Multiple Modes of Activity in a Model Neuron Suggest a Novel Mechanism for the Effects of Neuromodulators

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SUMMARY AND CONCLUSIONS

1. Previous examination of the phase space of a mathematical model of a bursting molluscan neuron has demonstrated the existence of multiple stable oscillatory modes. The present study examined the extent to which multistability could be regulated by known modulatory agents, the consequences of that regulation on the response of the neuron to synaptic inputs, the effects of noise, and the potential of multistability to enrich the repertoire of neuromodulatory effects.

2. Coexisting stable attractors may appear when a change is made in a voltage-dependent conductance in a manner that simulates the application of a neuromodulator. A small transient perturbation can shift the model neuron between stable modes, greatly amplifying the original perturbation. Thus the model becomes more sensitive to conventional synaptic inputs. These mode shifts are robust in the presence of low-amplitude synaptic noise.

3. In response to random high-amplitude synaptic noise, a model neuron rendered multistable by a simulated application of a neuromodulator produces apparently random activity, whereas in response to the same synaptic noise, a monostable model neuron produces barely perturbed regular activity. Thus an increase in the number of attractors enhances sensitivity to both conventional synaptic inputs and noise. Conversely, a decrease is associated with a reduction in sensitivity.

4. The response of a neuron to a subsequent transient perturbation in the level of neuromodulator depends on the steady-state level of the neuromodulator. For example, if the steady-state level is associated with a multistable neuron, a mode shift produced by such a transient change in the level of neuromodulator (manifested in our model as a conductance change) can persist after the conductance is returned gradually to its original value. Thus multistable dynamic activity permits the effects of a neuromodulator to persist when the neuromodulator is no longer present.

5. The mechanism of mode shifting between coexisting stable oscillatory modes introduces a number of novel possibilities with potentially profound implications for information processing and storage in a single neuron.

INTRODUCTION

Neuromodulators are agents that alter key biochemical and biophysical parameters in nerve cells. These parameter changes can manifest themselves via alterations in the spontaneous electrical activity of the cell, in its excitability, in the shape of the action potential, or in excitation-secretion coupling (e.g., Byrne et al. 1993; Kaczmarek and Levitan 1987). Recently, we described a novel, parameter-independent mechanism for altering neuronal activity that exploits the intrinsic nonlinear dynamical properties of neurons (Canavier et al. 1993a). Transient synaptic inputs, which produce transitions between various dynamic modes, also produce persistent changes in electrical activity. Thus there appear to be at least two fundamentally different ways of changing a cell's activity. In this study, we address the interaction between these two mechanisms, activity changes arising from neuromodulator-induced parameter changes and activity changes arising from mode-switching with fixed parameters. To examine these interactions, we have focused on a well-described example of a nonlinear oscillator, neuron R15 in the abdominal ganglion of Aplysia.

Several modulatory agents are known to affect the electrical activity of R15. Two such agents, serotonin (5-HT) and dopamine (DA), appear to act via the second messenger cascades associated with adenosine 3',5'-cyclic monophosphate (cAMP) and guanosine 3',5'-cyclic monophosphate (cGMP), respectively. Serotonin (at low concentrations) increases the anomalous rectifier conductance (g_R) (Adams and Benson 1985; Benson and Adams 1987; Benson and Levitan 1983; Levitan and Levitan 1988b; Lotshaw and Levitan 1988), and dopamine decreases a slow inward calcium conductance (g_S) (Levitan and Levitan 1988a, Lewis et al. 1984). The application of 5-HT or DA frequently renders a cell silent, but in other cases, 5-HT induces a type of bursting in which the hyperpolarized phase is enhanced (Levitan and Levitan 1988b), and cGMP (and by analogy DA) induces a beating mode (Levitan and Levitan 1988a). Some of the variability in the response to the application of neuromodulatory agents can be explained by the dependence of neuromodulation on the initial bias of the cell (Canavier et al. 1991).

