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Paradoxical Signal Transduction in Neurobiological Systems

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Abstract

Information processing in neurobiological systems is commonly thought to rely on the assessment of a signal-to-noise ratio as the key mechanism of signal detection; it assumes and requires that both signal and noise are concurrently available. An alternative theory holds that detection proceeds by the system appreciating any instantaneous input by the input's departure from the moving average of past activity. The evidence reviewed here suggests that this latter transduction mechanism provides a unique, formal account of the highly dynamic, neuroadaptative plasticity (i.e., tolerance, dependence, sensitization) that ensues upon μ-opioid receptor activation. The mechanism would appear already to operate with the receptor-G protein coupling that occurs upon agonist binding to μ-opioid receptors, and also with highly integrated responses such as whole-organism analgesia. The mechanism may perhaps operate ubiquitously with further neuronal and non-neuronal, cell surface, and intracellular-signaling systems, and may govern the experience-dependent regulation of synaptic strength. The transduction mechanism defines a continuously evolving process; the process's most peculiar feature is that it makes any input generate not one but two outcomes that are paradoxical, or opposite in sign.

Index Entries: Signal transduction; opioids; tolerance; dependence; sensitization; neuronal plasticity.

Introduction

We discuss here a formal theory of mechanisms whereby signal transduction may perhaps proceed in neurobiological systems. This Signal-Transduction (ST) theory originates from studies of the neuronal systems that in mammals utilize μ-opioid signaling, neurotransmitter substances, and G protein-coupled cell-membrane receptors in the control of such diverse physiological functions as respiration, gastrointestinal motility, and the perception of pain. The finding initiating this theoretical effort was evidence *(1,2)* that tolerance does not develop to a particular signaling

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property of opioid receptor ligands. This finding contradicts the century-old and widely held concept *(3,4)* that tolerance develops to opioids, a concept that continues to shape current neurobiological accounts of adaptation (e.g., *5,6*). In particular, the finding raised the question as to how function neuronal systems that remain immutably responsive to opioid signals yet also have generated an extraordinary body of empirical evidence suggesting that opioid receptor activation eventually becomes ineffectual.

A Theory of Signal Transduction

The information processing that occurs in neurobiological systems requires that they be capable of what is arguably the most elementary process, i.e., of detecting a discrete input that acts as a signal, or stimulus to some response. Few formal theories have attempted to conceptualize the mechanisms governing this process. Perhaps most influentially, Signal-Detection theory *(7,8)* proposed the assessment of a signal-to-noise ratio as the key mechanism of signal detection. Thus, Signal-Detection theory identifies the discrete input from a background input that is assumed to be observed simultaneously with the discrete input. The ST theory does not make, and neither does it require, the assumption that both instantaneous input and so-called noise are concurrently available to biological input channels. Rather, the ST theory proposes that detection proceeds by the system appreciating any instantaneous input by the input's departure from the moving, time-averaged activity that occurred in the input channel over a definite period in the recent past *(9,10).* With opioid analgesia constituting the most extensively studied of opioid actions, here we will specify this transduction mechanism as it applies to the case of opioid signals interacting with nociceptive signals that otherwise generate pain as a whole organism response.

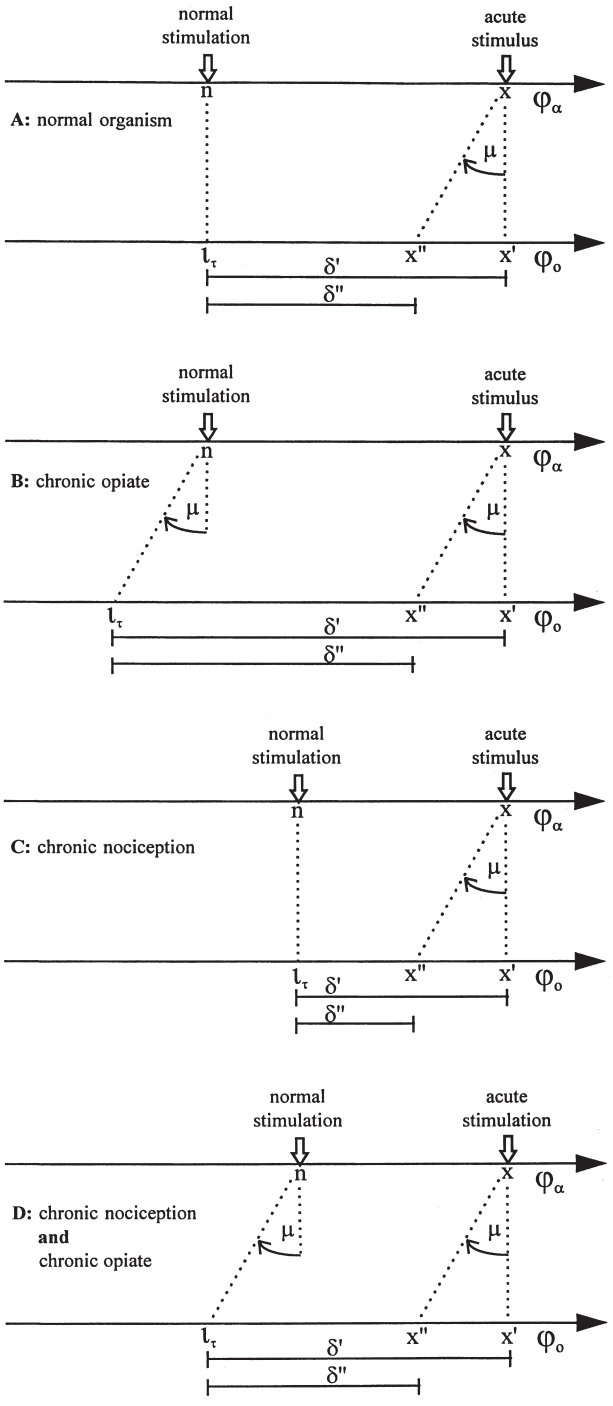
Detecting a Discrete Nociceptive Event

The theory assumes that any adequate stimulation that ultimately causes pain (that is, any exogenous [e.g., focal heat] or endogenous stimulus [e.g., the activation of substance P receptors by the putative pain-producing neurotransmitter substance P]) possesses a magnitude x along a variable that can be defined physically. This variable, termed φ_α, may thus represent the temperature of a thermal stimulus or the magnitude of substance P receptor activation (Fig. 1A). The magnitude x may be different from (e.g., larger than) the magnitude n which φ_α assumes most of the time and which for that reason is said to be normal. A transduction occurs so that the physically defined stimulus x causes a relevant physiological activity termed φ_0 (e.g., the firing of a spinal cord dorsal horn neuron). This transduction could be simply linear, so that x causes x′ along φ_0 (Fig. 1A). The transduction is made continuously, so that the usual value, too, is transduced whenever it occurs.

How can x′ now be detected, i.e., be found to constitute an event? In examining this question, it is useful to consider the analogy of an observer who continuously monitors a digital display that reports from a remote sensor. The number being displayed can assume any of a range of values and can, but does not necessarily, change from one point of time to the next. The observer's problem thus is to determine, at any point of time, whether the number that is currently on display represents any particular event that may have impacted on the sensor, i.e., represents a signal. The theory proposes that this problem be solved by the system determining to what extent x′ differs from the φ_0 that usually is being observed.

How can we define what usually is being observed and is not currently on display? The theory here proposes that the system continuously computes a temporally integrated value, termed ι_τ, of the physiological activity φ_0 that has occurred over a past, "sample period*" of time that immediately precedes the current

* The sample period remains constant for any particular system, but its duration can vary among different systems; it is expressed in arbitrary units (A.U.) of time. The term "system" here refers to the physiological substrate to which the events being considered serve as inputs and that yield the responses that are being described.



point of time. ι_τ is continuously computed as the moving average of the physiological activity φ_0 that occurred over the preceeding (e.g., 40 discrete units of) time. In so doing, φ_0 is weighted, however, so that more recent inputs have a greater impact than inputs that are more remote in past time (for a didactic account, *see* ref. *11*).

