonstrated the presence of TTX-sensitive 'ramp'

Didium currents which were activated by slow depolari-

ations close to resting potential. Both of the currents,

be fast transient current and the slow ramp current If the fast transient which were activated by slow depolariations close to resting potential. Both of the currents, he fast transient current and the slow ramp current, tere increased in salt-loaded magnocellular neurons ations close to resting potential. Both of the currents,
he fast transient current and the slow ramp current,
zere increased in salt-loaded magnocellular neurons.
There was an increase of 20% in the density of the fast he fast transient current and the slow ramp current, ransient sodium current in salt-loaded rats. In contrast,

Figure 9. Sodium-channel immunoreactivity with SP20 an body is increased in the supraoptic nucleus following salt loading (b) compared to controls (a). Immunobletting (c) Figure 9. Sodium-channel immunoreactivity with SP20 anti-
body is increased in the supraoptic nucleus following salt
loading (*b*) compared to controls (*a*). Immunoblotting (*c*)
shows a 230kD band (arrow) that is denser body is increased in the supraoptic nucleus following salt
loading (b) compared to controls (a). Immunoblotting (c)
shows a 230 kD band (arrow) that is denser in the salt-loaded
(S) supraoptic nucleus (SON) than in the co loading (b) compared to controls (a). Immunoblotting (c)
shows a 230kD band (arrow) that is denser in the salt-loaded
(S) supraoptic nucleus (SON) than in the control (C). There
is a less pronounced increase in density of (S) supraoptic nucleus (SON) than in the control (C) . There is a less pronounced increase in density of this band in the salt-loaded pituitary neural lobe (NL), which contains the is a less pronounced increase in density of this band in the
salt-loaded pituitary neural lobe (NL), which contains the
terminals of the axons of the supraoptic neurons. Scale bar,
 100 nm Modified from Tanaka et al. (salt-loaded pituitary neural lobe (NL), which
terminals of the axons of the supraoptic neuror
100µm. Modified from Tanaka *et al*. (1999).

100 μ m. Modified from Tanaka *et al.* (1999).
however, the ramp current density was approximately
50% larger in salt-loaded neurons (figure 10) an however, the ramp current density was approximately
50% larger in salt-loaded neurons (figure 10), an
increase that was significantly larger than the increase in however, the ramp current density was approximately
50% larger in salt-loaded neurons (figure 10), an
increase that was significantly larger than the increase in
the fast transient sodium current. The two sodium 50% larger in salt-loaded neurons (figure 10), an
increase that was significantly larger than the increase in
the fast transient sodium current. The two sodium
currents were thus both increased but to significantly increase that was significantly larger than the increase in
the fast transient sodium current. The two sodium
currents were thus both increased, but to significantly
different degrees the fast transient
currents were thus
different degrees.
The presence of currents were thus both increased, but to significantly
different degrees.
The presence of α -II and Na6 sodium channels in the

