Quantitative description of the voltage dependence of axonal excitability in human cutaneous afferents

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Summary

The voltage dependence of indices of axonal excitability were quantified for cutaneous afferents in eight normal subjects, using the threshold for a target compound sensory action potential as a measure of membrane potential. The membrane potential was altered using subthreshold depolarizing and hyperpolarizing currents of various sizes (–50% to +50% of threshold). Refractoriness and supernormality were determined as the threshold change required to produce the target potential when preceded by a supramaximal stimulus at appropriate conditioning–test intervals. The strength–duration time constant (τSD) was calculated from the threshold currents using unconditioned test stimuli of 0.1 and 1 ms. There was a near-linear relationship between each of these indices and the reciprocal of threshold (a measure of 'excitability'). It is argued that the voltage dependencies of refractoriness and τSD largely reflect the behaviour of transient and persistent Na⁺ channels, respectively, and that the present data therefore quantify aspects of Na⁺ channel behaviour in human nerves.

Keywords: Axonal excitability; refractory period; time constant; Na⁺ channels

Abbreviations: CSAP = compound sensory action potential; τSD = strength–duration time constant

Introduction

The excitability of axons undergoes substantial perturbations when they conduct single impulses, brief trains of impulses or prolonged trains, or when they are deprived of their blood supply or compressed. The fluctuations in excitability in each of these situations have been documented extensively in human subjects (e.g. Gilliatt and Willison, 1963; Bergmans, 1970; Stöhr, 1981; Taylor et al., 1992; Bostock et al., 1994; Bostock and Bergmans, 1994; Kiernan et al., 1996, 1997; Mogyoros et al., 1997), with increasing understanding of the underlying biophysical mechanisms. Such studies are important because they may help to explain the development of conduction block and ectopic impulse activity when the safety margin for impulse conduction is jeopardized by manoeuvres, such as those above, or by nerve pathology.

Ultimately axonal excitability reflects the activity of a variety of ion channels, energy-dependent pumps and ion exchange processes, that are activated during an action potential and then restore excitability so that the axon can maintain an impulse train. These mechanisms represent logical targets for investigation when their operation is disturbed such that patients develop positive symptoms of neuropathic pain, dysaesthesiae and paraesthesiae. Of these mechanisms, the voltage-dependent Na⁺ channel is generally afforded primacy. Indeed, the human action potential can be modelled satisfactorily using only the properties of Na⁺ channels (Schwarz et al., 1995). Agents used for the positive treatment of neuropathic symptoms include anticonvulsants, such as phenytoin, carbamazepine and lamotrigine, all of which have actions on Na⁺ channels (e.g. Schauf, 1987; Zimanyi et al., 1989; Cheung et al., 1992; Francis and Burnham, 1992; Lang et al., 1993), including those in the dorsal root ganglia (Song et al., 1996) and large myelinated peripheral nerve axons (Schwarz and Grigat, 1989). Because of their actions on Na⁺ channels, these agents may also be useful in limiting ischaemic injury to white matter (Fern et al., 1993; Rataud et al., 1994).

Using recently developed procedures for assessing the excitability of human axons, the present study was undertaken to develop quantitative descriptions of how different indices of axonal excitability change when the membrane potential is altered. The change in membrane potential was quantified as the change in threshold current required to produce a target sensory potential. The study focused on three indices of axonal excitability: refractoriness, supernormality and strength–duration time constant (τSD), because, as argued in the Discussion section, the mechanisms responsible for voltage-dependent changes of these indices are now reasonably established. While there have been previous...
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Fig. 1 Stimulus outputs. Stimuli were delivered at 1 Hz, rotating through the 10 different combinations listed on the left. Current was monitored to ensure that, when the conditioning and test stimuli (A) occurred during polarization (B), the currents added linearly (A + B).

studies of the changes in these excitability indices during manoeuvres that change the membrane potential [e.g. ischaemia and hyperventilation (Bostock et al., 1994; Mogyoros et al., 1997) and axonal tetanization (Bostock and Bergmans, 1994; Kiernan et al., 1997)], the changes in these indices were used as evidence that the manoeuvres had altered membrane potential. The manoeuvres probably had effects other than changing the membrane potential, and membrane potential may not have been the sole factor affecting threshold.

