Electrical Coupling Between Model Midbrain Dopamine Neurons: Effects on Firing Pattern and Synchrony

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Received 30 March 2001; accepted in final form 30 October 2001

Komendantov, Alexander O. and Carmen C. Canavier. Electrical coupling between model midbrain dopamine neurons: effects on firing pattern and synchrony. J Neurophysiol 87: 1526-1541, 2002; 10.1152/jn.00255.2001. The role of gap junctions between midbrain dopamine (DA) neurons in mechanisms of firing pattern generation and synchronization has not been well characterized experimentally. We modified a multi-compartment model of DA neuron by adding a spike-generating mechanism and electrically coupling the dendrites of two such neurons through gap junctions. The burstgenerating mechanism in the model neuron results from the interaction of a N-methyl-D-aspartate (NMDA)-induced current and the sodium pump. The firing patterns exhibited by the two model neurons included low frequency (2-7 Hz) spiking, high-frequency (13-20 Hz) spiking, irregular spiking, regular bursting, irregular bursting, and leader/follower bursting, depending on the parameter values used for the permeability for NMDA-induced current and the conductance for electrical coupling. All of these firing patterns have been observed in physiological neurons, but a systematic dependence of the firing pattern on the covariation of these two parameters has not been established experimentally. Our simulations indicate that electrical coupling facilitates NMDA-induced burst firing via two mechanisms. The first can be observed in a pair of identical cells. At low frequencies (low NMDA), as coupling strength was increased, only a transition from asynchronous to synchronous single-spike firing was observed. At high frequencies (high NMDA), increasing the strength of the electrical coupling in an identical pair resulted in a transition from high-frequency single-spike firing to burst firing, and further increases led to synchronous high-frequency spiking. Weak electrical coupling destabilizes the synchronous solution of the fast spiking subsystems, and in the presence of a slowly varying sodium concentration, the desynchronized spiking solution leads to bursts that are approximately in phase with spikes that are not in phase. Thus this transitional mechanism depends critically on action potential dynamics. The second mechanism for the induction of burst firing requires a heterogeneous pair that is, respectively, too depolarized and too hyperpolarized to burst. The net effect of the coupling is to bias at least one cell into an endogenously burst firing regime. In this case, action potential dynamics are not critical to the transitional mechanism. If electrical coupling is indeed more prominent in vivo due to basal level of modulation of gap junctions in vivo, these results may indicate why NMDA-induced burst firing is easier to observe in vivo as compared in vitro.

INTRODUCTION

Midbrain dopaminergic (DA) neurons have been shown to be of great importance in different aspects of brain function such as reward-mediated learning, movement control, cognition, and motivation (Schultz 1998). They are involved in such clinical disorders as Parkinson's disease (Ljungberg et al. 1992), schizophrenia (Weinberger 1987), and drug addiction (Koob et al. 1987). Midbrain DA neurons are located in three adjacent regions: ventral tegmental area (VTA or A10), the substantia nigra pars compacta (A9), and the retrorubral area (A8). These neurons comprise a relatively homogenous population by virtue of their similar electrophysiological properties (Cardozo and Bean 1995; Yung et al. 1991).

DA neurons exhibit two major patterns of membrane potential discharge in vivo: single spike firing and burst firing (Freeman et al. 1985; Grace and Bunney 1983a), whereas in a slice preparation, mostly single-spike firing is observed (Kita et al. 1986; Sanghera et al. 1984; Shepard and Bunney 1988; Yung et al. 1991), presumably due to the loss of synaptic afferents. Bursts may be observed experimentally in slice preparations using some pharmacological manipulations that may mimic the effects of synaptic afferents in vivo. Two mechanisms of bursting have been proposed for DA neurons based on two pharmacological manipulations that induce burst firing in vitro: the application of apamin (Nedergaard et al. 1993; Ping and Shepard 1996) and of N-methyl-D-asparic acid (NMDA) (Johnson et al. 1992). An intrinsic, voltage-dependent calcium current and calcium dynamics are implicated in the first, apamin-sensitive mechanism, whereas the NMDA-induced current and sodium dynamics are implicated in the second one. We postulate that the apamin-sensitive mechanism is largely located in soma, whereas the NMDA-burst firing mechanism is largely dendritic. There is some evidence that burst firing in midbrain DA neurons in vivo results from tonic activation of NMDA receptors by endogenous excitatory amino acids (Chergui et al. 1993). As a first approximation, in this study we have focused only on the NMDA-induced burst firing mechanism and its modulation by electrical coupling.

There is no consensus regarding the mechanisms of burst firing in vivo, and the mechanisms of burst firing in vitro are controversial as well. There is emerging data showing that the two mechanisms proposed in vitro are actually distinct, although they may exhibit synergy on occasion, because apamininduced burst-firing persists in the presence of the NMDA antagonist 2-amino-5-phosphonovalerate (APV) (Shepard et al. 2000) and NMDA-induced burst-firing persists in the pres-

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ence of nifedipine (Wu et al. 2000), which has been shown to block apamin-induced bursting (Ping and Shepard 1996). NMDA-induced burst firing in a slice preparation has often been overlooked, perhaps because to observe it certain manipulations are often required, such as the injection of hyperpolarizing current and/or the application of apamin (Johnson et al. 1992; Seutin et al. 1993) or waiting several minutes and using intracellular instead of extracellular electrodes (Wang et al. 1994). The sodium dependence of burst firing and the role of the sodium-potassium pump (Canavier 1999) are also not universally accepted, but there are examples of other cells with similar mechanisms (Angstadt and Friesen 1991; Ballerni et al. 1997; Del Negro et al. 1999), and this mechanism is the best fit to the available data (Johnson et al. 1992).

Electrical coupling via gap junctions is a widely observed phenomenon in assemblies of excitable cells. Recent theoretical and experimental studies point to a much more significant role for electrical synapses in neuronal communication than was previously realized (see for review Perez-Velazquez and Carlen 2000). The relevance of gap junction conductance to neuronal functions was previously thought to be limited to early brain development. In the immature brain, there are numerous gap junctions, but their numbers decline rapidly as maturation progresses (Peinado et al. 1993; Rozental et al. 1998). Therefore gap junctions were thought to be required for early brain development but mostly vestigial in the mature mammalian CNS. However, we now know that electrical gap junction communication exists even between mature nerve cells. Gap junctions have been proposed to be responsible for synchronization of signals in the inferior olive (Llinás et al. 1974), among hippocampal CA3 neurons (MacVicar and Dudek 1981), in the retina (Vaney 1993), and for generation and stabilization of bursting oscillatory behavior in hippocampal networks (Perez-Velazquez et al. 1994; Skinner et al. 1999).

An important feature of gap junctions is that they can be dynamically modulated by number of factors such as intracellular pH, voltage, neurotransmitters, and second messengers. The unitary conductance of different gap junction channels varies between 30 and 300 pS. This coupling is not constant as intracellular acidification (pH \leq 6.8) reduces gap junctional conductance and blocks electrical coupling, whereas intracellular alkalinization (pH \geq 7.8) increases junctional conductance. Gap junction conductance can be modified rapidly over a time scale of seconds (Spray et al. 1981, 1986). Gap junctions and electrical coupling can be modulated by DA in different neuronal networks (Cook and McReynolds 1998; Johnson et al. 1993; Velazquez et al. 1997), but the effects of DA on gap junctions between midbrain DA neurons are unknown.

There is some evidence for electrical and dye coupling between neighboring midbrain DA neurons (Grace and Bunney 1983b). Dye coupling was observed occasionally that occurred between somata and more frequently between initial thick segments of major dendrites. Within the substantia nigra pars compacta, a single DA neuron may be coupled with one to five similar cells. Simultaneous recordings from neighboring dopamine neurons in vitro (Grace and Bunney 1983b) provided indirect evidence of the importance of electrical coupling in synchronization of their firing discharges. However, it is not known if electrical coupling contributes to the regulation of burst firing in midbrain dopamine neurons, and corresponding direct experimental data regarding its possible role has not yet been obtained. Therefore we used computational simulations to predict how electrical coupling might change the firing pattern or synchronize the activity of DA neurons depending of level of NMDA excitatory inputs to them. Preliminary reports of our findings have been published in abstract form (Komendantov and Canavier 2000a,b).