magnocellular neurons appears to provide a molecular The presence of α -II and Na6 sodium channels in the magnocellular neurons appears to provide a molecular substrate for the fast transient and slow ramp sodium currents in these cells. It is known from studies in other magnocellular neurons appears to provide a molecular
substrate for the fast transient and slow ramp sodium
currents in these cells. It is known from studies in other
neuronal cell types, such as Purkinie cells, that the Na substrate for the fast transient and slow ramp sodium
currents in these cells. It is known from studies in other
neuronal cell types, such as Purkinje cells, that the Na6
sodium channel can produce a persistent or ramp cur currents in these cells. It is known from studies in other
neuronal cell types, such as Purkinje cells, that the Na6
sodium channel can produce a persistent or ramp current
(Vega-Saenz DeMiera et al. 1997; Raman et al. 199 neuronal cell types, such as Purkinje cells, that the Na6
sodium channel can produce a persistent or ramp current
(Vega-Saenz DeMiera *et al.* 1997; Raman *et al.* 1997). The
 α -II channel in contrast, has been shown to sodium channel can produce a persistent or ramp current (Vega-Saenz DeMiera *et al.* 1997; Raman *et al.* 1997). The α -II channel, in contrast, has been shown to produce a fast transient current (Noda *et al.* 1986*b*; (Vega-Saenz DeMiera et al. 1997; Raman et al. 1997). The α -II channel, in contrast, has been shown to produce a fast
transient current (Noda *et al.* 1986*b*; Auld *et al.* 1988). The
different voltage dependence and kinetics of these two
channels appear to permit them to co transient current (Noda *et al.* 1986*b*; Auld *et al.* 1988). The different voltage dependence and kinetics of these two channels appear to permit them to collaborate in electro-
genesis the Na6 current being evoked by s different voltage dependence and kinetics of these two
channels appear to permit them to collaborate in electro-
genesis, the Na6 current being evoked by small, slow
depolarizations close to threshold and thus serving to channels appear to permit them to collaborate in electrogenesis, the Na6 current being evoked by small, slow
depolarizations close to threshold and thus serving to genesis, the Na6 current being evoked by small, slow
depolarizations close to threshold and thus serving to
amplify depolarizing inputs, and the α -II current
underlying the rapid depolarizing unstroke of the action depolarizations close to threshold and thus serving to
amplify depolarizing inputs, and the α -II current
underlying the rapid depolarizing upstroke of the action
potential. The disproportional increases in the two amplify depolarizing inputs, and the α -II current
underlying the rapid depolarizing upstroke of the action
potential. The disproportional increases in the two
currents encoded by these two channels would be expected underlying the rapid depolarizing upstroke of the action
potential. The disproportional increases in the two
currents encoded by these two channels would be expected
to lower the threshold for action potential generation b potential. The disproportional increases in the two
currents encoded by these two channels would be expected
to lower the threshold for action potential generation by
exogenous stimuli and thus appears to effect a retuning currents encoded by these two channels would be expected
to lower the threshold for action potential generation by
exogenous stimuli and thus appears to effect a retuning of
the electrogenic membrane of these neurons to lower the threshold for action potential g
exogenous stimuli and thus appears to effect at
the electrogenic membrane of these neurons.
These changes demonstrate that the mole exogenous stimuli and thus appears to effect a retuning of
the electrogenic membrane of these neurons.
These changes demonstrate that the molecular struc-
ture of excitable membranes, even in the absence of

These changes demonstrate that the molecular strucdisease states, is subject to modulation in some types of ture of excitable membranes, even in the absence of disease states, is subject to modulation in some types of neurons. In a corresponding manner, the functional (electrogenic) properties of neurons, even within the disease states, is subject to modulation in some types of
neurons. In a corresponding manner, the functional
(electrogenic) properties of neurons, even within the
normal nervous system, are subject to modulation. Some neurons. In a corresponding manner, the functional (electrogenic) properties of neurons, even within the normal nervous system, are subject to modulation. Some neurons such as the magnocellular cells of the supraontic (electrogenic) properties of neurons, even within the normal nervous system, are subject to modulation. Some
neurons, such as the magnocellular cells of the supraoptic normal nervous system, are subject to modulation. Some
neurons, such as the magnocellular cells of the supraoptic
nucleus, can incorporate different mixtures of sodium
channels into their electrogenic machinery so as to re neurons, such as the magnocellular cells of the supraoptic
nucleus, can incorporate different mixtures of sodium
channels into their electrogenic machinery, so as to retune
it in response, to changing environmental stimuli nucleus, can incorporate different mixtures of sodium
channels into their electrogenic machinery, so as to retune
it in response to changing environmental stimuli or
different functional requirements. This molecular, and channels into their electrogenic machinery, so as to retune
it in response to changing environmental stimuli or
different functional requirements. This molecular and functional remodelling adds a dynamic non-synaptic