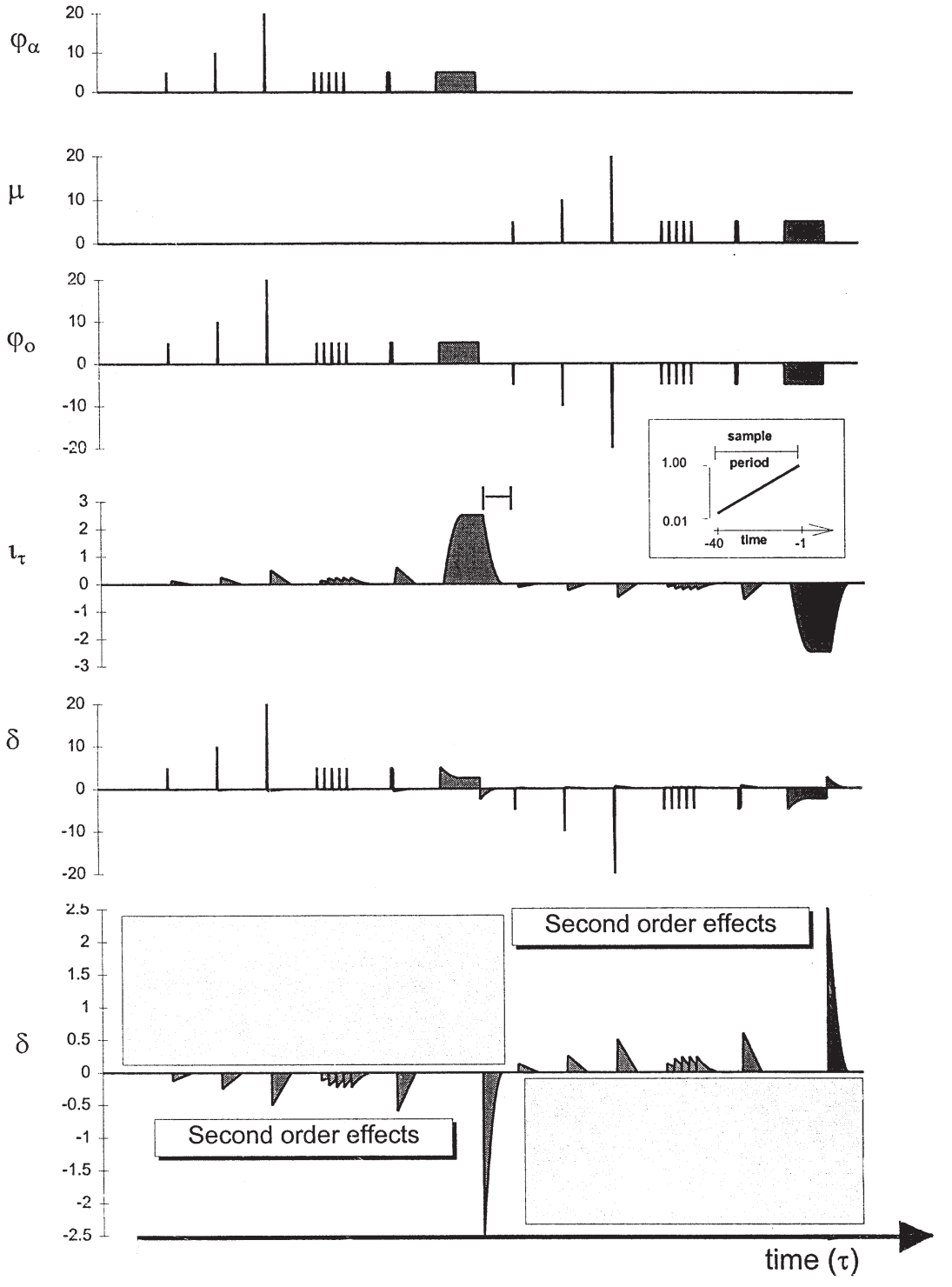
How now does detection proceed? As indicated earlier, it is proposed that the system appreciates any instantaneous input (e.g., value x′ of φ_0) by the input's departure from the time-averaged activity (the n value of ι_τ). That is, the observer both monitors instantaneous φ_0 and computes ι_τ continuously and is thus enabled to, also continuously, find the departure, termed δ. The observer finds this departure, quite simply, by the substraction $\delta = \varphi_0 - \iota_\tau$.

Response Features of Signal Transduction

It is apparent from Fig. 1A that the system's output variable δ not only detects the event (i.e., finds δ'), but is also proportional to the event's magnitude (i.e., to x). Thus, responses that are coupled (linearly) to δ can vary in a graded manner that depends on the event's magnitude. (If some criterion value were imposed on δ, then responses could also be binary.)

Other response features become apparent when considering the dynamic changes of its parameters as they vary over time. Figure 2 shows how ι_τ and δ vary as the system is

Fig. 1. Graphical representation of formal mechanisms whereby nociceptive stimuli can be detected and whereby this detection can be modified by opioids. Panels **(A–D)** consider different conditions, i.e., that of a normal organism, that of chronic exposure to an opioid, that of chronic exposure to nociceptive stimulation, and that of chronic exposure to both an opioid and nociceptive stimulation. In each condition, pain is examined; the pain is that which occurs upon the application of an acute stimulus in the absence (single prime) or presence (double prime) of an acutely applied opioid. Reproduced with permission from ref. *(10).*


φα
μ
φo
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δ
δ
sample
period
1.00
0.01
-40
time
-1
Second order effects
Second order effects
time (τ)

Fig. 2. *(opposite page)* Dynamic response features of a signal-transduction mechanism. The data demonstrate how nociceptive stimulations (φ_α) or doses of morphine (μ) of varying magnitude, frequency and duration determine physiological activity (φ_0) and its temporal integration ι_τ. Pain sensation is represented by the difference δ between φ_0 and ι_τ. All ordinates express arbitrary units (A.U.); the abscissa represents time (ι), also in A.U. The insert specifies how, in the computation of the mean activity ι_τ, the weight that is being attributed to φ_0 varies as a function of time. The calibration marks the sample period of ι_τ: i.e., 40 units of time. The lowest panel provides an optical magnification of the previous panel, and only shows directly observable second-order effects (first-order effects here are covered by shaded areas). The first three stimulations vary in intensity and last only one A.U.: note how they produce intensity-dependent second-order effects that outlast the stimulation. A train of five discrete stimulations induces five discrete first-order responses and the saw-tooth-like build-up of second-order effects. Rectangular stimulations produce second-order effects in a duration-dependent manner. Finally, μ-opioid receptor activations cause both first- and second-order effects that mirror those produced by nociceptive stimulations. Data were obtained from computer-assisted numerical simulations that implemented the equation $\delta = \varphi_0 - \iota_\tau$. Reproducted with permission from ref. *(10).*

being fed nociceptive inputs that vary in amplitude, frequency, and duration. Perhaps most strikingly, these stimulations show that any input produces not just one but two effects, those effects being paradoxical, or opposite in sign. The first-order effect (with nociceptive inputs: upward inflection of δ) results, rather directly, from the nociceptive stimulation; in the absence of prior nociceptive stimulation, ι_τ is zero, and any input that is larger than zero can generate a positive inflection of δ (when $\iota_\tau = 0$, then $\delta = \varphi_0 - 0 = \varphi_0$). The second-order effect results from the continued computation of δ at a later time; at the later time, ι_τ now incorporates the earlier impact ($\iota_\tau > 0$), so that even in the absence of any instantaneous input (i.e., when $\varphi_0 = 0$), the system yields a negative value (i.e., $\delta = 0 - \iota_\tau = -\iota_\tau$). The response features of these first- and second-order effects are exemplified in Figs. 2 and 3 and appear to be very different.