METHODS

Model

In present studies, we used a version of the three compartment model of a DA neuron described by Canavier (1999) that was modified by the addition of a spike-generating mechanism in each compartment. Each of two model neurons consisted conceptually of a soma and four dendrites, although symmetry considerations allowed the four dendrites to be lumped together.

The soma was modeled as a cylinder 15 μ M in diameter and 15 μ M long. The nonbranching dendrite was subdivided into proximal and distal compartments. Proximal dendrites and distal dendrites were also modeled as cylinders 2 and 1 μ M in diameter and 150 and 350 μ M in length, respectively. This simple model with few compartments maintains a general correspondence between its geometrical morphology parameters (Juraska et al. 1977; Preston et al. 1981; Tepper et al. 1987) and the electrical activity (Johnson et al. 1992; Paladini et al. 1999; Wang et al. 1994) of realistic DA neurons. The model was modified by adding a spike-generating mechanism in each compartment (Fig. 1A), including a fast sodium current I_{Na} and an outward potassium current I_A . Somatic and dendritic membranes of DA neurons have a similar sodium channel density (Häusser et al. 1995), therefore in our simulation, conductances for TTX-sensitive sodium current were equal in each compartment. Voltage-gated transient potassium channels in some of bursting CNS neurons (hippocampal pyramidal neurons) are distributed nonuniformly: their density increased with distance from soma (Johnson et al. 2000). Therefore we increased the conductance for I_A in distal dendritic compartments compared with soma and proximal dendrites. In addition, kinetics were added to the steady-state gating characteristics of delayed rectified current, $I_{K,DR}$ in the original model so that it could contribute appropriately to action potential repolarization.

Different values for specific capacitance in somatic and dendritic compartments (1 and 5 μ F/cm², respectively) were used in the original model of DA neuron (Canavier 1999) to match data on time constants measured experimentally at the soma. However, to more reliably model spiking, we reduced the dendritic capacitance to 2 μ F/cm². Different values for voltage for half-maximum activation of sodium channels $(V_{half,m})$ and voltage for half-maximal inactivation of sodium channels were required to permit an action potential in dendritic compartment to trigger an action potential in the soma (see Häusser et al. 1995)-this is an artifact caused by the large lumped compartments. As in the original model, NMDA-gated currents were localized to distal dendritic compartments, and kinetics were added to their steady-state characteristics (Mayer and Westbrook 1987). Alterations in sodium dynamics were made (Fig. 1B) to compensate for the addition of I_{Na} . Only one-quarter of the somatic volume was used for sodium accumulation.

As a first approximation, we did not include calcium dynamics or Ca-activated potassium conductances. Injection of hyperpolarizing current in both neurons was simulated to obtain a diversity of patterns, including burst firing, which correspond to experimental data. This manipulation is required in some experiments in slice preparation (Johnson et al. 1992; Seutin et al. 1993, 1994; but see Mereu et al. 1997) and presumably would not be required in an in vivo model. Two

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FIG. 1. Schematic representation of the model of single dopaminergic (DA) neuron. A: equivalent circuit representation. \rightarrow , a voltage-dependent conductance, whereas those without an arrow are linear. In the dendritic compartment, a switch is used to indicate that synaptic conductance may be turned on or off. B: sodium ion material balance. The currents contributing to the sodium material balance are indicated. Only part of volume of the soma is available for sodium accumulation.

synaptic currents that are important in vivo and that were included in the in vitro model of Canavier (1999) were omitted in this study: the current evoked by GABA agonists was not included because the application of GABA agonists was not simulated in this study, and the current evoked by AMPA was not included because only the subset of glutamatergic receptors activated by NMDA directly induces burst firing and was sufficient to show the effects of electrical coupling on burst firing.

The dynamics of membrane potential and sodium were described by eight first-order differential equations per compartment for variables V, $[Na]_{in}$, m, h, n, p, q, s (p in distal dendrite only). The single-model neuron and the two coupled-model neurons were therefore described by 22 and 44 differential equations, respectively. Simulations of coupled neurons were initialized with a 10 mV difference in dendritic membrane potential to break the symmetry. The model equations and parameters are described in the APPENDIX.

The simulations were conducted using values for all parameters that are in the physiologically observed range, including coupling conductance corresponding to several open gap junction channels with a conductance of 150–300 pS each. Frequencies of model neurons and burst duration also were in the range of experimental observations (Grace and Bunney 1984). Distal dendrites of two model neurons were coupled via a simulated gap junction (Fig. 2) in the majority of simulations. However, we also coupled these neurons via proximal dendrites and somata to check the effect of location of the coupling zone on activity and synchrony.

Model implementation

All simulations and programs for analysis were coded in the C programming language and run on a Compaq Alpha Server DS20E, a DEC Alpha 433au, and a Sun Ultra Enterprise 450. Numerical integrations of simulations of pairs of neurons were performed using an

implicit Runge-Kutta method of order five with variable step size (Hairer and Wanner 1996). The FORTRAN code implementation of this method is available at http://www.unige.ch/math/folks/hairer/ software.html. Typical run time for two coupled cells was \sim 5 min for 1 min of simulation in which high-frequency single spiking or bursting occurred.

Analysis of model activity

The time courses of V, intracellular Na and interspike intervals (ISI) were used for the analysis of model responses. Usually, the first 30-50 s of simulation time were excluded from analysis due to a transient period. The permeability for NMDA-induced current (P_{NMDA}) and the coupling conductance (G_{c}) were used as control parameters. The stationary and periodic solutions of the system were tracked in the parameter space order to detect bifurcation points for slow-wave oscillations in a model with blocked spike generation $(g_{\text{Na}} = 0)$. In a model when spike generation is enabled, ISIs were used for automated determination of modes of activity (single spiking, irregular spiking, bursting, or irregular bursting) and a quantification of their dynamics. For these purposes, the following special procedure was adopted: 1) run the simulation for 50 s of simulation time to allow the transients to decay. 2) Collect ISIs for 30 s. Let ISI_{max} equal the maximum and ISI_{min} equal the minimum of these ISIs. 3) If (ISI_{max} - ISI_{min} / $ISI_{max} \le 0.01$, the activity was classified as *regular spiking*. 4) If $ISI_{max}/ISI_{min} > 4$, the activity may be classified as one of *bursting* (regular or irregular). 5) If activity does not fulfill either the third or fourth selection criteria, then it was classified as *irregular spiking*. 6) To classify *bursting* activity the following test for regularity was used: a) the sequence of ISIs was checked again. The first interburst interval (IBI) was found in the series using following criterion: (IBI – $|ISI_{max}|/ISI_{max}| \leq 0.025$. b) After an IBI was identified, ISIs were collected until a subsequent IBI was found. Let $\{ISI_{1,n}\}$ and $\{ISI_{2,n}\}$



FIG. 2. Two model DA neurons electrically coupled by a gap junction with conductance G_c . DD, distal dendrite; PD, proximal dendrite.

define these two consecutive sequences of ISIs. Each pair of ISIs within each of the two successive bursts had to fulfill following criterion: $|(ISI_{1,i} - ISI_{2,i})/ISI_{1,i}| < 0.005$, where $i = 1, 2, 3 \cdots n$. 7) If bursting activity did not fulfill the sixth test, it was classified as *irregular bursting* or *leader/follower bursting* (see RE-SULTS). 8) For leader/follower bursting identification, ISIs of four consecutive burst cycles were selected from ISIs series (each burst cycle consists IBI and corresponding ISIs). If all ISIs of first and third burst cycles were fulfilled following criterion: $|(ISI_{1,i} - ISI_{3,i})/ISI_{1,i}| < 0.1$, and all ISIs of second and fourth burst cycles also were fulfilled the same criterion: $|(ISI_{2,i} - ISI_{4,i})/ISI_{4,i}| < 0.1$ (where $i = 1, 2, 3 \cdots n$) the activity was classified as *leader/follower bursting*. 9) If bursting activity did not fulfill the eighth test, it was classified as *irregular bursting*.