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or the ramp currents. Error bars indicate s.e.; $*$ denotes $p < 0.005$. From Tanaka *et al.* (1999). shown from representative supraoptic neurons acutely isolated from control (left panel) or salt-loaded (right panel) rats. The igure 10. Differential increases in two sodium currents in supraoptic neurons following salt loading. (a) Families of traces are
nown from representative supraoptic neurons acutely isolated from control (left panel) or sa nown from representative supraoptic neurons acutely isolated from control (left panel) or salt-loaded (right panel) rats. The urrents were elicited by 40-ms test pulses to various potentials from -60 to 30 mV. Cells w and salt-loaded (open symbols) neurons. Curves are fits to Boltzmann functions. Steady-state inactivation (filled symbols) neurons. Curves are fits to Boltzmann functions. Steady-state inactivation was measured with $00\text$ ctivation (circles) and steady-state inactivation (squares) curves show only small differences between control (filled symbols)
nd salt-loaded (open symbols) neurons. Curves are fits to Boltzmann functions. Steady-state i nd salt-loaded (open symbols) neurons. Curves are fits to Boltzmann functions. Steady-state inactivation was measured wit
00-ms inactivating prepulses, in cells held at prepulse potentials ranging from -130 to -10 mV 00-ms inactivating prepulses, in cells held at prepulse potentials ranging from -130 to -10 mV prior to a test pulse of 0 mV for 0 ms. Error bars indicate s.e. (*c*) Ramp currents are elicited in supraoptic neurons by xtending from -100 to $+40$ mV). The left panel shows that TTX (250 nM) blocks the ramp current in salt-loaded supraoptic xtending from -100 to $+40$ mV). The left panel shows that TTX (250 nM) blocks the ramp current in salt-loaded supraoptic
eurons, thus demonstrating that this current is produced by sodium channels. The right panel show eurons, thus demonstrating that this current is produced by sodium channels. The right panel shows the TTX-sensitive ramp
urrents in representative control and salt-loaded supraoptic neurons. Leak currents recorded after a urrents in representative control and salt-loaded supraoptic neurons. Leak currents recorded after application of 250 nM TTX
vere subtracted. Note the larger ramp current in salt-loaded neurons. (*d*) The peak and ramp cu fere subtracted. Note the larger ramp current in salt-loaded neurons. (d) The peak and ramp current densities (estimated by
ividing the maximum currents by the cell capacitance) are larger following salt loading; the incre

lement to circuits containing these cells. These neurons
ot only use their electrogenic machinery in different
value to generate different patterns of electrical activity lement to circuits containing these cells. These neurons mig
ot only use their electrogenic machinery in different sha
zays to generate different patterns of electrical activity ot only use their electrogenic machinery in different vays to generate different patterns of electrical activity—
ney can rebuild it.

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7. REBUILDING THE ELECTROGENIC MACHINE:
- A POLE IN LONG TERM POTENTIATION **EBUILDING THE ELECTROGENIC MACHINE:**
A ROLE IN LONG-TERM POTENTIATION
AND PERPESSION? A ROLE IN LONG-TERM POTENTIATION
AND DEPRESSION?

It is now well established that the properties of some eural circuits can be altered in an activity-dependent manner via processes such as long-term potentiation and eural circuits can be altered in an activity-dependent

) anner via processes such as long-term potentiation and

) ing-term depression, which are best understood in terms

funderlying changes in synaptic strength. Might ') nanner via processes such as long-term potentiation and

ong-term depression, which are best understood in terms

of underlying changes in synaptic strength. Might 'down-

ream' events also contribute to changes in trans) ing-term depression, which are best understood in terms
f underlying changes in synaptic strength. Might 'down-
ream' events also contribute to changes in transmission
long these circuits? Synaptic currents are integrate along the synaptic strength. Might 'down-
ream' events also contribute to changes in transmission
long these circuits? Synaptic currents are integrated at
cition potential trigger zones such as the initial segment The am' events also contribute to changes in transmission
long these circuits? Synaptic currents are integrated at
cition potential trigger zones such as the initial segment
there as noted above sodium channels are cluster long these circuits? Synaptic currents are integrated at
ction potential trigger zones such as the initial segment
there, as noted above, sodium channels are clustered. The
vailable evidence indicates that the threshold fo ction potential trigger zones such as the initial segment