In both theoretical and experimental studies, neuronal oscillators frequently are assumed to be monostable with respect to a given set of parameters. That is, irrespective of how the model is initialized, a single robust mode results from the convergence of all trajectories in the phase space of the model onto a single, globally attractive point or connected set of points (Rinzel and Ermentrout 1989). However, even the simplest nonlinear systems are capable of supporting multiple attractors consisting of single points (equilibria or steady states), and those with at least three state variables theoretically can support a veritable menagerie of equilibria, limit cycles, and strange attractors (Guckenheimer and Holmes 1983; Thompson and Stewart 1986). We recently reported the occurrence of multistability in a model of R15 (Canavier et al. 1993a), in which several types of bursting activity were found to coexist with beating activity, and a single simulated excitatory postsynaptic potential (EPSP) was sufficient to switch the mode of activity.
FIG. 1. Simulated effects of neuromodulators. Simulated electrical activity of the R15 model is shown under three conditions. A: in this control simulation, $I_{	ext{TETM}}$ is set to 1.3 nA, $g_{\text{Na}}$ is set to 0.32 $\mu$S, and $g_{\text{K}}$ has been set to 0.9 $\mu$S to avoid the region of multiple attractors (see Fig. 4). B: reducing $g_{\text{Na}}$ by 50% to simulate the effect of dopamine (DA) induces a beating state. This result agrees with those produced by experimental applications of cGMP (Levitan and Levitan 1988a), through which DA appears to exert its effects. C: increasing $g_{\text{K}}$ by 50% to simulate the effect of serotonin (5-HT) produces a type of bursting in which the hyperpolarized phase is enhanced, as is observed in response to low concentrations of 5-HT (Levitan and Levitan 1988b).

In the current study, we have extended our work on multimodal activity in R15 by exploring the interaction of coexisting stable modes of oscillatory activity with neuromodulation. These modes correspond to multiple attractors in the phase space of the model. By examining the evolution of the phase portrait of the system as a critical parameter is modified, we have identified two effects that could only be observed in the presence of these multiple oscillatory modes. The first observed effect is a transition from bursting to beating via a gradual increase in the number of attractors from one to many, followed by a gradual decrease to a single attractor. The second observation, namely hysteresis, is an inevitable corollary to the existence of the multistable transition. In the multistable transition, the neuromodulatory agent can be envisioned as driving the system through regions in which sensitivity to synaptic input is heightened. This heightened sensitivity results because transient synaptic inputs are amplified when they produce mode shifts from one attractor to another. These shifts can occur only in regions of parameter space that support multiple attractors. Hysteresis occurs because, in a region of multiple attractors, the electrical activity of the system depends not only on the current concentrations of neuromodulatory agents (incorporated into this model only as the relative values of their target conductances), but also on the past history of neuromodulatory activity. Preliminary reports of some of these results have appeared in abstract form (Canavier et al. 1993bc).

METHODS

Model simulations were performed on a Sun Microsystems SPARCstation 2. The code is written in “C” and calls a FORTRAN subroutine RADAU5.F provided by Dr. E. Hairer. The subroutine implements a variable step size fifth-order implicit Runge-Kutta integration method for stiff systems (Hairer and Wanner 1991). The phase portraits were produced by first using arbitrary initial conditions and then, as attractors were identified, by perturbing trajectories on identified attractors in an effort to identify adjacent attractors, as well as by picking initial conditions in what appeared to be a region of phase space that had not been well explored by the perturbed trajectories. The perturbations were accomplished using transient synaptic inputs as described in Canavier et al. (1993a). Also as in Canavier et al. (1993a), the simulations were allowed to run for 6 h of simulation time to confirm that the attractors, particularly those that were not simply periodic, were not merely transients. We did not implement more stringent tests, such as computing their Lyapunov exponents (Wolf 1986).

All equations and parameters (with the exception of the modifications described in the results) were as previously described in Canavier et al. (1991). Note that a factor of $1/g_{\text{NS}}$ was included erroneously in the scaling factor for $I_{\text{Na}}$ in the material balance equation for calcium in the original paper. All our simulations (Canavier et al. 1991, 1993a) including the current paper use the equation as published. This error has only the effect of changing our stated assumption regarding the fraction of the current carried by Ca$^{2+}$ ions. In view of the lack of data on this point, a somewhat arbitrary assumption is required in any case, and its exact formulation is not a critical aspect of the model. Thus our results are not compromised by this factor.