Methods
Experiments were performed on eight healthy adult volunteers of both sexes, all of whom gave informed consent to the experimental procedures, which had the approval of the Committee on Experimental Procedures Involving Human Subjects of the University of New South Wales.

Antidromic recordings of the compound sensory action potential (CSAP) were made using ring electrodes around the index finger of the right hand in response to current pulses delivered to the median nerve just proximal to the wrist, as described previously (Kiernan et al., 1996; Mogyoros et al., 1996, 1997). The remote stimulating electrode (the anode for the conditioning and test stimuli) was over forearm muscle, 15–20 cm proximal to the active electrode over the nerve. The stimuli were delivered at 1 Hz, rotating through a sequence of 10 different stimulus combinations, as detailed below and in Fig. 1, in order to study different aspects of axonal excitability. A fixed supramaximal stimulus of 0.2 ms duration was delivered using one stimulus output (stimulus 1 in Fig. 1). The intensity of the test stimuli on the other nine outputs was adjusted by computer, in steps of 2%, to produce a CSAP of 40% of that evoked by the supramaximal stimulus. ‘Threshold’ was measured using unconditioned test stimuli of duration 0.1 and 1 ms (stimuli 3 and 4 in Fig. 1). From these threshold measurements, \( \tau_{SD} \) was calculated off-line (see Bostock and Bergmans, 1994; Mogyoros et al., 1997), using the formula:

\[
\tau_{SD} = 0.1 \times (I_{0.1} - I_{1})/(I_{1} - 0.1 \times I_{0.1})
\]

where \( I_{0.1} \) is the threshold using test stimuli of 0.1 ms duration and \( I_{1} \) the threshold using test stimuli of 1 ms duration.

To measure refractoriness and supernormality, the recovery cycle of axonal excitability following a single maximal volley was measured using test stimuli of 0.1 ms duration delivered on different stimulus outputs 2, 3, 4, 5, 7 and 10 ms after a supramaximal conditioning stimulus of 0.2 ms duration (stimuli 5–10 in Fig. 1). Refractoriness was determined as the increase in current required to produce the target CSAP when a supramaximal conditioning stimulus was delivered 2 ms before the test stimulus. The increased current was normalized to the control threshold so that, by reference to the stimulus outputs in Fig. 1, refractoriness was calculated as: threshold current 5 minus threshold current 3, divided by threshold current 3. Supernormality was calculated in a similar way, but as the decrease in current required to produce the target CSAP when the conditioning–test interval was 5 or 7 ms (see Results). The conditioned test potentials were measured on-line after subtraction of the response to the supramaximal conditioning stimulus given in isolation (see Kiernan et al., 1996; Mogyoros et al., 1997).
To change membrane potential, DC (direct current) polarizing currents lasting 30 ms were delivered through the stimulating electrode at the wrist. Because the polarizing current and the conditioning and test stimuli were delivered through the same electrodes, the total current delivered to the patient was monitored to ensure that there was a true addition of the polarizing current and the conditioning and test stimuli (Fig. 1, right). The polarizing currents were delivered on the nine stimulus outputs described above, the start of the polarizing current being timed to occur 10 ms in advance of the test stimuli. The 10 ms duration was a compromise, chosen so that it would be sufficiently long to affect Na⁺ channel kinetics (see Schwarz et al., 1995) but short enough that there would be little effect on other voltage-dependent conductances (except for fast K⁺ conductances that are sparse at the human node of Ranvier, see the Discussion section). The intensity of the polarizing current was a variable percentage of the threshold for the target CSAP using test stimuli of 1 ms duration on the 10th stimulus output (stimulus 2 in Fig. 1). Accordingly, the threshold was measured twice using 1 ms test stimuli: once for time constant calculations, the stimulus being delivered during the polarizing currents (stimulus 4 in Fig. 1) and the second, unpolarized, used to set the strength of the polarizing current for the other channels (stimulus 2 in Fig. 1). The strongest depolarizing and hyperpolarizing currents were ±50% of \( I_1 \). It was ensured that the conditioning stimuli remained supramaximal, despite the strongest hyperpolarizing current, and that the depolarizing currents were insufficient to activate axons directly.