The selection criteria were determined empirically and confirmed by visual observation of the membrane potential waveform in many instances. Although these criteria for identifying burst firing were empirically determined and designed to apply specifically to the data set described in this study, they also correspond well with the available physiological data. Because the ratio between the shortest ISI and the average IBI was 1:5.5 for dopamine neurons in vivo (Grace and Bunney 1984) and was in the range of 1:7 to 28 for dopamine neurons in vitro (Seutin et al. 1994), our criterion of a ratio of 1:4 or greater between the shortest ISI and the longest IBI (which is also the longest ISI) would have identified bursting activity correctly in those cases as well.

Average and maximal frequencies and burst durations were calculated under different values of P_{NMDA} and G_c using collected ISIs. Also bifurcation diagrams for ISIs, Na-V phase plane projections were used for identification of different types of activity. To detect synchrony in two coupled cells, we applied a criterion of equality for 200 sequential corresponding pairs of membrane potential values: $V_{1,i}/V_{2,i} = 1 \pm 10^{-10}$, where $V_{1,i}$ and $V_{2,i}$ -computed values of membrane potential for first and second neuron, respectively; $i = 1, 2, 3 \cdots 200$. In addition, $V_1 - V_2$ phase portraits were used for detecting synchrony.

Nullcline analysis for the model simulated TTX block of spike generation

To use nullcline analysis, a graphical method in which the values of the state variables are plotted versus each other (see Rinzel and Ermentrout 1989), all state variables except the ones plotted ([Na] and V) have to be set to their steady-state value in terms of the plotted variables. Distal dendritic compartments are loci for NMDA-induced rhythmogenesis in DA neurons, and these neurons are coupled mainly via dendrites. Therefore a nullcline analysis was performed on the distal dendritic compartments in each neuron with the other neuron set to its fixed point to approximate its average activity. The analysis was simplified (Canavier 1999) using the assumption that the membrane currents in the soma and proximal dendrites can be approximated by an ohmic current that reverses at the resting membrane potential.

RESULTS

Activity of a single cell

As a prelude to the investigation of the dependence of a pair of coupled-model neurons on of $P_{\rm NMDA}$ and $G_{\rm c},$ the dependence of single-model neuron on P_{NMDA} was investigated. At the lowest values of P_{NMDA} , corresponding to a simulated low level of NMDA excitatory input, regular low-frequency (1–5 Hz) single-spike firing (Fig. 3A; $P_{\text{NMDA}} = 1.1 \cdot 10^{-6} \text{ cm/s}$) was observed. At higher levels of NMDA excitatory input, a bursting pattern is observed (Fig. 3A; $P_{\text{NMDA}} = 1.4 \cdot 10^{-6} \text{ cm/s}$), whereas at still higher levels of NMDA excitatory input, highfrequency spiking (>10 Hz) was observed (Fig. 3A; $P_{\text{NMDA}} =$ $1.7 \cdot 10^{-6}$ cm/s). In addition, at values intermediate between slow single-spike firing and regular burst firing, an irregular and possibly chaotic bursting waveform was observed (Fig. $3A; P_{\text{NMDA}} = 1.23 \cdot 10^{-6} \text{ cm/s}$). A bifurcation diagram was constructed by plotting the interspike intervals versus P_{NMDA} (Fig. 3B). At values of P_{NMDA} below $\sim 1.2 \cdot 10^{-6}$ cm/s, only a single value of the ISI is seen, as expected for regular single-spike firing. At values of P_{NMDA} between $\sim 1.2 \cdot 10^{-6}$ and $1.52 \cdot 10^{-6}$ cm/s, one long (>400 ms) and several short ISIs are observed, corresponding to the long interburst interval and the shorter ISIs within a burst. At values of $P_{\rm NMDA}$ above $\sim 1.52 \cdot 10^{-6}$ cm/s, a single value of the ISI is again observed, corresponding to high-frequency single-spike firing. Three instances of irregular firing can be observed in which there is a nearly continuous variation in the interspike intervals ($P_{\text{NMDA}} = 1.23 \cdot 10^{-6} \text{ cm/s}$, $P_{\text{NMDA}} = 1.26 \cdot 10^{-6} \text{ cm/s}$, and $P_{\text{NMDA}} = 1.335 \cdot 10^{-6} \text{ cm/s}$).

The bath application of TTX converts NMDA-induced burst firing in DA neurons to a slow "envelope" oscillation in membrane potential (without spikes) in the same frequency range as burst firing (Johnson et al. 1992). The presence of these slow oscillations was assumed to be the basis for burst firing (Canavier 1999; Johnson et al. 1992). Our simulations show that the same parameter settings that produce burst firing when g_{Na} is nonzero produce slow oscillations when g_{Na} is set to zero to simulate the application of TTX to block spike generation. For example, Fig. 4, —, shows a bifurcation diagram for the model with g_{Na} set to zero and an injected current of 56 pA. In this diagram, either the steady-state value of membrane poten-



FIG. 3. Dynamic response of model of a single DA neuron as a function of permeability for *N*-methyl-D-aspartate (NMDA)induced current (P_{NMDA}). To cut transient periods here and below, the first 30 s of simulations were not used for the analysis. A steady hyperpolarizing current $I_{\text{STIM}} = -28$ pA was applied. A: membrane potential. $\cdot \cdot \cdot , 0$ mV. A1: $P_{\text{NMDA}} = 1.1 \cdot 10^{-6}$ cm/s. A2: $P_{\text{NMDA}} = 1.23 \cdot 10^{-6}$ cm/s. A3: $P_{\text{NMDA}} = 1.4 \cdot 10^{-6}$ cm/s. A4: $P_{\text{NMDA}} = 1.7 \cdot 10^{-6}$ cm/s. B: bifurcation diagram for interspike intervals. The bifurcation parameter is P_{NMDA} . In this and subsequent figures, all parameters are given in the APPENDIX unless otherwise noted.

tial is plotted or, in the case of a slow oscillation, the minimum and maximum values of membrane potential are plotted, hence the oscillatory region is clearly demarcated. This region is contained within the region in which burst firing is observed when spike generation is enabled by setting g_{Na} to an appropriate value. A more extreme example of the extension of the oscillatory regime is given for an injected current value of 28 pA: the $\cdot \cdot \cdot$ in Fig. 4, for which g_{Na} is still equal to zero and which clearly shows that no slow envelope oscillation occurs at any value of P_{NMDA} . However, Fig. 3*B*, which was generated for the same value of injected current (28 pA), but with spike generation enabled by setting g_{Na} to 8,000 μ S/cm², shows that burst firing is observed for P_{NMDA} values between 1.2 and 1.5 \cdot 10⁻⁶ cm/s. Thus a slow oscillation in membrane potential in the absence of spikes is not a necessary condition for burst firing because the interaction of the fast spiking dynamics with the slow dynamics underlying the envelope oscillation extends the range of parameter settings that support burst firing. We predict that in some cases, the application of TTX to neurons exhibiting NMDA-induced burst firing will not exhibit slow



FIG. 4. Bifurcation diagrams of dendritic membrane potential for a single cell as a function of $P_{\rm NMDA}$ with $g_{\rm Na}$ set to $0. \cdot \cdot \cdot$, all parameters are as in Fig. 3 except $g_{\rm Na} = 0$. No "envelope" oscillation in membrane potential is observed, only a stable steady state. —, all parameters are as in Fig. 3 except $g_{\rm Na} = 0$ and the steady hyperpolarizing current was increased from 28 to 56 pA. In this case, an unstable steady state $(\cdot \cdot \cdot)$ and the associated "envelope" oscillations in membrane potential can be observed at $P_{\rm NMDA}$ values between ~ 0.95 and $1.1 \cdot 10^{-6}$ cm/s.

envelop oscillations at any value of applied current due to this phenomenon.

Activity of two coupled identical neurons

Having established the effects of varying P_{NMDA} on the firing pattern of a single-model neuron, we proceeded to examine the effect on both pattern and synchronization of varying G_{c} between a pair of identical neurons at each value of P_{NMDA} .