RESULTS

Conventional neuromodulation

We began by simulating the conventional effects of 5-HT and DA on the electrical activity of R15 (see also Canavier et al. 1991). In Fig. 1, the parameter values associated with the simulations shown in all three panels support only a single mode of activity (see below). Reducing $g_{\text{Na}}$ to simulate the effects of DA (Fig. 1B) induced a beating mode by changing the stability of the unique operating point of the system with respect to the slow oscillations underlying bursting activity (Canavier et al. 1991). Increasing $g_{\text{K}}$ to simulate the effect of 5-HT (Fig. 1C) enhanced the hyperpolarizing phase of the burst. Thus this figure illustrates conventional parameter-dependent neuromodulation, in which a shift in the output activity is the result of a change from a unique characteristic activity at one set of parameter
values to a second characteristic activity unique to the second set of parameter values.

Neuromodulation induces a multistable transition

Having examined the effects of relatively large changes in $g_R$ and $g_{Si}$, we proceed to examine the continuum of effects produced by the intermediate values of these parameters. These examinations revealed that there is another, not well-explored, mechanism by which neuromodulation can alter the activity of a neuron. Two-dimensional phase-plane projections that illustrate the phasic relationship of selected state variables of the model can provide useful insights into the dynamic activity of this complex, 11-dimensional model, particularly the projection that includes the following two slowly varying quantities: free calcium concentration and the activation of the slow inward current. Figure 2 shows seven different phase portraits of this type generated at seven different values of $g_R$, with all other parameters fixed. As one proceeds in a clockwise direction, the value of $g_R$ is increased. Initially, only a beating attractor is observed (Fig. 2A). Then a rather small bursting attractor appears, followed by the appearance of an intermediate 2P attractor (the activity repeats every other burst). As $g_R$ is increased, the amplitude of the slow oscillation underlying the burst (associated with the outmost attractor) is increased. This increase is reflected in a greater excursion in calcium concentration and activation of the slow inward current, as well as in membrane potential (see Fig. 1C as compared with Fig. 1A). $g_R$ is active in the subthreshold voltage range in which the slow oscillation in membrane potential occurs, hence the enhancement of this oscillation as $g_R$ is increased. As $g_R$ continues to increase, several more intermediate bursting attractors appear, then disappear until only beating and a single bursting mode remain. At the highest values of $g_R$ examined (Fig. 2G), only a single bursting attractor is supported, completing this complex transition from beating to bursting.

Because the external stimulus current ($I_{stim}$) also induces a transition from bursting to beating in the model (Canavier et al. 1991) via multistability (Canavier et al. 1993a), we examined the behavior of the model as a function of $I_{stim}$ as well as of $g_R$. By varying the two parameters at once and exploring the phase space, one can obtain information regarding the size of parametric region in which multistability occurs. If this region were very narrow, one could not expect to observe it experimentally nor for the cell to utilize it for some biological purpose. This parametric region appears to be relatively large, however. Figure 3 illustrates the multistable transition region in which at least two competing stable attractors coexist. So far, exactly one of these attractors has always been found to be a beating attractor. In the transition of Fig. 2, $I_{stim}$ was held constant so this transition occurs along a straight line in the $g_R$ vs. $I_{stim}$ plane of the parameter space of the model (as shown by the arrow in Fig. 3).

The examination of the continuum of responses to small incremental parameter changes was repeated with respect to another membrane conductance, $g_{Si}$. Like $g_R$, $g_{Si}$ is associated with the production of the slow wave and is a target of a neuromodulatory agent (DA in this case). Figure 4 illustrates a bifurcation from beating to bursting that is structurally quite similar to the one observed in Fig. 2. In this case, $g_{Si}$ is increased as one moves in a clockwise direction between the five phase portraits that are presented. In both cases, bi- or multistability occurs in a significant fraction of the parameter range. Thus the neuromodulatory agent can be conceived of as regulating the eligibility of a neuron for modal activity.