The polarizing current was stepped every 2–3 min from 50% depolarizing to 50% hyperpolarizing, in steps of ±10% (Fig. 2). In control experiments it was established that the direction of the polarizing steps (i.e. depolarizing then hyperpolarizing or vice versa) did not affect the results. Skin temperature was measured at two sites, at the volar aspect of the wrist, adjacent to the stimulating electrode and usually at the base of the index finger. Limb temperature was maintained at \( 32 \pm 0.5^\circ \text{C} \) throughout the study, using radiant heat and a blanket, if necessary, and it varied by less than ±0.5°C in each subject.

The latency of the CSAP was measured to the negative peak and its amplitude peak to peak. All data are given as mean ± SD.

**Results**

Subthreshold polarizing currents altered refractoriness, supernormality and \( \tau_{SD} \), consistent with their dependence on membrane potential (Fig. 2). The direction of these changes (i.e. increased refractoriness, decreased supernormality and increased \( \tau_{SD} \) with depolarizing currents and the reverse with hyperpolarizing currents) is that expected from previous studies on human nerves using a variety of manoeuvres such as ischaemia and hyperventilation (Bostock et al., 1991, 1994; Mogyoros et al., 1997), axonal tetanization (Bostock and Bergmans, 1994; Kiernan et al., 1997) and continuously applied polarizing currents (Bostock and Bergmans, 1994). However, in these studies, the experimental manoeuvres had effects other than changing membrane potential and therefore these data cannot be used to quantify ‘voltage dependence’.

Figure 2A illustrates the original threshold currents required to produce a CSAP of 40% of maximum, the test stimuli being of 0.1 ms duration (upper 3 traces) or of 1 ms duration (lower 2 traces), conditioned or unconditioned, as indicated. Four of the five thresholds were measured during polarizing currents. The fifth threshold was used to set the strength of the polarizing current, which started at 50% depolarizing and changed every 2 min through to 50% hyperpolarizing. The excitability indices derived from the threshold data in Fig. 2A are plotted in Fig. 2B.

With increases in threshold (an excitability measure related to membrane potential) there was initially a steep decrease in refractoriness, but the relationship then became less steep (Fig. 3A and C). This relationship could not be described...
Refactoriness was measured as the increase in current required to produce the conditioned CSAP when the conditioning–test interval was 2 ms. At rest (‘excitability’ of 1), refactoriness was 28.8 ± 8.7% (mean ± SD), i.e. the test stimulus had to be increased by, on average, 28.8% to produce the target potential when a supramaximal stimulus was delivered 2 ms before the test stimulus. With membrane hyperpolarization, the degree of refactoriness decreased, and in some subjects supernormality appeared at the 2 ms conditioning–test interval with 50% hyperpolarizing currents (Fig. 2). The slope of the relationship between refactoriness and excitability was 0.9573 ± 0.1061. To illustrate this change, the effects of depolarizing current that reduced threshold by 50% (i.e. doubling ‘excitability’) were calculated from the regression equations; refactoriness would have increased to 124.5 ± 16.0% if threshold was reduced to 50%, i.e. by >300% of the resting level (Fig. 5).

Supernormality was measured as the decrease in threshold for the test potential when a supramaximal conditioning stimulus preceded the test stimulus by 7 ms (in six subjects) or by 5 ms (in two subjects, in whom the threshold reduction was greatest at this interval). At rest, supernormality was -13.5 ± 3.6%, i.e. the test stimulus could be reduced to 86.5% of the unconditioned value when the supramaximal stimulus was given 7 ms (or 5 ms) earlier. As expected, supernormality increased with membrane hyperpolarization, and decreased with membrane depolarization (Figs 2 and 4). With depolarizing pulses of 50%, refactoriness was prolonged into the 7 ms conditioning–test interval in six subjects, such that the threshold reduction was replaced by a threshold increase (Figs 2 and 4). The slope of the relationship between supernormality and ‘excitability’ was 0.2022 ± 0.0960. A decrease in threshold of 50% (i.e. a doubling of ‘excitability’) would have required an increase in the test stimulus to 6.7 ± 12% to produce the target potential rather than a decrease (Fig. 5). The appearance of refactoriness at conditioning–test intervals normally associated with supernormality has been documented during ischaemia (Mogyoros et al., 1997), but in this instance the decrease in threshold was <20%.