Figure 5A shows time course of membrane potential and intracellular sodium concentration, as well as the phase plane representation, for high-frequency spiking activity of single model neuron ($P_{\rm NMDA} = 1.56 \cdot 10^{-6}$ cm/s). When such two identical neurons were electrically coupled via their distal dendrites with a conductance of $G_c = 6.2 \cdot 10^{-5}$ S/cm², they produced bursting activity (Fig. 5B). The slow wave in membrane potential is accompanied by oscillations in intracellular sodium concentration. All bursts in this series are not identical; rather there are two different types that alternate; in the phase plane, this is evident as 2P, or period two behavior, manifested as a limit cycle with two lobes. A detail of the spikes within the two types of bursts in each of the two neurons is shown in Fig. 6. At the end of the first burst, the spikes in one neuron lag those of its partner, whereas in the next burst it leads its partner. This pattern has been observed experimentally and labeled as "leader-follower" bursting. We retain this terminology. This pattern is a consequence of the interaction of the spike-generating mechanisms with the burst generating mechanism; in the absence of the spike-generating mechanism, only bursting limit cycles with a single lobe are observed.

Clearly, the firing pattern of coupled model DA neurons depends on both the activation of excitatory inputs and the strength of coupling. To illustrate this dependence, a G_c - $P_{\rm NMDA}$ two-parameter bifurcation diagram was constructed numerically (Fig. 7A). When G_c is equal to zero (*1st left column* of squares on the diagram), the firing pattern corresponds to that of uncoupled neurons with the sequences of changes in firing pattern as a function of $P_{\rm NMDA}$ as shown in the bifurcation diagram for a single neuron (Fig. 3B). In gen-



FIG. 5. Effects of electrical coupling (G_c) on the activity of a homogenous pair of cells with high-frequency spiking ($P_{NMDA} = 1.56 \cdot 10^{-6}$ cm/s). Only the activity of 1 cell is shown. *Left*: membrane potential. *Middle*: intracellular sodium concentration. *Right*: Na-V plane representations of activity corresponding to the *left* and the *middle*. A: $G_c = 0$; B: $G_c = 6.2 \cdot 10^{-5}$ S/cm².



FIG. 6. Anti-phase spiking in 2 weakly coupled DA neurons. Bursts are approximately synchronous but individual spikes are not synchronous. Alternation of "leader" and "follower" during silent phase is shown ($P_{\rm NMDA} = 1.7 \cdot 10^{-6}$ cm/s, $G_{\rm c} = 2.2 \cdot 10^{-5}$ S/cm²).

eral, intermediate values of G_c favor irregular burst firing at the expense of regular burst firing, high-frequency single-spike firing, and, to a lesser extent, low-frequency single-spike firing. At high values of G_c ($\sim 6 \cdot 10^{-5}$ S/cm²), the dependence of the firing pattern is very nearly the same as for uncoupled neurons

with the exception that in the single spike modes the spikes are synchronized and in the bursting modes the bursts are synchronized.

We also computed maximal and average spike frequency at each value of G_c and P_{NMDA} for a pair of identical neurons. The major effect was that a change in pattern to burst firing increased the maximal frequency. Irregular or leader/follower bursting corresponds to maximal frequency >25 Hz, while regular bursting corresponds to maximal frequency 15-23 Hz (Fig. 7B). There was no correlation between bursting firing patterns and average frequency of discharge (Fig. 7C), which increases with increasing P_{NMDA} , whereas G_{c} has no significant influence on average frequency. Increasing $P_{\rm NMDA}$ also increases the burst duration from 1 to 2 s, but intermediate levels of electrical coupling $(1 \cdot 10^{-5} - 5.5 \cdot 10^{-5} \text{ S/cm}^2)$ and high level of permeability for NMDA-induced currents (1.6 · 10^{-6} -1.8 · 10^{-6} cm/s) evoke bursts with duration of 3-15 s (Fig. 7D). Longer burst durations are associated with lower burst frequencies.

To investigate how changes in the firing pattern as a result of varying the strength of the electrical coupling correlated with synchronization or desynchronization of the coupled neurons, time domain observations in single neurons were plotted side



FIG. 7. Effects of G_c and P_{NMDA} on the dynamics of pairs of identical DA cells. Each figure is the result of 1,353 integrations of model equations with different values of parameters G_c and P_{NMDA} (33 and 41, respectively) and automatic detection of different modes. Incremental steps for $G_{\rm c}$ and $P_{\rm NMDA}$ are $0.2 \cdot 10^{-5}$ and $0.02 \cdot 10^{-6}$ cm/s, respectively. A: G_{c} - P_{NMDA} phase diagram for pair of coupled identical neurons. Light blue squares, low-frequency spiking (LFS); red, regular bursting (RB); blue, highfrequency spiking (HFS); light green, irregular spiking (IS); yellow, irregular bursting (IB); rose, leader/follower bursting (L/F). Outlined regions indicate areas of synchronization. The asterisk indicates a region of bistability described in Fig. 9. B: effects of $G_{\rm c}$ and $P_{\rm NMDA}$ on the maximal frequency of pair of identical neurons. The range of shaded values is indicated by the associated column of squares on the *right*. C: effects of G_c and P_{NMDA} on the average frequency of pair of identical neurons. D: effects of $G_{\rm c}$ and $P_{\rm NMDA}$ on the burst duration of a pair of identical neurons. Colored areas indicate regions of dynamic activity being quantified. Diagrams B-D have the same ranges of G_c and P_{NMDA} as the diagram A.

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by side with phase portraits in the V_{d1} versus V_{d2} plane (Fig. 8). Two identical neurons with high-frequency spiking ($P_{\text{NMDA}} = 1.58 \cdot 10^{-6}$ cm/s) produce identical firing patterns (Fig. 8A1), but because they were initialized differently, they oscillated with a constant phase shift (Fig. 8A2) while uncoupled ($G_c = 0$). The phase-locking is an artifact resulting from the identical nature of the oscillators—they will phase lock at whatever phase difference they are initialized with. The phase-locking is indicated by the simple closed curve in Fig. 8A2. Weak coupling ($2 \cdot 10^{-5}$ S/cm²) caused irregular bursting (Fig. 8B) and slightly stronger coupling ($6 \cdot 10^{-5}$ S/cm²) caused leader/ follower bursting (Fig. 8C). In coupled burst firing, bursts are synchronous but single spikes are not. This is indicated by the



closer approach to a 45° line of the lower leftmost portions of the trajectory (corresponding to the interbursts), than the upper rightmost portions (corresponding the spiking activity). This is most evident in the leader/follower example (Fig. 8*C2*). The duration of bursts decreased with increasing G_c until they finally disappeared and quasi-periodic spiking (Fig. 8*D*) took its place ($G_c = 6.8 \cdot 10^{-5}$ S/cm²). This regime is characterized by spikes with different amplitudes and phases relative to its partner. Further increases in coupling strength led to completely synchronized spiking (Fig. 8*E*, $G_c = 7 \cdot 10^{-5}$ S/cm²), that is evidenced by the 45° line in the $V_{d1}-V_{d2}$ phase plane. Increases in electrical coupling for pair of identical neurons at a constant P_{NMDA} corresponding to low-frequency

FIG. 8. Dynamic responses of pair of identical neurons. $P_{\text{NMDA}} = 1.58 \cdot 10^{-6} \text{ cm/s}$. A: $G_c = 0$; B: $G_c = 2 \cdot 10^{-5}$ S/cm^2 ; C: $G_c = 6 \cdot 10^{-5} \text{ S/cm}^2$; D: $G_c = 6.8 \cdot 10^{-5} \text{ S/cm}^2$; E: $G_c = 7 \cdot 10^{-5} \text{ S/cm}^2$. Left: membrane potential of 1 neuron. Right: phase portraits for membrane potentials (V_{d1} , V_{d2}) as a function of increasing coupling strength. Each phase portrait corresponds to firing patterns on the left. $G_c =$ 0—single spiking with phase shift; $G_c = 2 \cdot 10^{-5}-6 \cdot 10^{-5}$ S/cm^2 —different kinds of bursting activity; $G_c = 6.8 \cdot 10^{-5} \text{ S/cm}^2$ —asynchronous quasiperiodic spiking; $G_c = 7 \cdot 10^{-5} \text{ S/cm}^2$ —completely synchronized oscillations.

spiking led only to synchronization without any concomitant changes in pattern. These numerical simulations were repeated (not shown) with the coupling located in the proximal dendrites or somata, far removed from zone of initialization of bursting, and stronger coupling was required to produce similar effects to those obtained with distal dendritic coupling.