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FIG. 3. Multistable transition region in parameter space. This figure illustrates the $g_R$ vs. $I_{stim}$ plane section of the parameter space of the model. In the region shown, this plane is divided into a bursting region, a beating region, and a multistable transition region. For example, the evolution of the attractors in phase space (see Fig. 2) shows a multistable transition from beating to bursting as the parameter space is explored along the path indicated by the arrow at $I_{stim} = 1.3$ nA. The area of the bistable region should be considered the minimum possible region because our method does not guarantee that we have found all possible attractors in the regions that appear to be monostable.
Heightened sensitivity to synaptic input

If the application of a neuromodulatory agent caused a neuronal oscillator to enter a regime of multistability, what would be the observable effects? We have shown previously that in the regions of parameter space that support multiple attractors, a single transient synaptic input can change the mode of activity from one attractor to another in a highly phase sensitive manner (Canavier et al. 1993a). By regulating the occurrence of multistability in a neuron, a neuromodulatory agent could propel the system through a region of parameter space in which a synaptic input can have a dramatic and long-lasting effect on the output electrical activity. For example, Fig. 5 compares the response of a multistable (Fig. 5A) and a monostable (Fig. 5B) neuron to an identical train of synaptic input. The multistable neuron is eligible for a mode shift (from a bursting to a beating mode in this case), whereas the monostable neuron is not. Thus in B the train of synaptic input produces a transient change in the activity of R15, but bursting identical to that before the stimulation appears after ~1 min. In contrast, the train of synaptic input in A produces a persistent change in the activity of R15 by inducing a mode transition.

For mode shifts such as the one illustrated in Fig. 5 to be biologically relevant, these shifts must be able to withstand moderate amounts of background noise. Figure 6 illustrates a mode shift from a bursting mode to a beating mode. This simulation was conducted in the presence of low-amplitude, random EPSPs (Poisson process interevent intervals) intended to approximate synaptic noise. Thus the mode shifts are robust in the presence of such noise. On the other hand, because we have shown that a single simulated large
amplitude EPSP in R15 can induce a mode shift, such a mode shift would not be robust to subsequent EPSPs of the same amplitude. The effect of a random train of large amplitude EPSPs on both a monostable and a multistable simulated neuron is contrasted in Fig. 7. In a monostable neuron, the effects of such perturbations are minimal (Fig. 7A). In a multistable neuron, however, the EPSPs often perturb the activity away from its current basin of attraction, producing highly variable activity (Fig. 7B). The simulated neuron has the phase space ranging from the innermost attractor to the outermost attractor available to it rather than just a narrow band in the vicinity of a single attractor. In 0.1-Hz mean-frequency noise, the simulation is continually in a transient state, never really “settling down” on one attractor.

Neuromodulatory hysteresis

The finding that neuromodulators could regulate the expression of multistability raised the possibility that the effects of neuromodulators may themselves be dependent on the state of the system. Here we refer to the parameter settings associated with steady-state levels of neuromodulators as the state of the system, as opposed to the engineering usage of the state of the system defined by the values of the state variables of the model. As a transient modulatory effect dissipates, the mode of activity could fail to return to the original pattern and instead settle on a competing attractor. To test this possibility, we ran simulations that compared the response of the model to simulated pulses of neuromodulator that drove the concentration of neuromodulator to identical levels, but from two different initial background levels of neuromodulator. Fig. 8A shows the consequences of monostable dynamics at both initial, intermediate, and final values of the simulation. Here, the simulation was initiated with an initial value of $g_{SI} = 0.9 \mu S$ (bursting attractor only, Fig. 4E), then $g_{SI}$ was treated as a time varying parameter to simulate a change in the level of a neuromodulatory agent. The value of $g_{SI}$ was depressed to 0.6 $\mu S$ (beating attractor only, Fig. 4A) long enough to establish beating activity. Then $g_{SI}$ was allowed to return gradually to its original value. As expected in the conventional view of neuromodulation, the original pattern of activity is reestablished after the simulated washout. In contrast, Fig. 8B illustrates a simulation initiated in the outermost bursting mode, shown in the phase portrait in Fig. 4C, associated with $g_{SI} = 0.747 \mu S$ (8 attractors). Then $g_{SI}$ was again reduced to 0.6 $\mu S$ to induce beating, and $g_{SI}$ was allowed to return gradually to its original value. However, the initial bursting activity was not reestablished because this manipulation resulted in the trajectory in phase space being “captured” by the innermost beating attractor. The gradual return (analogous to washout) is critical. For shorter time constants, the resultant trajectory is captured by one of the intermediate attractors.