The first-order effect is ipsi-directional to the stimulus and immediate; it begins at the very point of time when stimulation begins to be implemented. Both the initial amplitude and the duration of the first-order effect are proportional to those of stimulation. However, as stimulation is repeated (within a length of time that is shorter than the sample period) or maintained, the effect's magnitude decays from the initial peak to eventually reach an asymptote that lasts as long as the (here: rectangular) stimulation is maintained.

The second-order effect is contra-directional to the stimulus and quasi-immediate; it begins only at the point of time that follows the stimulus onset. The effect's amplitude depends on that of stimulation; however, as (rectangular) stimulation is maintained, the effect's magnitude grows to reach a steady asymptote after a duration of stimulation that is equal to the sample period. As discrete stimulations are spaced in time but repeated, the second-order effect also grows from zero to an asymptote that is then dented (Fig. 2). Again unlike the first-order effect, the second-order effect outlasts the stimulation; it does so by a length of time that equals the sample period.

Finally, and regardless of the number, amplitude, and duration of stimulations, both of the system's responses eventually disappear as stimulation is discontinued; and importantly, the system's output returns to the resting state from which it originated prior to any stimulation.

Opioid Analgesia

Having specified how a physically defined (e.g., nociceptive) stimulus can be transduced so as to become a biological signal (e.g., pain), one can now ask how another stimulus such as the activation of opioid neurotransmitter receptors can act to diminish that signal, as is the case with morphine in producing analgesia. The theory here proposes that, like the first

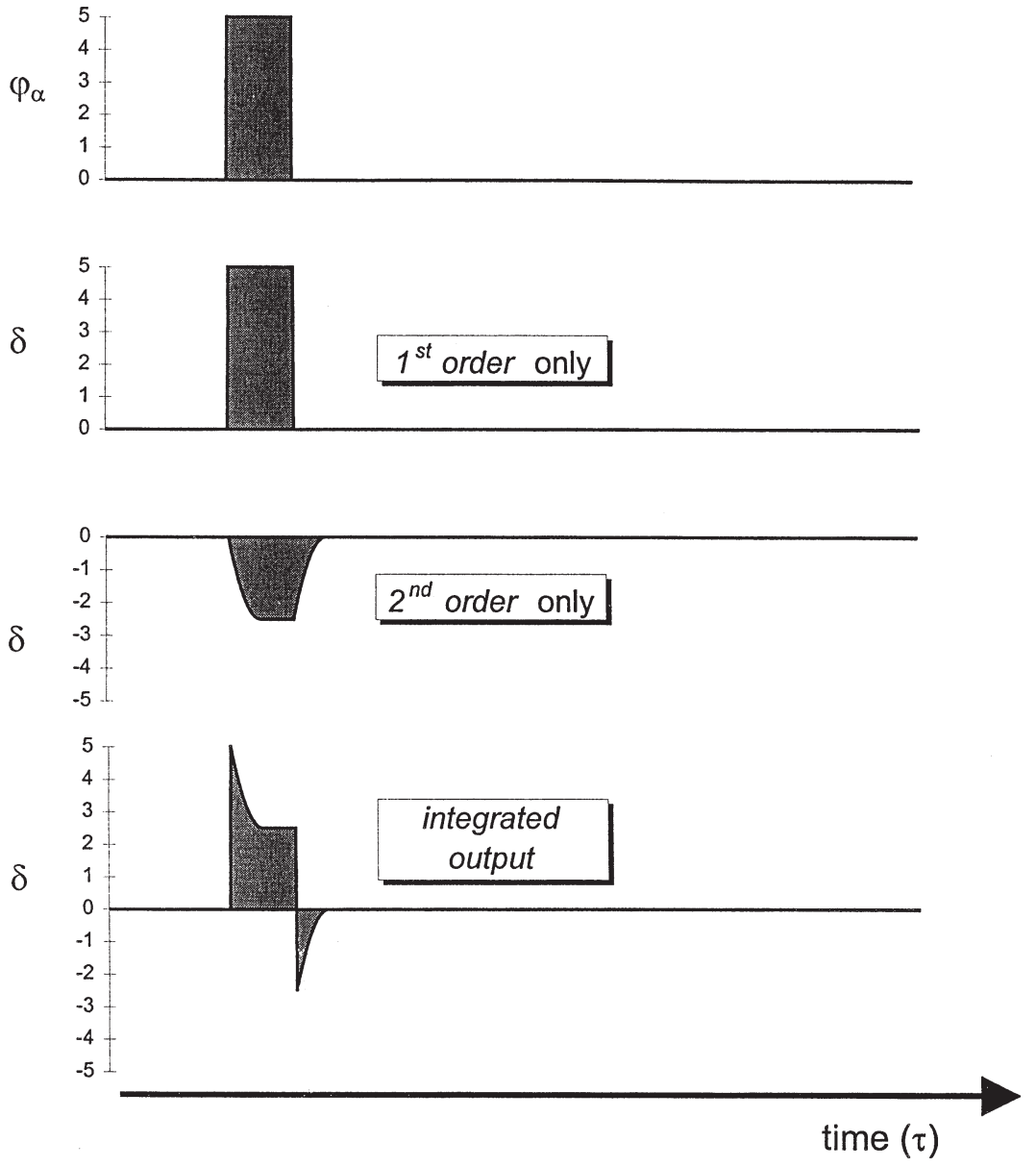

Fig. 3. A detailed display of first- and second-order effects as they determine the eventual, integrated output. The data identify the output (δ) that is produced by a rectangular stimulation (φ_α) that has a magnitude of 5 A.U. and a duration of 80 A.U. One panel ("first-order only") indicates what the output would be if the second-order effect would not be allowed to impact on the output; the output then conforms perfectly to the input in all respects (onset, direction, amplitude, shape, duration). Another panel ("second-order only") indicates what the output would be if the first-order effect would not be allowed to impact on the output; the output is then solely determined by the second-order effect and now differs from the input in many respects. The last panel ("integrated output") indicates how the output evolves when both the first- and second-order effects are allowed to impact on the output; this output represents the effects as they can be observed directly without any intervention (as in Fig. 2; for experimental data, *see* ref. *(11).*

stimulus (i.e., φ_α), the second stimulus also contributes to relevant physiological activity, but in a manner that differs. For example, while nociceptive stimulation (φ_α) can increase the firing of dorsal-horn neurones, opioid receptor activation (here termed μ) can decrease this firing *(12).* Figure 1B demonstrates how this permits morphine to produce analgesia; x in the presence of μ no longer yields x′ but a φ_0 value x″ that is of smaller magnitude than x′. x″ generates a departure δ'' that is smaller than δ', thus indicating opioid receptor activation to have produced analgesia.

Figure 2 demonstrates how activations of opioid receptors make ι_τ and δ vary over time. The activations cause effects that mirror but are otherwise identical to those produced by nociceptive stimulation. Importantly, opioid receptor activation similarly produces both first- and second-order effects, i.e., it produces both analgesia and, quite remarkably, pain.