there, as noted above, sodium channels are clustered. The

vailable evidence indicates that the threshold for action

dential initiation is in part a function of there, as noted above, sodium channels are clustered. The

vailable evidence indicates that the threshold for action
 \bigcirc otential initiation is, in part, a function of sodium

orductance and thus of the density singlevailable evidence indicates that the threshold for action
of sodium onductance and thus of the density, single-channel
onductance and kinetics of sodium channels (Matzner $\&$ b otential initiation is, in part, a function of sodium

onductance and thus of the density, single-channel

onductance and kinetics of sodium channels (Matzner &

channels (Matzner &

channels (Matzner &

channels (Matzn onductance and thus of the density, single-channel
onductance and kinetics of sodium channels (Matzner &
bevor 1992; Colbert *et al.* 1997; Jung *et al.* 1997). At these onductance and kinetics of sodium channels (Matzner &)evor 1992; Colbert *et al.* 1997; Jung *et al.* 1997). At these rigger zones, even relatively small changes in the densities furrious types of channels including sodi Devor 1992; Colbert *et al.* 1997; Jung *et al.* 1997). At these rigger zones, even relatively small changes in the densities f various types of channels, including sodium channels, *F* various types of channels, including sodium channels,
hil. Trans. R. Soc. Lond. B (2000)

From Tanaka *et al.* (1999).
might be expected to alter electroresponsiveness, thus
shaning the input-output function for the neuron might be expected to alter electroresponsivenes
shaping the input-output function for the neuron.
Sodium channels serve in some types of neur Exemple in the expected to alter electroresponsiveness, thus aping the input—output function for the neuron.
Sodium channels serve, in some types of neurons, to solid was applify synaptic depolarizations (Stuart & Sakmann