The areas of synchronization of electrical activity are indicated on Fig. 7A. Different patterns may be synchronized with increased coupling strength, including high-frequency spiking, regular bursting, and low-frequency spiking. Only irregular bursting activity that is intrinsic (not induced by electrical coupling) can be characterized by either synchronous or nonsynchronous spiking within bursts (for example, $G_c = 0$ under $P_{\text{NMDA}} = 1.26 \cdot 10^{-6}$ cm/s). On the other hand, spikes occurring during irregular bursting activity induced by electrical coupling are never synchronized. Higher levels of electrical coupling result in synchronous spiking activity as well as a transition from irregular bursting to either high-frequency synchronous spiking or regular bursting. However, a few zones of synchronization may be observed under weak coupling ($G_c =$ $0.1 \cdot 10^{-5} - 0.2 \cdot 10^{-5}$ S/cm²). Strongly coupled identical neurons revert to the uncoupled solution ($G_c \ge 6.5 \cdot 10^{-5}$ S/cm²).

The computer simulations used to generate Fig. 7 resulted from a single set of initial conditions in which the initial difference in membrane potential between neurons was 10 mV. Spot checks at different initial conditions for sodium concentration were conducted to detect bistability. There are indeed zones where several types of activity coexist (Fig. 7A, see asterisk), for example, at low levels of P_{NMDA} (1.1 · 10⁻⁶– $1.26 \cdot 10^{-6}$ cm/s) and $G_c (0-2 \cdot 10^{-5} \text{ S/cm}^2)$. In addition to the synchronized low-frequency regular spiking observed at $P_{\text{NMDA}} = 1.1 \cdot 10^{-6}$ cm/s, an initial difference of sodium concentration ~ 2 mM led to the attractive basin of lowfrequency spiking in antiphase (Fig. 9, A1-D1). Weak coupling $(G_c = 1.0 \cdot 10^{-5} \text{ S/cm}^2)$ modulates complex multirhythmic activity including low-frequency spiking and slow waves (Fig. 9, A2 and B2). These oscillations are asynchronous (Fig. 9, C2 and D2). This mode transition is reversible: the simulated blocking of the coupling of neurons renews regular low-frequency spiking in antiphase. Stronger coupling ($G_c = 4.0$ · 10^{-5} S/cm²) is able to synchronize spiking activity without changing the pattern (Fig. 9, A4-D4). The nonsynchronous mode cannot be recovered by decreasing G_c in the absence of an asymmetric perturbation in sodium concentration.

Activity of two heterogeneous cells

We also studied more physiologically plausible cases in which the two neurons had substantial differences in parameters and firing patterns. As in the homogenous case, coupling can promote burst firing in the heterogenous case. Figure 10 shows how electrical coupling can change the activity of two DA neurons with different levels of activation of NMDA inputs and therefore different intrinsic frequencies. The two neurons differ in only one parameter, P_{NMDA} such that they were biased in different oscillatory modes: high-frequency spiking ($P_{\text{NMDA}} = 1.1 \cdot 10^{-6}$ cm/s) and low-frequency spiking ($P_{\text{NMDA}} = 1.1 \cdot 10^{-6}$ cm/s). Strong coupling between them ($G_c = 9 \cdot 10^{-5}$ S/cm²) converts the activity in both neurons from single spike firing to burst firing. This transition can be reversed by blocking the coupling. The bursting regimes of the two neurons have significant differences in the amplitudes of the resultant slow-waves (burst envelopes), spikes, and sodium dynamics.

The rhythmogenic effect of coupling can be observed in a heterogeneous pair of neurons lacking spike-generating mechanisms. Figure 11A shows the dynamics of the membrane potential in two such neurons with different P_{NMDA} before, during, and after a 15-s interval in which the coupling is activated. The corresponding dynamics of intracellular sodium concentration are shown in Fig. 11B. Both oscillations of membrane potential and intracellular sodium concentration in the two neurons have different amplitudes. The parameter regimes that produce slow-wave oscillations in the absence of the spike-generating mechanism $(I_{\rm Na})$ would clearly produce bursting regimes if the spike-generating mechanism was turned on, whereas the quiescent modes would likely produce single spike firing. Because the induction of slow wave oscillations by electrical coupling does not require spike generation, we can infer that the induction of burst firing by the electrical coupling likewise is not dependent on spike-generating mechanisms. A similar result was obtained in a model of neurons of the inferior olive that do not oscillate spontaneously when isolated but may form low-amplitude oscillations when electrically coupled (Manor et al. 1997). The projections of the two limit cycles in the models with $g_{Na} = 0$ onto Na-V phase plane are situated in different regions (Fig. 11C). We hypothesize that the neuron with the lower value of P_{NMDA} acts to bias the other neuron into an actively bursting regime, whereas the neuron with the lower P_{NMDA} is merely passively following its partner. Figure 11D shows the bifurcation diagrams the same models with $g_{Na} = 0$ of the same pair of nonidentical neurons. The minima and maxima of the oscillatory solutions were plotted as a function G_{c} (treated as the bifurcation parameter). With increasing G_c , Hopf bifurcations appear at the branch points of the steady states. The periodic branches eventually coalesce but at such large values of $G_{\rm c}$ that they are not physiologically plausible.

The neuron with high level of P_{NMDA} (1st neuron) is an active burster in the coupled state, whereas the one with low level of P_{NMDA} (2nd neuron) is a passive follower. To check this hypothesis, a nullcline analysis for the model of each coupled neuron with $g_{Na} = 0$ was performed (see Canavier 1999). Indeed, the coupling changed the branch of the potential nullcline (dV/dt = 0) of the first neuron in which the intersection with sodium nullcline (d[Na]/dt = 0) occurs. The isolated neuron had a region of positive slope at the potential nullcline, but sodium nullcline crossed the potential nullcline in the region of the negative slope (Fig. 12A), therefore the neuron was silent (tonically firing if action potentials were enabled). The modulation of electrical coupling moves the fixed point to the unstable region of positive slope (Fig. 12B), enabling the oscillations shown in Fig. 11. As the first neuron is hyperpolarized (moving from point d to point a as shown in Fig. 12B), the positive slope of potential nullcline causes the voltage to rapidly jump from point a to b. The same process occurs during depolarization (system moving from point b to c), and the jump occurs from point c to d. The second neuron with low P_{NMDA} passively follows the oscillations of the first.

DISCUSSION

A model of two coupled multicompartmental neurons mimicked a wide range of dynamic activity exhibited by DA neurons including single-spike firing, bursting, regular or ir-



FIG. 9. Effect of electrical coupling a pair of identical model neurons. $P_{\text{NMDA}} = 1.1 \cdot 10^{-6}$ cm/s. Response of coupled neuron to step changes in G_c . A: membrane potential. B: intracellular sodium. Only the activity of 1 neuron is shown. C: difference in membrane potentials of the 2 neurons. D: phase portraits $(V_{d1} - V_{d2})$ that correspond to different kinds of activity in A.



FIG. 10. Effect of electrical coupling on 2 DA neurons with different levels of activation of NMDA inputs. *Top*: low activation of NMDA inputs ($P_{\text{NMDA}} = 1.1 \cdot 10^{-6}$ cm/s). *Bottom*: high activation of NMDA inputs ($P_{\text{NMDA}} = 1.7 \cdot 10^{-6}$ cm/s). Strong coupling can convert these neurons to bursts. Blocking of coupling converts activity to single spiking again. *Left*: dynamics of membrane potentials. *Right*: Na-V projections of bursting firing patterns corresponding to the *left*.

regular, slow-wave oscillations under application of TTX. The model was used to predict the influence of electrical coupling between DA neurons on firing patterns and synchrony. At different simulated levels of activation of NMDA excitatory inputs, different sequences of dynamical activity were observed as the strength of their electrical coupling was changed.