τSD was calculated off-line from the thresholds recorded using unconditioned test stimuli of 0.1 and 1 ms, as described in the Methods section. In absolute terms, the threshold to 1 ms test stimuli was lower and underwent smaller changes with changes in membrane potential (Fig. 2A). However, when both threshold measures were normalized so that the control value was 1.0, the threshold changes with the 1 ms stimulus were relatively greater, indicating that the strength–duration properties were changing with changes in membrane potential. At rest, time constant was 526 ± 142 µs. It decreased with hyperpolarization, presumably due to closure of ‘threshold’ channels, and it
Excitability of human axons

Fig. 4 Plots of supernormality (A and B) and $\tau_{SD}$ (C and D) against normalized threshold (A and C) and the reciprocal of normalized threshold (i.e., ‘excitability’; B and D) for a single subject. In B and D, linear regression yielded correlation coefficients of 0.9680 and 0.9586, respectively.

Fig. 5 The change in refractoriness, supernormality and time constant with depolarizing pulses that decrease threshold to 50% (i.e., double excitability). The panel on the left shows the data for the eight subjects individually, and the panel on the right the six corresponding means (±SD). Refractoriness and supernormality were measured at the 2 ms and the 7 ms (or 5 ms) conditioning–test intervals. The data at rest (‘excitability’ of 1.0) and at ‘excitability’ of 2.0 were obtained for each subject using linear regression of data such as those in Figs 2 and 3.

increased with membrane depolarization, as voltage-gated channels were activated (Fig. 2). The slope of the relationship with ‘excitability’ was 0.3925 ± 0.1137. A decrease in threshold of 50% (i.e., a doubling of ‘excitability’) would have increased time constant by 75% to 918 ± 176 µs (Fig. 5).

The time course of the recovery cycle was altered by polarizing currents. Depolarization prolonged the relatively refractory period in addition to increasing the degree of refractoriness at any one interval. In each subject, a family of conditioning–test intervals from 2 to 10 ms were investigated (as in Fig. 6). When these data were plotted as conventional recovery cycles (Fig. 7), it became clearer that depolarization caused refractoriness to extend into conditioning–test intervals normally associated with supernormality, displacing the peak of supernormality a few milliseconds to longer conditioning–test intervals in five of the eight subjects (Fig. 7).

Conversely, hyperpolarization decreased refractoriness at the 2 ms conditioning–test interval to the extent that the supernormal period began earlier, in three subjects at the 2 ms conditioning–test interval (Figs 2 and 7). In addition, the peak of supernormality occurred earlier than at rest in five of the eight subjects. Accordingly, when monitoring supernormality using a fixed conditioning–test interval, it is possible that the full extent of any change in supernormality would not be measured (though the discrepancy would probably be small because the shifts in interval for peak supernormality were small).

Discussion

This study has quantified, for human cutaneous afferents, the relationship between changes in the threshold for a target CSAP and various indices of axonal excitability. Refractoriness, supernormality and $\tau_{SD}$ varied with threshold (and presumably, therefore, with membrane potential), much as expected from extensive data in the literature. However,
Fig. 6 Plots of threshold differences against ‘excitability’ (the reciprocal of threshold) for conditioning–
test (c–t) intervals of 2, 3, 4, 5, 7 and 10 ms. For each interval, the threshold difference was calculated
as: conditioned threshold minus unconditioned threshold, divided by unconditioned threshold. Note that,
at rest (excitability of 1.0), supernormality was present at conditioning–test intervals from 4 to 10 ms
and greatest at the 7 ms interval (open circles).

Fig. 7 The effect of polarizing currents on the time course of the
recovery cycle after a single supramaximal conditioning stimulus.
The change in threshold of the conditioned volley is plotted
against the conditioning–test interval, with three consecutive
assessments at rest, three when 50% hyperpolarized and six with
increasing depolarization. When hyperpolarized, axons were
supernormal at the 2 ms interval, and peak supernormality
occurred at 5 ms. When depolarized, there was a dramatic
increase in refractoriness, and peak supernormality occurred 2 ms
later, as indicated by the vertical arrows on the horizontal axis.
Data are from a single subject.

the near-linear relationship between these indices of
excitability and the reciprocal of threshold could not have
been predicted, and quantifying the relationship has potential
uses, as discussed below.