Signal Transduction in Opioid Actions

Extensive theoretical research has been carried out *(10)* to determine whether this theory of signal transduction can account for the huge body of empirical findings that experimental studies have generated on the biological actions of opioids. Simulations were conducted using the equation $\delta = \varphi_0 - \iota_\tau$, and their outcomes were compared with empirical data. One issue that must be considered is the proposed but controversial assumption that no tolerance develops to the primary action of opioids *(2,9).* In particular, how can it be maintained that the primary action of opioids remains immutable if empirical studies (e.g., refs. *13,14*) find opioid analgesia to diminish? In its mathematical form, the transduction theory provides an accurate albeit highly abstract explanation *(10);* a more didactic representation is offered in Fig. 1B. In this panel, opioid receptors are activated at some intensity μ (e.g., dose μ of morphine) for a long period of time (i.e., long enough to cover ι_τs sample period). In defining morphine's mechanism of action earlier, it was specified that the opioid causes a shift to the left, by an angle μ, of the projection from φ_α to φ_0, this shift applying to any value of φ_α including the value n. Chronic opioid receptor stimulation, during an entire sample period, will result in ι_τ now shifting to the left by an angle μ along the φ_0 axis. Importantly, note that this shift is by an angle μ* and that for this to be possible we must adhere to the assumption that tolerance did not develop to morphine while it was being applied. Let us now discontinue the morphine and apply a nociceptive stimulus of magnitude x. As in a normal organism, x will again yield x′, and a difference δ' is found between x′ and ι_τ. Let us then, in this same organism, again administer acutely both the dose μ of morphine and nociceptive stimulation x. And let us continue to adhere to the no-tolerance assumption so that μ's effects are unchanged despite the previous exposure to morphine. In the presence of the test dose μ of morphine, x generates x″ and a difference δ'' is found between x″ and ι_τ. Morphine's apparent effect, computed as $e_r = \delta'/\delta''$, is now smaller than it was in panel A. This explains how morphine's apparent analgesic effect can diminish while morphine's primary action in fact remains immutable. Since the tolerance that so occurs to morphine is only apparent, we will refer to it as apparent tolerance.

A second fundamental issue that the theory resolves is the disparity of the definitions of apparent tolerance. The different definitions *(4)* are satisfied by empirical studies, such as studies of opioid analgesia, and require that the exposure to one intensity of opioid receptor activation (i.e., dose or concentration of opioid): 1) causes the effect of that same dose

* A simplification is being made here for the sake of clarity. In fact, the extent to which chronic μ can make ι_τ decrease is not merely the same as that to which μ can make the effects of φ_α decrease at any particular point of time. This is because the weight that in the computation of ι_τ *(10)* is being accorded to the effects of φ_α decays as a function of time.

to become smaller, 2) results in a higher dose being required to generate the same effect, and 3) causes a shift to the right of the dose-response curve. Simulations applying $e_r = \delta'/\delta''$ indicate the operations of the transduction mechanism to satisfy each of the three definitions; indeed, these operations specify transposition to be the mechanism whereby the exposure to any dose co-determines the effects of any other dose that is administered subsequently *(10).* The theory thus identifies the single and same mechanism that has long been assumed must exist *(4)* to account coherently for the disparate definitions of tolerance.

While the transduction mechanism accounts for apparent tolerance to opioid analgesia, empirical studies have shown that this tolerance possesses a number of hallmark features that have so far been left unexplained. Numerical simulations indicate the theory to accommodate these properties. Thus, both the theory and empirical studies *(15,16)* indicate the magnitude of apparent tolerance, according to each of its three definitions, to be dose-dependent, i.e., proportional to the dose to which the organism was exposed. A second such property is duration-dependence *(17,18).* The theory finds the apparent tolerance initially to increase in a manner that is proportional to the duration of the exposure and this until a duration is reached that is equal to the sample period; beyond that duration, apparent tolerance remains at an asymptotic value. This biphasic relationship between duration and the magnitude of apparent tolerance occurs in empirical studies *(17,19).* Thirdly, apparent tolerance is reversible; once established by an opioid treatment, which is then discontinued, apparent tolerance decays with the mere passage of time, and opioid analgesia recovers to a magnitude similar to that in previously nonexposed organisms *(13,14,20).* Consistent with these empirical observations, simulations find apparent tolerance to immediately start to decay upon discontinuation of the exposure and entirely to disappear after one sample period has elapsed. A fourth characteristic and complex feature of apparent tolerance to opioid analgesia is that its induction is plurimodal; apparent tolerance can be induced by such widely differing modes of opioid receptor activation as continuous exposure *(19),* intermittent stimulation *(16),* and even a single, acute stimulation *(13).* Simulations indicate that the theory can effectively accommodate these plurimodal inductions. Furthermore, the theory specifies that apparent tolerance develops as of the unit of time onward that opioid receptors are activated, thus implying that it is practically impossible for empirical experiments to accurately determine the magnitude of an opioid effect. Finally, empirical studies show that apparent cross-tolerance can be obtained with opioids and that its occurrence demonstrates molecular specificity *(4);* apparent tolerance occurs to other opioids that activate the same, but not to other opioids that activate other receptors than those at which the tolerance was induced. The theory explains this feature of apparent tolerance by having different systems, that operate according to the proposed signal-transduction mechanisms (Signal-Transduction systems; STs), be arranged in a parallel configuration *(10).* The theory thus accounts for the five hallmark features of apparent tolerance to opioid analgesia that empirical studies have identified but never so far explained.

The theory also generates a number of novel and intriguing predictions. One such prediction follows from panel B in Fig. 1 showing opioids to produce not only apparent tolerance (i.e., a smaller e_r), but also an enlarged δ' (i.e., δ' is larger in panel B than it is in panel A). The enlarged δ' represents hyperalgesia, i.e., a sensitization to the effects of x; the theory hence predicts chronic opioid exposure to produce both apparent tolerance and real hyperalgesia (i.e., pain), the two phenomena being proportional to each other since they result from a single and same cause (i.e., a decrease of ι_τ). Note that this sensitization that the theory predicts occurs not only with pain-processing systems, but also with several other systems that are coregulated by opiate receptors (e.g., *21–23;* for reviews, see: ref. *24–26*). Further predictions

can be derived from a condition where the system is fed chronic nociceptive stimulation (panel C). This stimulation increases ι_τ so that δ' is smaller than it normally is, thus predicting chronic nociceptive input to cause hypoalgesia. The analgesia, computed as $e_r = \delta'/\delta''$, which the test does μ produces in this condition is larger than it normally is, so that the theory here also predicts, intringuingly, the existence of the inverse of apparent tolerance (i.e., inverse apparent tolerance). Furthermore, the co-stimulation of nociceptive and opioid receptors, and in as much as the two stimulations match each other, acts (panel D) so as to eliminate the consequences of each. Thus, the hyperalgesia and the apparent tolerance that opioid receptor stimulation produces when it is applied alone are eliminated by the hypoalgesia and the apparent inverse tolerance that nociceptive stimulation would produce when it is applied alone. The theory specifies that for these mutual eliminations to occur, the two stimulations must match each other in terms of their intensity, their duration, and their location in time. Because they are multifactorial and dynamic over time, it may be difficult to establish accurate matches. But provided that such matches are engineered, the theory makes the medically relevant prediction that opioids can entirely and lastingly relieve chronic pain without ever inducing even apparent tolerance. Each of these predictions have been verified by experimental studies *(27,28)* and are consistent with the large body of other empirical evidence that is now available *(10).* The theory may thus settle a medical controversy concerning the use of opioids in the treatment of chronic pain and, in principle, solves the tolerance that constitutes one of the most difficult problems that is being encountered *(29)* in providing clinical pain relief.