shaping the input–output function for the neuron.
Sodium channels serve, in some types of neurons, to
amplify synaptic depolarizations (Stuart & Sakmann
1995: Linowsky *et al* 1996) This has been especially well Sodium channels serve, in some types of neurons, to amplify synaptic depolarizations (Stuart & Sakmann 1995; Lipowsky *et al.* 1996). This has been especially well studied in dendrities (Huguenard *et al.* 1989; Regebr *et* amplify synaptic depolarizations (Stuart & Sakmann 1995; Lipowsky *et al.* 1996). This has been especially well studied in dendrites (Huguenard *et al.* 1989; Regehr *et al.* 1993). As a result of the high input impedance 1995; Lipowsky *et al.* 1996). This has been especially well studied in dendrites (Huguenard *et al.* 1989; Regehr *et al.* 1993). As a result of the high input impedance of dendrites, even a small sodium conductance would be 1993). As a result of the high input impedance of dendrites, even a small sodium conductance would be expected to produce large potential changes within them (lack *et al* 1983; Miller *et al* 1985; Perkel & Perkel 1985) dendrites, even a small sodium conductance would be expected to produce large potential changes within them (Jack *et al.* 1983; Miller *et al.* 1985; Perkel & Perkel 1985), and the sensitivity of the amplification factor expected to produce large potential changes within them (Jack *et al.* 1983; Miller *et al.* 1985; Perkel & Perkel 1985), and the sensitivity of the amplification factor to changes in sodium-channel density would thus be (Jack *et al.* 1983; Miller *et al.* 1985; Perkel & Perkel 1985), and the sensitivity of the amplification factor to changes in sodium-channel density would thus be expected to be and the sensitivity of the amplification factor to changes
in sodium-channel density would thus be expected to be
especially high within dendrites. It is an intriguing
possibility that in addition to changes in synaptic ef in sodium-channel density would thus be expected to be especially high within dendrites. It is an intriguing possibility that, in addition to changes in synaptic efficacy due to alterations in transmitter release or effect especially high within dendrites. It is an intriguing
possibility that, in addition to changes in synaptic efficacy
due to alterations in transmitter release or effects on
receptors (see for example I issin *et al.* 1998; possibility that, in addition to changes in synaptic efficacy
due to alterations in transmitter release or effects on
receptors (see, for example, Lissin *et al.* 1998; Turrigiano *et*
 al 1998; O'Brien *et al.* 1998) chan due to alterations in transmitter release or effects on receptors (see, for example, Lissin *et al.* 1998; Turrigiano *et al.* 1998; O'Brien *et al.* 1998), changes in membrane excit-
ability reflecting altered sodium-chan receptors (see, for example, Lissin *et al.* 1998; Turrigiano *et al.* 1998; O'Brien *et al.* 1998), changes in membrane excitability reflecting altered sodium-channel expression may contribute to activity-dependent change al. 1998; O'Brien et al. 1998), changes in membrane excitability reflecting altered sodium-channel expression may contribute to activity-dependent changes in the physioability reflecting altered sodium-channel expression may
contribute to activity-dependent changes in the physio-
logical properties of neuronal circuits. A logical
consequence of this would be the involvement of sodium contribute to activity-dependent changes in the physio-
logical properties of neuronal circuits. A logical
consequence of this would be the involvement of sodium
channels in forms of neuronal plasticity that have been logical properties of neuronal circuits. A logical
consequence of this would be the involvement of sodium
channels in forms of neuronal plasticity that have been
thought of as 'synaptic'. Consistent with this speculation consequence of this would be the involvement of sodium
channels in forms of neuronal plasticity that have been
thought of as 'synaptic'. Consistent with this speculation, channels in forms of neuronal plasticity that have been
thought of as 'synaptic'. Consistent with this speculation,
computer simulations have demonstrated that a switch in
sodium-channel properties (positive shift in the v thought of as 'synaptic'. Consistent with this speculation,
computer simulations have demonstrated that a switch in
sodium-channel properties (positive shift in the voltage

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dependence of activation) can reproduce changes in
herebold that have been experimentally observed in a ependence of activation) can reproduce changes in
hreshold that have been experimentally observed in a
nodel of operantly conditioned motor neuron plasticity ependence of activation) can reproduce changes in
hreshold that have been experimentally observed in a
nodel of operantly conditioned motor neuron plasticity
 H alter *et al* 1995). As noted above, there is in fact hreshold that have been experimentally observed in a nodel of operantly conditioned motor neuron plasticity Halter *et al.* 1995). As noted above, there is, in fact, vidence for activity-related regulation of sodium-channe hodel of operantly conditioned motor neuron plasticity Halter *et al.* 1995). As noted above, there is, in fact, vidence for activity-related regulation of sodium-channel Halter *et al.* 1995). As noted above, there is, in fact, vidence for activity-related regulation of sodium-channel xpression in some types of neurons, suggesting that elec-
corenic properties of these cells may be modula vidence for activity-related regulation of sodium-channel
xpression in some types of neurons, suggesting that elec-
rogenic properties of these cells may be modulated in an
civity-dependent manner. It could be relatively s xpression in some types of neurons, suggesting that elec-
rogenic properties of these cells may be modulated in an
ctivity-dependent manner. It could be relatively straight-
larger to determine whether in addition to chang for these cells may be modulated in an
interview dependent manner. It could be relatively straight-
invarid to determine whether, in addition to changes in
invarid strength due to alterations in transmitter release Find the relatively straight-
Find to determine whether, in addition to changes in
praptic strength due to alterations in transmitter release
reflicacy alterations in sodium-channel expression and or expansion and to determine whether, in addition to changes in enably approximate the reflicacy, alterations in sodium-channel expression and expliciant changes in threshold or other aspects of action ynaptic strength due to alterations in transmitter release
r efficacy, alterations in sodium-channel expression and
esultant changes in threshold or other aspects of action r efficacy, alterations in sodium-channel expression and
esultant changes in threshold or other aspects of action
otential generation contribute to activity-dependent
shanges in neuronal circuit properties esultant changes in threshold or other

denotial generation contribute to a

danges in neuronal circuit properties. **EXAMPLE SET ASSESS**
8. THE NEURON AS A DYNAMIC ELECTROGENIC