**Does threshold reflect membrane potential?**
Under many circumstances changes in membrane potential
will be paralleled by quantitatively appropriate changes in
threshold but, as demonstrated by Bostock *et al.* (1991),
there may be no simple relationship between membrane
potential and threshold: there are circumstances in which the
pattern of threshold change will depend upon the duration
and/or the waveform of the test stimulus used to measure
threshold. In addition, during ischaemic depolarization,
threshold changes do not precisely mirror the underlying
changes in electrotonus (Baker and Bostock, 1989).
Accordingly, it would be unrealistic to expect a linear
relationship between membrane potential and threshold, and
it would be imprudent to assume that numerically equal
increases and decreases in threshold involved equal but
opposite changes in membrane potential.

The linear relationships between ‘excitability’ and refract-
oriness, supernormality and $\tau_{SD}$ are largely empirical, and
not predictable on the basis of current knowledge. Presumably
there is a systematic disparity between membrane potential
and threshold with depolarization, but whether this contributes
to the apparent linearity of the relationships between the
excitability indices and the reciprocal of threshold is conjec-
tural. Nevertheless, that the relationships can be so simply
described allows them to be quantified easily, and this
increases their value as a clinical tool.

**Biophysical mechanisms underlying the voltage-
dependent changes**
Inactivation of transient $\text{Na}^+$ channels at the node of Ranvier
is largely responsible for the absolutely and relatively
refractory periods (Hodgkin and Huxley, 1952). Fast $\text{K}^+$
channels are sparse at mammalian nodes (Chiu *et al.*, 1979;
Brismar, 1980; Röper and Schwarz, 1989) and there are probably even fewer at human nodes than those of the rat and cat (Bostock and Baker, 1988). Accordingly, even when axons are depolarized, such conductances probably make a negligible contribution to repolarization after an action potential and to the refractory periods. The voltage-dependent behaviour of refractoriness at the 2 ms conditioning–test interval can be adequately explained by the voltage dependence of the recovery from Na$^+$ channel inactivation, there being greater inactivation when the axon is more depolarized.

That hyperpolarization decreased refractoriness is consistent with inactivation of some Na$^+$ channels at rest, a conclusion that is not surprising given that, in voltage-clamp experiments on single axons, it is conventionally assumed that 30% of Na$^+$ channels are inactivated at the resting membrane potential (Chiu et al., 1979; Brismar, 1980; Schwarz and Eikhof, 1987; Schwarz et al., 1995). The appearance of supernormality in three subjects at the 2 ms interval when maximally hyperpolarized could reflect the more complete removal of background inactivation.

In myelinated axons, the supernormal (or superexcitable) period results from a depolarizing after-potential due to the passive discharge of current stored on the internodal membrane through low-resistance pathways under or through the myelin sheath (Barrett and Barrett, 1982; Blight and Someya, 1985; Bowe et al., 1987; for review, see Ritchie, 1995). The voltage dependence of supernormality is attributed to the change in capacitance of the internodal membrane due to activation of voltage-dependent channels in the internode, particularly paranodal fast K$^+$ channels (Baker et al., 1987; Vogel and Schwarz, 1995). Thus, depolarization reduces supernormality because activation of voltage-dependent K$^+$ channels in the paranodal region shunts current stored on the internodal membrane. That hyperpolarization increases supernormality can be attributed to two factors: (i) the reduction in refractoriness, on the decaying tail of which supernormality is superimposed and (ii) the closure of voltage-gated channels that are presumably open at rest.

The value of supernormality as an index of membrane potential is limited by the finding that peak supernormality can be shifted by membrane depolarization or hyperpolarization to slightly longer or shorter conditioning–test intervals, respectively. Theoretically, the full extent of a change in supernormality might not be appreciated if only a single conditioning–test interval was used. This problem could also arise with studies of refractoriness, but only with extreme hyperpolarization, and it could be avoided with the use of a shorter conditioning–test interval, perhaps 1.5 ms.