In addition to controlling signal transduction in pain systems, opioid receptors in mammals also govern a host of such other physiological functions as respiration and gastrointestinal motility *(30).* Apparent tolerance to opioids may develop with all of these functions, but empirical evidence indicates that it does so at rates of induction and of subsequent decay that differ *(31–34).* Simulations show the theory to accommodate these empirical data by having each of these functions be controlled by ST systems that operate different sample periods. By defining this single mechanism in accounting for differential rates, the theory makes unnecessary other concepts that postulate the need for multiple mechanisms *(31–34).* Indeed, very long sample periods will generate data that misleadingly suggest apparent tolerance not to develop *(10).*

In considering Fig. 1B, it is clear that opioids cause hyperalgesia (i.e., an increased δ'). The hyperalgesia indicates that the system's ability to appreciate nociceptive stimulation in a normal manner is compromised. The hyperalgesia of course is aberrant but can be rendered to a normal value by again activating the opioid receptor. Drug dependence is said to occur when the normal functioning of an organism requires the organism to again be exposed to the drug; this requirement is evidenced by the disruption of function on discontinuation of exposure *(4).* The increased δ' thus appears to constitute the mechanism of dependence. For larger-than-normal δ' values to reflect dependence is elegantly consistent with empirical evidence; hyperalgesia in fact constitutes a sign and measure of opioid dependence *(15,20,35),* though it has not been accounted for so far *(36).*

As with apparent tolerance, empirical studies have found opioid dependence also to possess the hallmark features of: dose-dependence, duration-dependence, reversibility, plurimodality, and cross-dependence *(19,20,37,38).* Simulations indicate opioids to induce increases in δ' that accommodate each of these features. This is no longer surprising, since panel B of Fig. 1 shows that both apparent tolerance and increases in δ' are caused by a single and same mechanism, i.e., result from decreases of ι_τ. It has been recognized *(20)* that (apparent) tolerance to and dependence on opioids result from a "common underlying process," though the nature of the relationship and the mechanisms of both phenomena have remained elusive *(4).*

Indeed, apparent tolerance always occurs when dependence is being induced *(37–39).* The present theory thus is the first to explain apparent tolerance and dependence, and to specify the intimate relationship that exists between them; it renders unnecessary theories *(37,38)* that have sought to explain tolerance and dependence by mechanisms that differ. Finally, the theory explains why the manifestations of opioid dependence are opposite in sign to the effects that opioids produce in naive organisms *(30).* The relationship that the theory defines between apparent tolerance to and (genuine) dependence on opioids also signifies that dependence is incompatible with real tolerance. The theory indicates that dependence can in fact develop *because* tolerance does not and explains why in dependent organisms, opioids remain ever capable of preventing signs of abstinence *(10,17).* This point underscores the usefulness of distinguishing tolerance from what is referred to here as apparent tolerance.

The transduction theory specifies that just as reliably as opioids produce one, so-called first-order effect (i.e., decrease δ so that δ″ is smaller than δ′; e.g., analgesia), they also produce the paradoxical, second-order effect (i.e., increase δ; e.g., hyperalgesia and other instances of so-called sensitization). The theory also specifies that these first- and second-order effects occur with all physiological functions that are (co-)regulated by opioid receptors, albeit that the rates at which the second-order effects arise may differ between these functions. As mentioned earlier, the physiological functions that are regulated by opioids include pain perception, respiration, gastrointestinal motility, and reward *(40);* hyperalgesia, hyperpnea, diarrhea, and dysphoria are signs of opioid dependence *(30,41).* The theory thus also accounts for opioid addiction. That is, just as reliably and powerfully as opioids can produce euphoria as a first-order effect, the theory specifies the opioids to also produce dysphoria as a second-order effect. Since the reward function likely operates a long sample period *(10),* the dysphoria develops insidiously but can attain a very large magnitude. Once established, another exposure to opioids affords a brief relief from the dysphoria, but the exposure will also act to re-set the timer that ticks off the decay of the dysphoria that persists. The only available means by which the dysphoria can be made to disappear is simply due passage of time—a long time during which it will progressively decay. The ST theory thus explains opioid addiction as a particular case of opioid dependence. Time not being compressible, the theory also elucidates why addiction has remained inaccessible to treatment though it suggests a theoretical solution to this medical problem: because of the operations of ι_τ, inverse *mu* opioid agonists could conceivably act to, in physiological effect, compress time *(10).*

So far, we have considered the transduction mechanism as it accounts for the apparent tolerance and the dependence that opioids produce in mammals, whole organisms having been the level at which these phenomena were discovered *(3,42).* However, transduction in both nociceptive and opioid-signaling systems of course already occurs at the less integrated, higher-resolution levels of cell-surface receptors and cellular-signaling pathways. It is important to point out, therefore, that apparent tolerance, dependence, and their hallmark features can be observed in such cell assemblies as the myenteric plexus of the guinea pig ileum, in individual neurons *in situ* as well as in cultured cells *(12,39),* and with such subcellular entities as receptor density, receptor coupling to G proteins, second-messenger systems, and gene expression *(43–45).* Importantly, recent research provides evidence that bi-directional responses occur already at these early steps in opioid-signaling pathways (for review *see* ref. *46*). Examples are the both inhibitory and stimulatory effects of opioids on cAMP formation in SK-N-SH neuroblastoma cells *(47)* and in the myenteric plexus *(48),* on the uptake by and intracellular levels of Ca^{2+} in different neuronal cell lines *(49),* on the duration of the Ca^{2+} component of the action potential of dorsal-root ganglion neurons *(50),* and on electrically stimulated met-enkephalin release from the

guinea pig myenteric plexus *(51).* Consistent with the ST theory, these paradoxical responses depend on prior opioid exposure *(52)* and on the magnitude of ongoing neuronal excitation *(53).* While a full analysis of this evidence is beyond the scope of the present review, it would appear that the transduction mechanism may perhaps account for these findings for which a satisfactory explanation has not been forthcoming *(4,54,55).*

The ST mechanism can thus explain how adequate stimulations of (e.g., nociceptive) transducing mechanisms can generate signals to which such responses as pain are coupled, and specifies how other stimulations (e.g., of opioid receptors) can in turn generate signals and interfere with those produced by the first stimulation. The mechanism explains tolerance to opioids as a consequence of the paradoxical, second-order effect of opioid receptor activation. The mechanism accounts for apparent tolerance, identifies the transposition mechanism that is required for its disparate definitions to converge, and accounts for the hallmark features that empirical studies indicate apparent tolerance to possess. The mechanism uncovers the occurrence of inverse apparent tolerance and suggests a theoretical solution for the long-standing medical problem of the opioid treatment of chronic pain. The theory explains dependence, specifies that dependence can only develop if real tolerance does not, identifies the single mechanism whereby both apparent tolerance and dependence emerge, and elucidates the relationship that exists between them. As the transduction mechanism may operate with all physiological functions that are regulated by opioid receptors, the theory explains opioid addiction as a special case of opioid dependence, and suggests a theoretical method by which time can in biological effect perhaps be compressed. The transduction mechanism appears to operate with different physiological functions, but also at levels of analysis that range from the poorly integrated, high-resolution molecular level to the highly integrated, low-resolution level of whole mammals. This theory is the first to account for many of the host of empirical findings that we have considered, and is the only one to provide a single coherent explanation for all of them. Apparent tolerance to and dependence on opioids have over the past 50 years constituted the object of a particularly massive and sophisticated research effort in neurobiological science. The mechanism can resolve this effort, but to do so requires that be abandoned the century-old notion *(3)* that tolerance develops to opioids. Thus, opioid signal transduction would constitute an instance where the molecular-signaling event is immutable and induces dynamic, time-dependent actions because of a transduction mechanism that appreciates any current input by its departure from mean past activity and for that reason invariably causes two paradoxical effects. The following section explores whether similar transduction mechanisms may operate with nonopioid-signaling systems.

Nonopioid Signal Transductions

A number of nonopioid central nervous system (CNS) neurotransmitter receptor systems share with opioid receptors the ability to generate several of the dynamic features (e.g., apparent tolerance, sensitization, and dependence *[4])* that the transduction mechanisms generate. Also, instances abound where a same signaling event causes paradoxical, bidirectional effects. Examples are the both facilitatory and inhibitory modulations of pain by neurotensin *(56)* and by neuropeptide FF *(57),* the transient depression of excitability that follows the activation of developing nervous system networks *(58)* the bidirectional gene modulation mediated by muscarinic acetylcholine receptors *(59),* and the operation of opposite-action protein kinase and protein phosphatase enzymes in an apparently self-regulating signaling complex *(60–62).* In what follows, we will consider in more detail two further, disparate instances where available evidence suggests this transduction mechanism to operate.