MACHINE

It is becoming increasingly clear that the neuron is not only an electrogenic machine—it is a dynamic electro-
nic machine Sodium channels which lie at the heart of It is becoming increasingly clear that the neuron is not
nly an electrogenic machine—it is a dynamic electro-
enic machine. Sodium channels, which lie at the heart of
euronal electrogenicity are now known to be encoded by nly an electrogenic machine—it is a dynamic electro-
enic machine. Sodium channels, which lie at the heart of
euronal electrogenicity, are now known to be encoded by
family of genes, and the heterogeneity of the proteins enic machine. Sodium channels, which lie at the heart of euronal electrogenicity, are now known to be encoded by family of genes, and the heterogeneity of the proteins euronal electrogenicity, are now known to be encoded by
family of genes, and the heterogeneity of the proteins
hat they encode imparts an important richness to the
lectrogeneive behaviour of neurons We have begun to family of genes, and the heterogeneity of the proteins
hat they encode imparts an important richness to the
lectroresponsive behaviour of neurons. We have begun to
netertand that the expression of sodium-channel genes is they encode imparts an important richness to the
lectroresponsive behaviour of neurons. We have begun to
nderstand that the expression of sodium-channel genes is
ot a fixed process: it is mutable and in at least some types lectroresponsive behaviour of neurons. We have begun to nderstand that the expression of sodium-channel genes is ot a fixed process; it is mutable and, in at least some types nderstand that the expression of sodium-channel genes is
ot a fixed process; it is mutable and, in at least some types
f neurons, it is highly dynamic. This is manifested by
polecular changes in sodium-channel expression w ot a fixed process; it is mutable and, in at least some types
f neurons, it is highly dynamic. This is manifested by
nolecular changes, in sodium-channel expression, which
cur not only following various injuries to neurons f neurons, it is highly dynamic. This is manifested by idecular changes, in sodium-channel expression, which ccur not only following various injuries to neurons, but lso as neurons move between various functional states rolecular changes, in sodium-channel expression, which ccur not only following various injuries to neurons, but lso as neurons move between various functional states. ccur not only following various injuries to neurons, but
lso as neurons move between various functional states.
These molecular changes may have important functional
milications since they are reflected in the electrogenic Iso as neurons move between various functional states.

These molecular changes may have important functional

mplications, since they are reflected in the electrogenic

unior that underlies the normal and pathological gen These molecular changes may have important functional
mplications, since they are reflected in the electrogenic
uning that underlies the normal and pathological genera-
ion of electrical activity within neurons. In patholo mplications, since they are reflected in the electrogenic
uning that underlies the normal and pathological genera-
ion of electrical activity within neurons. In pathological ining that underlies the normal and pathological generation of electrical activity within neurons. In pathological tuations, this may present some novel therapeutic oppor-
inities since the distinct molecular structure of ion of electrical activity within neurons. In pathological tuations, this may present some novel therapeutic oppor-
inities, since the distinct molecular structure of different
adium channels may make them amenable to sele tuations, this may present some novel therapeutic oppor-
inities, since the distinct molecular structure of different
odium channels may make them amenable to selective
lockade modulation up-or downregulation anties, since the distinct molecular structure of different odium channels may make them amenable to selective lockade, modulation, up- or downregulation. dium channels may make them amenable to selective
pckade, modulation, up- or downregulation.
The full range of plasticity in the building, and
puilding of neuronal electrogenic machinery within the