$\tau_{\text{SD}}$ depends on the passive membrane time constant and a local response due to voltage-dependent channels active at threshold (Bostock and Rothwell, 1997). Such channels are likely to include slow K$^+$ channels and persistent Na$^+$ channels, but the latter are probably more important, and differences in their contribution largely determine that $\tau_{\text{SD}}$ of human cutaneous afferents is longer than that of human motor axons (Bostock and Rothwell, 1997; see also Panizza et al., 1994; Mogyoros et al., 1996). When manoeuvres such as polarization, hyperventilation and ischaemia are used to alter nerve excitability, the changes in $\tau_{\text{SD}}$ are paralleled by, and can be fully explained by, a rapidly activating but non-inactivating depolarizing current that is active at threshold—presumably a persistent Na$^+$ current (Bostock and Rothwell, 1997; Mogyoros et al., 1997; see also Stys et al., 1993; Crill, 1996; Baker and Bostock, 1997). Accordingly this atypical Na$^+$ current is probably the major conductance contributing to the voltage dependence of $\tau_{\text{SD}}$ in the present study.

It can be concluded that the changes in refractoriness and in $\tau_{\text{SD}}$ documented in the present study reflect the behaviours of two different Na$^+$ channel populations: refractoriness, the quantitatively greater (transient) Na$^+$ channel population (estimated to be ~97.5% of the total Na$^+$ conductance; see Bostock and Rothwell, 1997), and $\tau_{\text{SD}}$, the quantitatively minor (persistent) Na$^+$ channel population (estimated at ~2.5% of the total conductance). These percentages are estimates based on the accuracy with which a computer model of a human myelinated axon reproduced the physiological responses recorded in human subjects, but they are consistent with the percentages quoted for CNS neurons (see Crill, 1996). It is less likely that other Na$^+$ conductances contribute significantly to the voltage-dependent behaviours in the present study. For example, slow Na$^+$ channels that are present on mammalian cutaneous afferents (Honmou et al., 1994) inactivate slowly and are unlikely to affect refractoriness at the tested intervals. In addition, they require activation by depolarization and their effects become apparent only if fast K$^+$ channels are blocked. They are therefore unlikely to contribute to the threshold responses that underlie $\tau_{\text{SD}}$. Other Na$^+$ channels have been identified in mammalian dorsal root ganglia neurons (e.g. Caffrey et al., 1992; Roy and Narahashi, 1992; Ogata and Tatebayashi, 1993), and neurons in dorsal root ganglia express a variety of different mRNAs for Na$^+$ channels (Black et al., 1996). However, whether such channels are expressed on large myelinated axons and, if so, how they behave physiologically is, for the moment, unknown.

**Implications and clinical utility**

The biophysical mechanisms underlying different manoeuvres that can affect axonal excitability (e.g. ischaemia, high-frequency stimulation, membrane polarization and hyperventilation) have been probed in studies on healthy volunteers and patients with a number of disease processes, e.g. diabetes mellitus, amyotrophic lateral sclerosis, taxol/cisplatin toxicity (for review, see Bostock et al., 1998). Excitability indices such as those studied here have been used to explain the nature of the threshold changes. Documentation of the relationship between threshold and these indices, when the only changes are of membrane potential (and of potential-dependent processes), can provide further insight into mechanisms by indicating whether the induced changes in
excitability are appropriate, or whether additional processes not directly related to membrane potential need to be invoked.

A number of therapeutic agents used to control neuropathic pain and other manifestations of neural hyperexcitability target Na\(^+\) channels—particularly the anticonvulsants, carbamazepine, phenytoin and lamotrigine. For example, carbamazepine and phenytoin affect tetrodotoxin-sensitive Na\(^+\) channels on rat dorsal root ganglia neurons (Song et al., 1996), presumably the large dorsal root ganglia neurons (Roy and Narahashi, 1992; Ogata and Tatebayashi, 1993), which give rise to large myelinated axons expressing anticonvulsant-sensitive Na\(^+\) channels (Schwarz and Grigat, 1989). It is likely that the channels underlying the behaviour studied in the present report are analogous to those shown, in the rat, to be responsive to phenytoin and carbamazepine. Interestingly, phenytoin preferentially diminishes the late Na\(^+\) channel openings responsible for the persistent Na\(^+\) conductance in hippocampal neurons (Segal and Douglas, 1997), raising the possibility that, if it acts similarly on peripheral nerve Na\(^+\) channels, it might alter \(\tau_{SD}\) preferentially. Using the techniques described in the present report, it may be possible to demonstrate whether, in human subjects, these channels are targets for the agents. If so, such studies could be used as an assay to document biological effects and compare them with therapeutic efficacy.

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