Neuronal Plasticity

Interestingly, the ST theory resembles some of the theoretical schemes that propose to account for plasticity in central neural networks *(63,64).* Here, one seeks to identify a mechanism detecting covariation changes between input and output, and that consequently affects the responsiveness of the transducing system to new inputs. The synaptic analogue that we will develop below suggests that the relationship between φ_α signaling events and the outcome δ is similar to the dynamic changes in synaptic efficacy that occur in the neocortex. The presynaptic term would be φ_α; δ is the postsynaptic term. The transduction algorithm relating φ_α to δ is equivalent to that of a synapse, whose efficacy is encoded by the covariation history of both variables.

In order to apply this analogy and devise an adequate plasticity algorithm, the following requirements are to be satisfied: the chosen adaptation rule should account for a change in the postsynaptic responsiveness threshold due to prior activity, and the system should show some form of lasting memory. At least two options are available: 1) one may decide to store or filter out the repeated associations in the synaptic gain, and correlation-based models offer interesting possibilities to do so; or 2) one may implement the sensitivity change in a postsynaptic threshold of integration that will be subtracted from the output baseline (in the same manner as neuronal output is simulated by a linear function of the input minus a postsynaptic threshold). Both options result in an apparent "floating threshold," which affects either the synapse itself or the neuronal element's spiking threshold.

Let us consider the first option. In studies of experience-dependent neuronal plasticity, a long-recognized need exists for plasticity rules that keep the firing rates of individual neurons within certain boundaries. Such stabilized activity is probably required for allowing Hebbian (or anti-Hebbian) learning mechanisms to modify synaptic strengths in a selective manner and avoid indiscriminate saturation or depression of synaptic weights after repeated correlation between pre- and postsynaptic events (*65–67;* for review, *see* refs. *64,68,69*). A similar need for some form of normalization (some synaptic weights potentiate, whereas others depress) is being encountered in behavioral studies of associative learning *(70,71).*

What type of synaptic plasticity rule could apply here? Positive correlation rules would predict sensitization to the repeated presentation of the same input; negative correlation rules would predict classical adaptation, similar to a behavioral habituation process. In both cases, the sign of the synaptic change being ignored, the algorithm can be written as a covariance equation detecting instantaneous deviations from a continuously updated "trace" of past activity *(72–74);* the absolute value of the synaptic change is predicted by the product of the presynaptic and postsynaptic changes (instantaneous value of the variable *minus* its past mean value). Since the phenomenology we want to reproduce here is closer to perceptual filtering than to associative memory, anti-Hebbian algorithms (i.e., repeated correlation between input and output resulting in a depression of the transduction gain) should be preferred.

Such a form of plasticity, which, owing to the preponderance of Hebbian theories, has long been overlooked, has now been well-established in the cerebellum and in the striatum of higher vertebrates as well as in the electrosensory lobe of the electric fish. In these structures, specific sets of synapses may display a behavior that is opposite to that predicted by Hebb and acts as a perceptual filter. Remarkably, the algorithm results in a subtraction of the "prediction" fed by the modifiable synapses, from the current input. In the electric fish, the predictive signal, initiated by intermittent motor activity (saccadic eye movement for the oculomotor system, electric discharge for electrolocation), is in fact the prediction of the sensory input modification due to the motor act that has been engaged *(75,76).* Being somewhat equivalent to the mammalian cerebellum, the electrosensory lobe integrates the message

transduced by the different electroreceptors and receives a copy of the motor discharge ("outflow" or "efferent copy," *see* ref. *77*). Most interestingly, the plasticity algorithm found at the synapse between parallel fiber and Purjinje-like cells *(78,79)* is the mirror image of that recently established in sensory neocortex *(80,81).* Thus, through anti-Hebbian (negative correlation) plasticity rules, cells in the electrosensory lobe respond to the efferent copy input by generating a negative image of the expected input, thus subtracting it from any sensory signal that occurs concurrently. In accordance with the ST mechanism, the element that acts like the efferent copy would be some kind of moving average of past sensory input. Thus, a negative covariance detector would be ideally suited to detect any changes from a trace of "expectation," which may reflect the past experience of the organism.

Neural plasticity literature offers additional twists to the analogy developed here. The concept of a "floating threshold" has been much explored in cortical networks. For example, in recent research, chronic blockade of cortical pyramidal neurons in culture increased the amplitude of miniature excitatory postsynaptic currents without changing their kinetics; conversely, (bicuculline-induced) disinhibition of activity initially increased firing rates, but rates subsequently decreased to close-to-control values (*82; see* also *83,84*). Not unlike the ST theory, current accounts *(72,85)* do indeed attribute these variations to their being governed by a threshold that floats as the possible result *(63,68)* of it referring to a mean past activity that fluctuates continuously (*see* also refs. *86,87*). According to the Bienenstock-Cooper-Munro theory, the floating threshold in synaptic plasticity is itself a nonlinear function of the past postsynaptic activity that was previously evoked in the network. This nonlinearity helps to explain why two different outcomes, namely both long-term potentiation (LTP) and long-term depression (LTD), can be observed if the system has been previously exposed to relatively low or high levels of input, respectively (*72,88* for review, *see* ref. *85*). Such complexification of the algorithm where the term subtracted from the instantaneous variable is not the mean itself but some (>1) power function of the mean has the following advantage. With a weak mean input level, the threshold drops faster to zero than the mean, thus favoring potentiation (or hypersensitivity); with a strong mean input level, the threshold increases faster than the mean, thus favoring depression (or habituation). Other ways exist for changing the threshold, by considering not only the postsynaptic term, but applying this theory to the presynaptic term as well *(89,90);* the latter authors introduced the term of metaplasticity (i.e., plasticity of plasticity) to denote the complex outcomes that can then be obtained.

The abovementioned second option also appears to be feasible. That is, the simulations in Fig. 2 fit the concept of a postsynaptic plasticity threshold that is linearly related to the mean and simulated in a simplified manner by considering the postsynaptic term only. They demonstrate how the amplitude of the response to any new discrete input is diminished while its kinetic features are preserved by preceding, similar input; inputs of long duration generating an output that decays to then reach a closer-to-baseline asymptote. These response features of course derive from the transduction mechanism appreciating input by its departure from mean past activity ι_τ; resulting from integrating past input over a sliding temporal window, this mean varies over time, acting as a "floating postsynaptic threshold" that determines first- and second-order, up- and downward variations of the output variable δ. Figure 2 demonstrates how ι_τ mediates two changes that are long-term (i.e., outlast the signaling event and last as long as the sample period's duration). Specifically, φ_α-induced increases in ι_τ both decrease responses that are induced by further φ_α signaling events and that are coupled positively to δ, and increase responses that are also induced by further φ_α stimulation but are coupled negatively to δ. Thus, the adaptation rule may be thought of as a negative covariance detector. Further, changes in ι_τ that thus deter-

mine long-term effects on responses can of course be produced by large inputs, but are also, and inevitably, produced by any input, however small or infrequent. This observation accords with the evidence discussed earlier (*see* also ref. *85*) that neural activity, which by itself produces little change in synaptic effectiveness, can set in motion changes that for a long time alter the properties of synaptic plasticity.