DISCUSSION

We have used nonlinear dynamical analysis of a model of a neuronal oscillator to predict that biological neurons with the capacity to exhibit bursting behavior also can exhibit multistability under certain conditions (e.g., at an intermediate concentration of neuromodulator between those that produce bursting and beating activity). Thus at certain levels of neuromodulation, changes in neuronal activity, which we have termed parameter-independent mode shifts, should be observable that can be explained in terms of the nonlinear dynamics of the oscillatory neuron. We further suggest that such activity may characterize many bursting neurons (under the appropriate circumstances), and that depending on the particular context, multistability may have important functional consequences. In the following discussion, we cite support for the generality of the exis-
tence of multistable transitions, give some specific examples of rhythmic neuronal activity in which we suggest that multistability may exist, and speculate on its functional significance.

Although the physiological role of bursting in R15 is unclear (Alevizos et al. 1991), recent experimental work indicates that the neuron exhibits multistability (Lechner et al. 1994a,b). Additional experimental work is necessary to gain insights into the physiological relevance of multistability in R15. Irrespective of the answers that R15 provides to these questions, we believe the insights gained from this modeling study may be quite general and that the instances of their application may be found in a variety of neurons and neural circuits.

Existence and generality of the multistable transition

In addition to our own observations of coexisting oscillatory modes in our model of R15, there is support for the generality of this phenomenon from other modeling and empirical studies. Other models of bursting cells (e.g., Bertram 1993; T. Chay, personal communication) have parametric regions in which beating and one or two types of bursting coexist. This observation, coupled with the presence of more than one attractor in certain parametric regions of many oscillatory systems (Doedel 1981; Guckenheimer and Holmes 1983; see also Destexhe et al. 1993; Rinzel and Lee 1987), suggests that bi- or multistable transitions may be a generic attribute of models that can produce bursting activity. Thus physiological neuronal oscillators very likely have the potential for multistability. A separate issue is whether, under physiological conditions, bursting neurons ever enter the regions of parameter space that support the coexistence of stable oscillatory modes. Preliminary results indicate that R15 does indeed exhibit this type of multistability (Lechner et al. 1994a,b). Intracellular injection of brief depolarizing current pulses at various times during the burst phase and postburst afterhyperpolarization can switch the electrical activity of R15 between bursting and beating modes. These transitions are produced most readily in low concentrations of 5-HT. In addition, data from lobster stretch receptor somata support the coexistence of at least two oscillatory modes (Calvin and Hartline 1977).

The functional significance of coexisting bursting and beating modes in R15 is presently unknown. However, several types of differential functional effectiveness for the two modes have been suggested. For example, in an identified crayfish motor neuron (Gillary and Kennedy 1969) that has

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**FIG. 7.** Multistability amplifies the response to synaptic inputs: high-amplitude noise generates apparently random activity. The response of a monostable simulated neuron to a train of random synaptic inputs ($\beta_{SVN} = 1 \mu S$) is contrasted with the response of a multistable neuron to an identical train. $I_{\text{STIM}}$ is 1.3 nA, and $g_{\text{e}}$ is 0.747 $\mu S$. $A$: at $g_{R} = 0.25 \mu S$ (Fig. 2A) only a single attractor exists, and it is associated with beating activity. The simulated EPSPs barely perturb the pattern of output activity in the monostable case. $B$: here $g_{R} = 0.32 \mu S$ (Fig. 2D) and numerous bursting attractors coexist with the beating attractor. This simulation is much more random in appearance because of the competition between the attractors. A half-dozen potential mode shifts occurred in the space of 3 minutes. $C$: timing of the synaptic inputs.
both a bursting mode and a beating mode, the bursting pattern is far more effective in evoking muscle contractions than the beating pattern. Similarly, bursting patterns of activity have been shown to be more effective than beating patterns with the same average frequency in releasing hormones from neurosecretory cells (Dutton and Dyball 1979; Poulain and Wakerly 1982) and in neurotransmitter release (Gonon 1988). Another type of differential effectiveness of bursting and beating (also referred to as single spike or tonic) firing modes has been suggested for both thalamic neurons (Livingstone and Hubel 1981; McCormick and Feeder 1990; McCormick et al. 1992) and cortical neurons (Metherate et al. 1992; Steriade and McCarley 1990): the responsiveness of thalamic neurons to sensory input and of cortical neurons to thalamic input is reduced when they are in a bursting mode compared with a beating mode (Livingstone and Hubel 1981; for a review see Steriade et al. 1993).