Model predictions and agreement with existing data on electrical coupling

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Leader/follower alternation in spikes has been observed both in our modeling studies (Fig. 6) and other modeling studies of electrically coupled bursters (see following text). Interestingly, Grace and Bunney (1983b) also reported such leader and follower cells, stating that on occasion leading and following cells would reverse order. The same study reported that DA cells fired together more frequently while firing in a burst pattern, moreover burst firing coupled cells tended to burst together. This is certainly consistent with our simulations that show nearly synchronized bursts even when the spikes are not synchronized, thus in burst firing there is an additional, low-frequency available for synchronization. According to our simulations, electrical coupling promotes not only synchrony but also burst firing, which, as we have just mentioned, itself promotes a type of synchrony. At any given value of G_c in Fig. 7A, the range of values of P_{NMDA} that supports burst firing is





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FIG. 12. Nullcline analysis for the active oscillator in the heterogeneous pair. $P_{\rm NMDA} = 1.7 \cdot 10^{-6}$ cm/s. The neuron with a low level of $P_{\rm NMDA}$ is biased at its fixed point ($V_{\rm d2} = -53$ mV). —, potential nullclines; ..., sodium nullclines. A: $G_c =$ 0. A positive slope region exists in the potential nullcline, but the system is not biased in this region, so no oscillations were observed in the simulations. B: parameter settings are the same as in A except $G_c = 9 \cdot 10^{-5}$ S/cm². Because the system is now biased in the region of positive slope of potential nullcline, a slow oscillation is generated. Arrows indicate the trajectory *abcd* that corresponds to the slow oscillations.

either greater than in the absence of coupling, or at worst in the case of very strong coupling, equal to the range in its absence. For heterogenous coupling, this range is extended even further, hence the model predicts that burst firing will be observed more often in the presence of electrical coupling. Experiments using freely moving rats (Freeman et al. 1985) indicated that electrical coupling is only rarely observed in anesthetized or paralyzed rats compared with freely moving rats. Thus perhaps a higher level of electrical coupling in vivo can account for some of the difficulties that were encountered producing NMDA-induced burst firing in vitro compared with in vivo; furthermore, pattern changes induced by electrical coupling or its modulation may be especially relevant in vivo in light of the data of Freeman et al. (1985).

Comparison to previous model studies: single-neuron model

The model in this study is an extension of a previous model of a dopamine neuron (Canavier 1999) based on the hypothesis that the bath application of NMDA causes burst firing in vitro by inducing an oscillation in dendritic sodium concentration and calibrated where possible using experimental data. An even earlier, more generic, model (Li et al. 1996) included both NMDA-induced (sodium-dependent) and apamin-induced (calcium-dependent) burst firing mechanisms. The model of Amini et al. (1999) modeled two calcium-dependent oscillations, the slow oscillatory potential underlying repetitive single-spike firing, and an apamin-induced square-wave, or plateau potential, though to underlie a type of burst firing. The contribution of the model of Amini et al. (1999) to the present study is limited to descriptions of the potassium currents, which were modified to accommodate spike firing. The major difference between the model in this paper and that of Canavier (1999) is the incorporation of spiking dynamics into all model compartments, enabling the full range of dose-dependent effects of NMDA to be modeled, from low-frequency spiking, to burst firing, to high-frequency spiking. For example, burst firing can only be observed experimentally at a range of concentrations in the bath \sim 30 nM. Lower concentrations lead to only to single-spike firing, and sufficiently high concentrations to depolarization block (Wang et al. 1994). We did not examine values of P_{NMDA} that were high enough to induce depolarization block.

Although examining the slow dynamics that underlie burst firing can provide helpful insights (e.g., Figs. 4, 11, and 12),

often the fast dynamics associated with spiking are required for the expression of the full range of dynamics exhibited by the modeled system. For example, burst firing in homogenous pairs of model DA neurons that do not burst in isolation was shown to be critically dependent on action potential dynamics, and the single-neuron model bursts at values of injected current that did not produce a slow oscillation in the model with action potentials blocked ($g_{Na} = 0$). The numerous modes of irregular bursting and double period bursting observed in this study are dependent on action potential dynamics and could not have been demonstrated in a model without spikes.

Comparison with related model studies

IDENTICAL CELLS. Sherman and Rinzel (1992) used a model of a square-wave burster to illustrate how electrical coupling can modulate the firing pattern. In a square-wave burster, there is a single slow variable and a fast subsystem that exhibits bistability between tonic spiking and quiescent with a certain range of values of the slow variable. An oscillation in the slow variable causes the system to alternate between quiescence and bursts of spikes in which the ISIs increase monotonically. Sherman and Rinzel (1992) examined the fast action potential dynamics by treating the slow variable as a parameter and found that weak coupling destabilized the synchronous solution in the fast subsystem, causing spikes within a burst to be 180° out of phase, or antiphase. Explanations of the destabilization of synchronous spiking by electrical coupling are given by Han et al. (1995) and Chow and Kopell (2000). The loss of stability of the synchronous solution in the fast subsystem enables the alternation between spiking and quiescence characteristic of bursting when the slow variable (Sherman 1994) is allowed to have dynamics and no longer treated as a fixed parameter. In our model, synchronous high-frequency spiking ($P_{\rm NMDA} \approx$ $1.6 \cdot 10^{-6}$ cm/s) is observed at low levels of electrical coupling, and increasing the coupling strength causes a transition to burst firing. If, however, the sodium concentration is held constant at its average value during tonic spiking, the same increase in coupling strength causes a transition from synchronous to antisynchronous spiking. On the other hand, the synchronous solution for low-frequency spiking ($P_{\text{NMDA}} \approx 1.1 \cdot 10^{-6} \text{ cm/s}$) does not lose stability as coupling strength is increased; this is consistent with theoretical work (Chow and Kopell 2000) that indicates stability is lost only at higher frequencies.

We found that bursts in weakly coupled model neurons were

nearly synchronized with double period, and the out-of-phase spikes in one neuron lead its partner in one burst and then lag it in the next, similar to that in leader-follower bursting. Such double period modes were encountered in the present study and others (Pinto et al. 2000; Sherman 1994; Sherman and Rinzel 1992). In the limit of strong electrical coupling, synchrony is always reestablished and for identical neurons, therefore the single-neuron solution is always recovered. Thus as coupling strength is increased, burst period first increases by 50-100%, then decreases (Fig. 7D) consistent with previous studies (Sherman and Rinzel 1991, 1992; Smolen et al. 1993).

A square-wave burster can be induced to fire tonically by slight alterations in certain parameters. The model is more accurately called a conditional burster at these parameter settings, because a constant depolarizing stimulus could induce burst firing. Our Fig. 5 shows a transition to double period bursting when identical tonically firing cells are coupled, and Fig. 7 shows a number of possible transitions. Sherman (1994) referred to the conversion of two identical single-spike firing neurons to bursters as delicate, meaning that it was not robust, and parameters had to be chosen carefully to observe this phenomenon. Figure 7A indicates that in our model, the phenomenon is indeed robust, and heterogeneity (not shown) causes it to be even more robust.

HETEROGENOUS CELLS. Smolen et al. (1993) proposed the heterogeneity hypothesis to account for the activity of pancreatic beta cells that did not seem to burst in isolation, but only when electrically coupled to a cluster of other beta cells. The basic idea was that electrical coupling extended the narrow parameter range in which burst firing could be observed. Motivated by this hypothesis, Sherman (1994) extended the work of Sherman and Rinzel (1992) to heterogenous pairs of model square-wave bursters and coupled a quiescent and a tonically firing cell to obtain asymmetric bursters. Figures 10 and 11 of our paper show an example of asymmetric burst firing in heterogenous cells. Our numerical explorations of the parameter space of the dopamine neuron model give added support to the heterogeneity hypothesis.

Other examples of stabilization of a synchronous burst pattern

We have shown that in our two-neuron networks, gap junctional coupling stabilizes synchronous bursting. Using an electronic circuit to artificially electrically couple neurons (Sharp et al. 1992) showed that electrical coupling between two neuronal oscillators depends on the membrane potentials, intrinsic properties of the neurons, and the coupling strength; increasing the coupling results in synchronized firing. Networks of model interneurons coupled by gap junctions between dendritic compartments have been shown to be capable of generating synchronous network bursts (Traub 1995), but only under conditions in which the dendrites are excitable enough to support action potential initiation and there were at least two gap junctions per neuron on average. In other modeling studies of interneuronal networks, Skinner et al. (1999) were able to generate and maintain stable bursting in the presence of electrical coupling and recurrent inhibitory GABAA- receptor synapses. These studies support the idea that gap-junctional coupling could be crucial not only for synchrony but also for stabilization of the bursting pattern.