Resistance

Cancer is considered to be the prolific replication of cells that is due to a deficient control by genes governing cell replication and cell death. Chemotherapeutic agents act by different, intracellular mechanisms. The antimetabolites 5-fluorouracil and methotrexate inhibit enzymes (i.e., thymidylate synthase and dihydrofolate reductase, respectively) involved in DNA synthesis, while alkylating agents (e.g., cisplatin, cyclophosphamide) disable protein synthesis. Anticancer antibiotics such as bleomycin intercalate between DNA base pairs, disabling RNA synthesis. Epipodophyllotoxins (e.g., etoposide) inhibit the topoisomerase II enzyme, preventing DNA to uncoil for translation or replication. Further downstream, *Vinca* alkaloids (e.g., vinorelbine) bind to microtubules, inhibit their polymerization, and cause mitotic arrest *(91,92).* Thus, chemotherapeutic agents interfere with the transduction of signals that control cell replication.

As with the opioid treatment of chronic pain, apparent tolerance similarly develops to chemotherapeutic agents, and allegedly *(93)* constitutes the single most important problem in the treatment of cancer. This tolerance is also called "acquired drug resistance" *(93),* though its defining characteristics are like those recognized with opioid tolerance. That is, prior exposure of whole organisms (i.e., patients) or of cells in culture can reduce the therapeutic and cytotoxic activity, respectively, of chemotherapeutic agents *(94–96).* The resistance depends on the dose and on the duration *(97–99)* of the drug exposure, and appears to be reversible *(100,101).* Transposition occurs in that the resistance can be observed either as the same dose producing a smaller effect, as a higher dose being required to produce a same effect, or as a shift to the right of the dose-effect curve *(102–106).* The resistance is plurimodal; it can occur following prolonged exposure (as with infusion) *(97),* but also following intermittent doses or after a single, brief exposure *(102–106).* The resistance established to one particular agent may be associated with a decreased apparent efficacy of other agents, and is then referred to as multidrug or cross-resistance *(107).* Also, the rate at which resistance develops to one particular chemotherapeutic agent can differ depending on the cell line or tumor type *(108).* The resistance to chemotherapeutic agents that occurs with cells and whole organisms thus possesses the many complex, and characteristic features of apparent tolerance to opioids. Furthermore, the transduction mechanism has generated the remarkable, *de novo* hypothesis of inverse apparent tolerance, e.g., of the analgesic effects of opioids being apparently enlarged in organisms exposed to nociceptive stimulation. And similarly, the apparent inhibitory effects of chemotherapeutic agents have been found to be larger with rapidly growing tumors and cycling cells than with slowly growing tumors and quiescent cells, respectively *(109–112).*

Chemotherapeutic treatment of cancer typically is initiated in an aggressive manner; a highest tolerable dose is being administered, most commonly by intravenous infusion *(113).* It is under these conditions that a resistance is often encountered that is then said to be intrinsic, the cancer apparently failing to respond to the chemotherapeutic agent and the disease proceeding at a pace that defies treatment. Intrinsic resistance is thought *(114,115)* to reflect a lack of specificity or even of activity, the agent presumably affecting normal tissues as well as the tumor. The transduction theory's account of resistance suggests that mismatching exposure to the agent may rapidly make the tumor apparently escape the first-order effect and, by increasing δ', to sensitize the tumor to the stimulus that makes it grow. As a

result, an experimenter may readily find the agent to have exerted no effect whatsoever while in fact the mismatching exposure to the agent would have accelerated the disease's progression. It is of interest to note here that the theory's operations conceivably endow the chemotherapeutic agents with selectivity; much as the apparent analgesic effects of opioids are larger in the presence than in the absence of nociceptive stimulation, the apparent inhibitory effects of chemotherapeutic agents on cell proliferation could be larger in cells that are stimulated to proliferate as opposed to quiescent cells. Furthermore, to suggest that chemotherapeutic agents increase δ′ is to imply that they produce dependence. It is this dependence that may indeed explain another, remarkable phenomenon: exposure of normal or only mildly stimulated organisms to chemotherapeutic agents should readily be mismatching and may hence cause a dependence that eventually results in rapid cell proliferation. Thus, much as mismatching exposure to opioids can paradoxically cause pain *(116–119),* the transduction mechanism can explain why chemotherapeutic agents can be powerfully carcinogenic and perhaps induce relapse in patients after having initially provided remission *(120,121).*

Resistance also develops to agents used in the treatment of infectious diseases *(122)* and looms as the largest current threat to human health *(123),* infectious disease being the first mondial cause of early death. Infectious diseases become increasingly inaccessible for therapy, the resistance and cross-resistance developing whether the infecting organisms be bacteria, viruses, fungi, or parasites *(124–127).* The resistance is often linked *(122)* to excessive use of chemotherapeutics but, as with cancer *(93),* its mechanisms remain elusive. Again as with cancer, aggressive exposure to anti-HIV agents is being advocated *(128)* for the treatment of autoimmune deficiency syndrome (AIDS). The transduction mechanism can account in principle for the resistance that develops to anti-infectious agents and suggests that aggressive treatments might paradoxically generate a violent and fatal acceleration of the disease. Consistent with this suggestion is evidence *(129)* that the development of resistance to zidovudine (AZT) constitutes a marker of subsequent disease progression in AIDS. It remains to be demonstrated that accurately matching exposures to chemotherapeutic agents can be engineered so as to provide lastingly effective treatments of cancer and of infectious diseases. Clinical evidence demonstrates, however, that sufficiently matching exposures to opioids can be established so as to provide long-lasting relief of pain in large samples of patients *(130–133).* The individual patients for whom chemotherapeutic treatment has apparently resolved the disease suggest the matching to be feasible, albeit so far this has been achieved in a perhaps inadvertent manner.

Adaptation and Homeostasis

Remarkably, and despite the diversity of the evidence that they propose to account for, other current theories have in common that they rely on the notions of adaptation and homeostasis. Adopting Himmelsbach's *(42)* integration of these notions in the analysis of opioid actions, current theories of the molecular *(5,6,45)* and cellular *(6,40,44,134)* and also of the whole organism effects of opioids *(135,136)* invoke adaptive processes that would act to maintain homeostasis and would explain how "the body … [counters] the acute effects of [morphine]…" *(5).* Equally authoritative accounts of resistance hold that the cancerous "cell [is] seeking to avoid (…) injury by cytotoxic agents" *(137)* and endow infectious organisms with an adaptive capability "to counterattack with their own strategies for [homeostasis and] survival" *(122).* Similarly, following episodes of chronic blockade or an increase of neuronal activity in cultured systems, compensatory mechanisms are proposed to maintain a neuron's total synaptic strength within homeostatic boundaries *(68,69).* The question thus arises whether the ST theory can provide a formal mechanism of adaptation

and homeostasis that these theories have not specified.

Adaptation can be defined as a change in an organism's response to a signaling event so that, in spite of this event, the organism's output parameters and behavioral responses remain within boundaries that are considered normal or physiological *(138–141).* The response features of the transduction mechanism fit this definition; whatever its direction, any signaling event causes a response δ that initially is proportional to the event's magnitude, but which then decays to reach a close-to-normal, asymptotic value even as the stimulation is maintained (Fig. 2). Also, the mechanism acts so that any signaling event or series of events, whatever their direction, magnitude, frequency, and shape, will, upon their discontinuation, allow the system to eventually return to the very same output value that it assumed before. Thus, the signal transduction can provide the mechanism for adaptation and homeostasis but this conclusion requires the following qualifications.

Departures from Baseline

As in the citations referred to earlier, adaptation and homeostasis are often implied to supervise the promotion of survival *(141),* and normophysiological conditions and health are often held to be a state in which all physiological parameters have normal values *(140).* Homeostasis-through-adaptation thus is held to generate the "complex control systems that permits organisms to function and survive in the most hostile environments" *(142).* The ST account deviates from this view in some respects. The transduction mechanism constitutes an algorithmic process that does not invoke any supervision; here it corresponds to proposed learning rules that govern the adaptation of neuronal firing rates in that they too are unsupervised *(84).* Also, when fed inputs that are large, the ST mechanism generates large and changing outputs like those observed under physiological conditions *(140)* and that disrupt the constancy of what is often held to be an equilibrium (e.g., ref. *143*). When fed extreme inputs, however, the transduction mechanism generates outcomes that are meaningless *(10),* thus rendering its output variable δ inadequate for eliciting any response or as an input to further transduction downstream. This attribute of the mechanism accommodates the observation *(142)* that breakdowns do occur and must be accounted for. Finally, though the ST mechanism's output changes as a function of input, no input ever changes the mechanism of transduction. Thus, the ST theory may account for adaptation and homeostasis, but does so by a process that can break down and that—since it is immutable—does not itself adapt.