Neuronal oscillators with the potential for functional neuromodulator-induced multistable transitions

Neuromodulator-induced multiple attractors analogous to those observed in R15 also might play an important role in other neurons and neural circuits such as those generating patterned motor activity (Delcomyn 1980; Selverston 1985). For example, a multistable neuron in a central pattern generator (CPG) could be induced to function as a mode selector. Random synaptic input to the CPG could serve to sample its phase space. As the activity produced increasingly desirable results, feedback circuitry could reduce the frequency and/or the duration of the synaptic inputs, until the CPG stabilized in the favored attractor. This type of mode selection assumes that all modes are somewhat robust to noise (see Fig. 6). A simpler variation on the theme of mode selection is illustrated by the dynamics of
the R15 model with $g_R = 0.33 \mu S$. In this case, there are two attractors (see Fig. 2F), but the basin of the beating attractor is very small (not shown). That is, any perturbation or noise will lead to bursting activity, except for strong synaptic input that has a frequency close to that of the beating attractor. Thus a presynaptic input with an appropriate frequency and intensity could select the beating mode that is otherwise unattainable in a bistable neuron. Alternatively, if the circuit governed flight or avoidance behavior, unpredictability might be an asset, and synaptic input or noise could produce nonstationary output as the CPF continually bounced between attractors. The circuit then would function as a generator of apparently random activity (see Fig. 7B). A neuromodulator could regulate the expression of this random activity, which also could serve to prevent entrainment. Similar functions have been suggested for chaotic activity (Conrad 1986).

Recent research on the stomatogastric ganglion of crustaceans has contributed to the prevailing view that many pattern-generating circuits are polymorphic; that is, neuromodulatory inputs can reconfigure these circuits in numerous ways to produce different patterns, which in turn are associated with different behaviors (for reviews, see Harris-Warrick and Marder 1991; Harris-Warrick et al. 1992; Selverston 1992). The neuromodulator-induced shifts from one pattern to another heretofore have been interpreted solely in terms of parameter-dependent shifts; however, if one considers the entire network as a single dynamical system, the possibility exists that some of the pattern shifts correspond to parameter-independent mode shifts. Neuromodulator-induced transitions between oscillatory modes also have been observed in thalamic and cortical neurons. For example, brain stem cholinergic activation of thalamocortical cells or direct application of neuromodulator (e.g., acetylcholine) changes the firing pattern of thalamocortical relay neurons from a bursting pattern to tonic firing of single spikes (beating) (McCormick 1992). Functionally, this transition to beating is associated with an increase in responsiveness to synaptic input. Cholinergic modification of rhythmic burst generation also occurs in the bursting pyramidal neurons found in the cortex. These neurons burst rhythmically when a small tonic depolarization is applied, and acetylcholine induces a transition to the beating mode. Metherate et al. (1992) suggest that these neurons act as cortical pacemakers and that the neuromodulator-induced transition from bursting to beating in these neurons contributes to activation, or the transition undergone by the electroencephalogram during waking. It is not unreasonable to suppose the nonlinear dynamics underlying the bursting activity in thalamic and cortical cells also have parametric regions that support multistability. It is intriguing to speculate that certain conditions might invoke multistable modes and that transitions between these modes could potentially either disrupt or enhance normal rhythmic brain activity associated with arousal and attentiveness.

Future directions

Although our focus is on the physiological significance of multistability, further theoretical work is necessary to understand what gives rise to multistability from a nonlinear dynamical perspective. Given the equations of our model (or any model) we cannot predict a priori the parameter regions in which multistability will occur. In fact, other models of bursting cells predict a chaotic rather than a multistable transition region between bursting and beating in some cases (Canavier et al. 1990; Chay and Rinzel 1985), and such a transition has been observed experimentally in an Onchidium pacemaker neuron (Hayashi and Ishizuka 1992). Because it is not clear under what conditions one should expect one type of transition versus the other, the clarification of this point may prove a fruitful area for further research.

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