Model interpretations and predictions

This paper presents results using a specific model of a system of two coupled dopamine neurons. It is reasonable to inquire about which aspects of this work generalize to other models, other systems, and in particular to systems of more than two coupled neurons. A recent modeling study (de Vries and Sherman 2001) using simple neural models in which the two parameters varied were a heterogeneity parameter and the coupling strength, showed that systems of more than two electrically coupled oscillators showed a qualitatively similar dependence on the coupling strength as a system of two oscillators. Other studies of electrically coupled bursters (Sherman 1994; Sherman and Rinzel 1992) as well as our own unpublished simulations using model formulations slightly different from that shown in Fig. 7A, suggest that the qualitative result, that electrical coupling greatly extends the parameter region in which burst firing can be observed, is robust for many populations of neurons with a tendency to fire in bursts.

In addition, we make the following testable experimental predictions. 1) NMDA-induced burst firing should persist for a larger range of values of injected current than the NMDAinduced slow oscillation observed in the presence of TTX (see Fig. 3 and Fig. 4). 2) The presence of gap junctional coupling can be inferred from single-neuron recordings if that neuron experiences a change in firing pattern (from bursting to single spiking, between irregular and regular burst firing, or between double period burst firing and some other type of burst firing) as a result of the application of a selective gap junctional blocker or vice versa in the presence of an agent that promotes coupling (see Figs. 5, 7, and 8). 3) NMDA-induced burst firing should be observed more often in the presence of manipulations that increase the level of gap junctional coupling and less frequently in the presence of manipulations that decrease it (see Fig. 7 for case of homogenous cells and Fig. 10 for case of heterogeneous cells).

There may be some problems testing the second and third predictions due to the nonspecific nature of many gap junction blockers, which can have substantial effects on membrane excitability (Rekling et al. 2000). However, if we can make an analogy between burst firing in vitro and burst firing in vivo, these predictions have very important implications for information processing in dopamine neurons. The firing pattern in dopamine neurons has been implicated in both reward-mediated learning (Schultz 1998) and in the selection of a response to behaviorally relevant stimuli. For example, in vivo recordings of freely moving rats, certain neurons were observed to change their firing pattern between tonic firing and burst firing when such a stimulus was presented. Furthermore, dopamine neurons release two to three times as much dopamine per spike in a bursting mode compared with a single-spike firing mode (Gonon 1988). Neurochemical studies (Manley et al. 1992) indicate that spikes clustered in bursts are more effective that tonic firing at increasing DA levels in medial forebrain, and burst-like but not tonic stimulation of the medial forebrain bundle increases immediate early gene expression in certain dopaminergic projection areas (Chergui et al. 1996). Thus the ability of electrical coupling to promote burst firing may be functionally important.

A role for electrical coupling is that weak electrical coupling of high-frequency spiking neurons can change their pattern to bursts, thereby preventing a progression into depolarization block and the resultant of breakdown of dopaminergic function (Harden and Grace 1995). Yet another important role may be not just the stabilization of burst firing but rather the synchronization of bursts, which may convey completely different information than single spikes (Lisman 1997); certain projection areas, in the forebrain, for example, may only be capable of being activated by simultaneously arriving (synchronous) bursts. Finally, the results of our computational studies also show that the interaction of electrical coupling with intrinsic membrane properties may be a source of irregularity in firing pattern of midbrain DA neurons.

APPENDIX

Single-cell model

Basic equations governing membrane behavior in each compartment

$$\begin{split} &-C_{\mathrm{m,d}}(\mathrm{d}V_{\mathrm{d}}/\mathrm{d}t) = I_{\mathrm{Na,d}} + I_{\mathrm{A,d}} + I_{\mathrm{KDR,d}} + I_{\mathrm{NaP,d}} + I_{\mathrm{L,d}} + I_{\mathrm{NMDA}} + I_{\mathrm{dp}} \\ &-C_{\mathrm{m,p}}(\mathrm{d}V_{\mathrm{p}}/\mathrm{d}t) = I_{\mathrm{Na,p}} + I_{\mathrm{A,p}} + I_{\mathrm{KDR,p}} + I_{\mathrm{NaP,p}} + I_{\mathrm{L,p}} + I_{\mathrm{pd}} + I_{\mathrm{ps}} \\ &-C_{\mathrm{m,s}}(\mathrm{d}V_{\mathrm{s}}/\mathrm{d}t) = I_{\mathrm{Na,s}} + I_{\mathrm{A,s}} + I_{\mathrm{KDR,s}} + I_{\mathrm{NaP,s}} + I_{\mathrm{L,s}} + I_{\mathrm{sp}} + I_{\mathrm{stimul}} \end{split}$$

The subscript "i" indicates a nonspecific compartment, whereas subscripts "d", "p", and "s" indicate distal dentritic compartment, proximal dendritic compartment and somatic compartment, respectively.

Membrane slow oscillation generation mechanisms¹

NMDA-induced current

$$I_{\rm NMDA} = I_{\rm NMDA,Na} + I_{\rm NMDA,K} + I_{\rm NMDA,Ca}$$

 $I_{\rm NMDA,Na} = P_{\rm NMDA} p(\rm VF^2/RT)(\lambda[Na]_{in} - \lambda[Na]_{out} \exp(-\rm VF/RT))/$

 $(1 - \exp(-VF/RT))$

(1

 $I_{\text{NMDA},\text{K}} = P_{\text{NMDA}} p(\text{VF}^2/\text{RT})(\lambda[\text{K}]_{\text{in}} - \lambda[\text{K}]_{\text{out}} \exp(-\text{VF}/\text{RT}))/$

$$-\exp(-VF/RT))$$

$$M_{\rm NMDA,Ca} = 10.6 \times P_{\rm NMDA} p \times (4 V F^2/RT)$$

$$\times ([Ca]_{in} - \lambda_{Ca}[Ca]_{out} \exp(-2VF/RT))/(1 - \exp(-2VF/RT))$$

$$\mathrm{d}p/\mathrm{d}t = p_{\infty} - p$$

$$p_{\infty} = 0.05 + 0.95/(1 + ([Mg]_{out}/K_{m,Mg}) \exp(-V/q))$$

Linear leakage current

$$\begin{split} I_{L,i} &= I_{L,Na,i} + I_{L,K,i}; \quad I_{L,K,i} = g_{L,K,i}(V_i - E_K); \quad I_{L,Na,i} = g_{L,Na,i}(V_i - E_{Na,i}) \\ &= E_{Na,i} = (\text{RT}/F) \ln \left(\lceil \text{Na} \rceil_{\text{out}} / \lceil \text{Na} \rceil_{\text{in},i} \right) \end{split}$$

Sodium pump current

$$I_{\text{NaP,i}} = I_{\text{NaP,max,i}} / (1 + (K_{\text{m,Na}} / [\text{Na}]_{\text{in,i}})^{1.5})$$

Sodium balance

$$\begin{split} d[\mathrm{Na}]_{\mathrm{in,d}}/\mathrm{d}t &= 4 \times f_{\mathrm{d}}(-I_{\mathrm{Na,d}} - I_{\mathrm{L,Na,d}} - I_{\mathrm{NMDA,Na}} - 3I_{\mathrm{NaP,d}})/(\mathrm{d}_{\mathrm{d}}F) \\ d[\mathrm{Na}]_{\mathrm{in,p}}/\mathrm{d}t &= 4 \times f_{\mathrm{p}}(-I_{\mathrm{Na,p}} - I_{\mathrm{L,Na,p}} - 3I_{\mathrm{NaP,p}})/(\mathrm{d}_{\mathrm{p}}F) \\ d[\mathrm{Na}]_{\mathrm{in,s}}/\mathrm{d}t &= 4 \times f_{\mathrm{s}}(-I_{\mathrm{Na,s}} - I_{\mathrm{L,Na,s}} - 3I_{\mathrm{NaP,s}})/(\mathrm{d}_{\mathrm{s}}F) \end{split}$$