Opponent-Process

It is appropriate to consider here an empirical, psychological theory upon which some current accounts rely to specify the role of adaptation in the particular case of opioid addiction. The theory *(144)* holds that any event possessing an affective valence generates two different processes that oppose each other, each of the two processes possessing its own peculiar time course. As the event is repeated, the so-called "a" process (e.g., euphoria) remains unaltered, but the opponent process (the "b" process; dysphoria) for some unspecified reason undergoes three changes (*see* Fig. 7 in ref. *144*). Eventually, as a result of these changes, and since the outcome is supposedly determined by the sum of the two processes' opposing forces, the effects of process b dominate. This opponent-process (OP) theory, like ST theory, invokes the induction by the same stimulating event of two effects that are bidirectional. Most current accounts of opioid addiction identify the second of these effects as a putative mechanism of adaptation, this second effect presumably "opposing," "compensating for" or being "opponent to" the primary action of opioids *(26,37,40,135,136,143,145,146).*

The ST and OP theories differ, however, in several respects. The ST theory provides a mechanism of signal transduction as it is initi-

ated, by opioid receptor ligands, at the molecular level (i.e., at cell-surface opioid receptors). In so doing, ST theory defines two paradoxical effects that result from a single and same transduction process; these effects are referred to as first- and second-order effects, respectively, since the second-order effect depends on the actual realization of the first-order effect *(9,10).* In contrast, OP theory proposes a rule according to which the same event initiates two processes that evolve independently, have different time-courses, and oppose each other *(144).* The available evidence concerning opioid actions (for review, *see* refs. *10,147*) supports the ST theory, and cannot be accounted for by OP theory. Both theories specify the two bidirectional effects to originate from opioid receptor activation and thus explain why an opioid antagonist prevents an opioid agonist from producing the two effects. However, experiments where the antagonist naloxone is administered after rather than before morphine, indicate the second-order effect to depend on the realization of the first-order effect *(11).* OP theory does not account for these findings, since it assumes the two effects to evolve independently. According to OP theory, naloxone, when given after morphine, should act to erase both effects; in fact, naloxone in these conditions selectively preserves the second-order effect *(11).* Finally, OP theory postulates that repeated morphine administration leaves the a process unchanged, but shortens the latency, increases the asymptotic value, and lengthens the decay of the b process *(144).* These changes, which the theory again postulates empirically without explaining them, do not occur; in keeping with ST theory, evidence indicates that the second-order effect's overall magnitude increases, but that both its time of onset and its duration remain the same *(10,11).*

An Adaptive Memory of Opioid Addiction

According to the ST theory, opioid addiction constitutes a particular case of opioid dependence *(10).* That is, just as much as morphine may induce euphoria as a first-order effect, through sensitization it also induces dysphoria as a second-order effect. The magnitude of the second-order dysphoria increases as exposure to morphine is repeated or prolonged, and can thus come to constitute an extremely powerful, so-called acquired drive *(10,143).* Addiction in this account results from an adaptation that is intrinsic to the operation of a signal transduction that itself does not change, rather than from a dysregulation of an equilibrium (also referred to as counteradaptation: *see* ref. *143*). The duration of this second-order dysphoria is, limited, however, to that of the sample period. The sample period's duration is *a priori* unknown, but it is finite *(10).* It is of interest to point out, then, that the following recent findings identify a mechanism whereby an acquired second-order effect of opioid receptor activation can persist beyond this sample period and for a time that may be long-lasting.

State-dependent learning refers to the observation that a response that has been acquired in a given state, may be better recalled when the organism is in the same then in a different state. We have recently found *(148)* that rats that have learned a response while in the normal state, show adequate retrieval when tested in the same normal state, but fail to recall the response when given morphine. The features of this morphine-induced retrieval deficit suggest that it is a first-order effect; the deficit parallels the time course both of morphine's concentration in the brain and of its analgesic action *(149).* When rats in otherwise similar conditions are trained with morphine, retrieval again is adequate in the same (morphine-induced) state, but not in the normal state. The temporal features of the retrieval deficit that occurs in this case suggests that this state is a second-order effect; this deficit reaches peak later and lasts longer than the saline-to-morphine deficit, and parallels morphine's hyperalgesic action (Fig. 3 in ref. *149*). This second-order memory state likely constitutes the addiction memory state; it can encode reinforcing events and is highly specific to a particular activation state of μ-opioid receptors *(149).* It is this state

that sets the opportunity for the organism to learn and encode the uniquely powerful reinforcing effects that opioids possess *(10)* in this second-order, presumably dysphoric state. While this state itself lasts only as long as the sample period's duration, the memory that is thus established is likely to persist *(150).*

Signal Transduction Process

The ST mechanism that we have considered here consists of three maneuvers: 1) the translation of inputs into some physiologically relevant variable φ_0; 2) the establishment of mean past activity ι_τ; and 3) the determination of the departure δ of instantaneous φ_0 from ι_τ. These maneuvers collectively are represented by the equation $\delta = \varphi_0 - \iota_\tau$, which operates at all times and defines one single, continuously evolving process that possesses a number of interesting features. One feature is that the process sovereignly determines when a signal occurs (and to which a response can be coupled); any event or stimulation is ineffectual until and in as much as the process finds φ_0 to differ from ι_τ. Thus, signals are not merely being translated but emerge as a result of transduction. Another peculiar feature is that the process transduces any input into not one but two outcomes that are paradoxical, its output variable δ assuming values that initially are ipsi-directional with stimulation, but that later are of the opposite direction. Through the notion of ι_τ, the process incorporates the mere passage of time as an indispensable, independent variable. Because of the operation of ι_τ, stimulus events can in physiological effect act to stretch or compress time, and exert effects that outlast the events' duration. The process appears to be algorithmic; it seems to operate ubiquitously with actions that are initiated at neuronal cell-surface receptors but also with transductions that occur at intranuclear, molecular entities. The process is expressed at these molecular and cellular levels, but also at those of cell assemblies and whole organisms. This same quality of substrate neutrality is consistent with the process constituting a mechanism of adaptation and homeostasis, though the process does not itself change as a consequence of input and does not require that any normative equilibrium be defined. Not unlike phenomena encountered in physics *(151–153),* the process is simple-complex; through steps that are utterly simple, it is capable of generating many different, highly complex, and seemingly chaotic outcomes.

Conclusion

The information processing that occurs in neurobiological systems requires them to be capable of what would seem to constitute the most elementary process, i.e., of detecting a discrete event that eventually acts as a signal to some response. The theory we have considered here is that detection proceeds by the system appreciating any instantaneous input by its departure from past activity. This mechanism of signal transduction provides a uniquely powerful and coherent account of the formal features of the actions of neuronal cell-surface, opioid-signaling systems as well as of cytotoxic agents acting on the nuclear systems that govern cell replication and the adaptive plasticity that regulates synaptic strength. The mechanism defines a single process, a remarkable feature of which is to generate outcomes that are paradoxical and outlast stimulation. One challenge for future research is the identification of the neurobiological substrates of what is here referred to as mean past activity. In the particular case of opioid-responsive nociceptive systems, evidence suggests that the expression of immediate-early genes (i.e., *C*-fos in spinal-cord dorsal-horn neurons) may perhaps *(10)* constitute one such substrate.

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