lockade, modulation, up- or downregulation.
The full range of plasticity in the building, and
ebuilding, of neuronal electrogenic machinery within the
ormal nervous system remains to be determined. At a The full range of plasticity in the building, and
ebuilding, of neuronal electrogenic machinery within the
ormal nervous system remains to be determined. At a
inimum we have learned that neurons are not fixed or ebuilding, of neuronal electrogenic machinery within the
ormal nervous system remains to be determined. At a
inimum, we have learned that neurons are not fixed or
atic electrogenic devices: on the contrary, the electroormal nervous system remains to be determined. At a
inimum, we have learned that neurons are not fixed or
atic electrogenic devices; on the contrary, the electro-
sponsive properties of some neurons appear to be state inimum, we have learned that neurons are not fixed or
atic electrogenic devices; on the contrary, the electro-
esponsive properties of some neurons appear to be state dependent, and the mutability of their excitable membranes suggests that incoming messages may be processed in a highly dynamic way via neuronal algo-
processed in a highly dynamic way via neuronal algo-
ithms that change over time. It remains to be learned rembranes suggests that incoming messages may be
processed in a highly dynamic way via neuronal algo-
ithms that change over time. It remains to be learned
bether changes in sodium-channel expression contriprocessed in a highly dynamic way via neuronal algo-
thms that change over time. It remains to be learned
there changes in sodium-channel expression contri-
wite together with changes in transmitter release and/or Lithms that change over time. It remains to be learned
Unhether changes in sodium-channel expression contri-
Lite, together with changes in transmitter release and/or whether changes in sodium-channel expression contri-
atte, together with changes in transmitter release and/or
 $\frac{1}{2}$ fficacy associated with long-term potentiation and/or
enression and with other activity-related chan the dependence of the dependence of the dependence of the dependence of the epoch of the epo fficacy associated with long-term potentiation and/or
epression, and with other activity-related changes in
eural activity, to learning and memory. Given the tools
urrently available which permit the examination of the epression, and with other activity-related changes in eural activity, to learning and memory. Given the tools urrently available, which permit the examination of the enes transcripts, proteins and physiological properties eural activity, to learning and memory. Given the tools
urrently available, which permit the examination of the
enes, transcripts, proteins and physiological properties
at shape electrogenic behaviour in neurons, we will urrently available, which permit the examination of the
enes, transcripts, proteins and physiological properties
hat shape electrogenic behaviour in neurons, we will
adoutedly learn much more about these questions in enes, transcripts, proteins and physiological properties
hat shape electrogenic behaviour in neurons, we will
 Ω ndoubtedly learn much more about these questions in
he relatively near future $\begin{array}{l} \text{hat shape} \text{ electromagnetic} \text{b} \\ \text{indoubtedly learn much in} \\ \text{he relatively near future.} \end{array}$

E FERRIVELY ITERT THEORY.

Work in the author's laboratory has been supported, in part, by

rants from the Department of Veterans Affairs: the National Vork in the author's laboratory has been supported, in part, by
rants from the Department of Veterans Affairs; the National
Jultiple Sclerosis Society: the Paralyzed Veterans of America Vork in the author's laboratory has been supported, in part, by
rants from the Department of Veterans Affairs; the National
fultiple Sclerosis Society; the Paralyzed Veterans of America *Phil. Trans. R. Soc. Lond.* B (2000)

and the Eastern Paralyzed Veterans Association. I thank my
many colleagues, especially I. A. Black, S. Dib-Haii, T. R and the Eastern Paralyzed Veterans Association. I thank my
many colleagues, especially J. A. Black, S. Dib-Hajj, T. R.
Cummins J. D. Kocsis M. Rizzo O. Honmou and M. Tanaka and the Eastern Paralyzed Veterans Association. I thank my
many colleagues, especially J. A. Black, S. Dib-Hajj, T. R.
Cummins, J. D. Kocsis, M. Rizzo, O. Honmou and M. Tanaka,
for permission to reproduce figures from stud many colleagues, especially J. A. Black, S. Dib-Hajj, T. R.
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1998 A rat brain Na⁺ channel α subunit with novel gating
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1998 A rat brain Na⁺ channe
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