Spike-generating mechanisms

Fast sodium current

$$I_{\text{Na,i}} = g_{\text{Na,i}}m_i^*h_i(V_i - E_{\text{Na,i}})$$

$$dm_i/dt = 1/(1 + (\exp((V_{\text{half,m,i}} - V_i)/6))) - m_i$$

$$dh_i/dt = (1/(1 + \exp((V_{\text{half,h,i}} - V_i)/7.8)) - h_i)/\tau_h$$

$$\tau_h = 56/(1 + \exp((V_i - 27.8 - V_{\text{half,h,i}})/4.5)) - 56/$$

$$(1 + \exp((V_i - 7.8 - V_{\text{half,h,i}})/2.0)) + 1.0$$

Delayed rectified current

$$I_{\text{KDR},i} = g_{\text{KDR},i} n_i^3 (V_i - E_{\text{K}})$$
$$dn_i / dt = (1/(1 + \exp((-30 - V_i)/10)) - n_i) / 15.0$$

Outward potassium current

$$I_{A,i} = g_{A,i}q_is_i(V_i - E_K)$$

$$dq_i/dt = (1/(1 + \exp((-V_i - 42)/4)) - q_i)/15.0$$

$$ds_i/dt = (1/(1 + \exp((V_i + 63)/4)) - s_i)/50.0$$

Interneuronal coupling currents

$$\begin{split} G_{\rm sp} &= 10^2 \pi d_{\rm p}^2 d_{\rm s}^2 / 2R_{\rm a} (L_{\rm p} d_{\rm s}^2 + L_{\rm s} d_{\rm p}^2); \quad G_{\rm pd} = 10^2 \pi d_{\rm p}^2 d_{\rm d}^2 / 2R_{\rm a} (L_{\rm p} d_{\rm d}^2 + L_{\rm d} d_{\rm p}^2) \\ g_{\rm sp} &= 4 \times 10^8 G_{\rm sp} / (\pi d_{\rm s} L_{\rm s}); \quad g_{\rm ps} = 10^8 G_{\rm sp} / (\pi d_{\rm p} L_{\rm p}) \\ g_{\rm pd} &= 10^8 G_{\rm pd} / (\pi d_{\rm p} L_{\rm p}); \quad g_{\rm dp} = 10^8 G_{\rm pd} / (\pi d_{\rm d} L_{\rm d}) \end{split}$$

$$I_{dp} = g_{dp}(V_d - V_p); I_{pd} = g_{pd}(V_p - V_d); I_{ps} = g_{ps}(V_p - V_s); I_{sp} = g_{sp}(V_s - V_p)$$

Applied microelectrode current

interoclectrode current

$$I_{\text{stimul}} = I_{\text{STIM}} / (\pi d_{\text{s}} L_{\text{s}})$$

Parameters of single-cell model

$$g_{\text{Na,i}} = 8000 \ \mu\text{S/cm}^2; \quad g_{\text{L,Na,i}} = 40 \ \mu\text{S/cm}^2$$
$$g_{\text{KDR,i}} = 400 \ \mu\text{S/cm}^2; \quad g_{\text{L,K,i}} = 100 \ \mu\text{S/cm}^2$$
$$g_{\text{A,d}} = 3000 \ \mu\text{S/cm}^2; \quad g_{\text{A,p}} = 300 \ \mu\text{S/cm}^2; \quad g_{\text{A,s}} = 100 \ \mu\text{S/cm}^2$$
$$V_{\text{half,m,d}} = -26.6 \text{ mV}; \quad V_{\text{half,m,p}} = -41.6 \text{ mV}; \quad V_{\text{half,m,s}} = -41.6 \text{ mV}$$
$$V_{\text{half,h,d}} = -48.8 \text{ mV}; \quad V_{\text{half,h,p}} = -63.8 \text{ mV}; \quad V_{\text{half,h,s}} = -63.8 \text{ mV}$$
$$C_{\text{m,d}} = 2 \ \mu\text{F/cm}^2; \quad C_{\text{m,p}} = 1 \ \mu\text{F/cm}^2; \quad C_{\text{m,s}} = 1 \ \mu\text{F/cm}^2$$
$$E_{\text{K}} = -100 \text{ mV};$$
$$[\text{Na}]_{\text{out}} = 145 \text{ mM}; \quad [\text{K}]_{\text{out}} = 2.5 \text{ mM}; \quad [\text{K}]_{\text{in}} = 140 \text{ mM}$$

$$[Ca] = 2.0 \text{ mM}; [Ca] = 70 \cdot 10^{-6} \text{ mM}; [Mg] = 1.2 \text{ mM}$$

$$K_{\rm m Na} = 10 \text{ mM}; \quad K_{\rm m Ma} = 50.7 \text{ mM}; \quad q = 9 \text{ mV};$$

 $d_{\rm d} = 1 \ \mu{\rm m}; \ d_{\rm p} = 2 \ \mu{\rm m}; \ d_{\rm s} = 15 \ \mu{\rm m}; \ L_{\rm d} = 350 \ \mu{\rm m};$

$$L_{\rm p} = 150 \ \mu {\rm m}; \ L_{\rm s} = 15 \ \mu {\rm m};$$

$$f_{\rm p} = 1; f_{\rm d} = 1; f_{\rm s} = 4; I_{\rm NaP,max} = 0.012 \text{ mA/cm}^2$$

$$R_{\rm a} = 200 \ \Omega \ {\rm cm}; \ R = 8,314 \ {\rm J/kg} \ {\rm mol} \ {\rm K}; \ T = 308 \ {\rm K}; \ \lambda = 0.75; \ \lambda_{\rm Ca} = 0.3$$

Two-cell model

Coupling via distal dendrites

$$\begin{split} -C_{\rm m,d}({\rm d}V_{\rm d,j}/{\rm d}t) &= I_{\rm Na,d,j} + I_{\rm A,d,j} + I_{\rm K,DR,d,j} + I_{\rm NaP,d,j} + I_{\rm L,d,j} + I_{\rm NMDA,j} + I_{\rm dp,j} + I_{\rm c,d,j} \\ I_{\rm c,d,l} &= G_{\rm c}(V_{\rm d,l} - V_{\rm d,2}); \quad I_{\rm c,d,2} = G_{\rm c}(V_{\rm d,2} - V_{\rm d,1}) \end{split}$$

¹ There were typographical errors in the model equations given in Canavier (1999): the activity coefficient (λ_{Ca}) that multiplies $[Ca]_{in}$ in the equation for $I_{NMDA,Ca}$ should have been 1 (due to the low concentration of $[Ca]_{in}$), the value given for $K_{m,Mg}$ was incorrect, and there were several sign errors in the equations describing the sodium balance. The corrected versions appear in the present paper.

Coupling via proximal dendrites

$$-C_{m,p}(dV_{p,j}/dt) = I_{Na,p,j} + I_{A,p,j} + I_{KDR,p,j} + I_{NaP,p,j} + I_{L,p,j} + I_{pd,j} + I_{ps,j} + I_{c,p,j}$$
$$I_{c,p,1} = G_c(V_{p,1} - V_{p,2}); \quad I_{c,p,2} = G_c(V_{p,2} - V_{p,1})$$

Coupling via somata

$$-C_{m,s}(dV_{s,j}/dt) = I_{Na,s,j} + I_{A,s,j} + I_{KDR,s,j} + I_{NaP,s,j} + I_{L,s,j} + I_{sp,j} + I_{stimul,j} + I_{c,s,j}$$
$$I_{c,s,1} = G_c(V_{s,1} - V_{s,2}); \quad I_{c,s,2} = G_c(V_{s,2} - V_{s,1})$$

Here I_c is coupling current; G_c , conductance of electrical coupling (μ S/cm²). The subscript "j" indicates a nonspecific neuron, whereas subscripts "1" and "2" indicate "neuron 1" and "neuron 2," respectively.

This work was supported by National Institute of Neurological Disorders and Stroke Grant NS-37963.

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