STOCHASTIC RESONANCE IN THE MOTOR SYSTEM: EFFECTS OF NOISE ON THE MONOSYNAPTIC REFLEX PATHWAY OF THE CAT SPINAL CORD

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ABSTRACT

In sensory systems the presence of a particular non-zero level of noise may significantly enhance the ability of an individual to detect weak sensory stimuli through a phenomenon known as stochastic resonance (SR). The aim of this study was to demonstrate if such phenomenon is also exhibited by the motor system; in particular, in the Ia-motoneuron synapse of the cat spinal cord. Monosynaptic reflexes elicited by periodic electrical stimulation to the medial gastrocnemius nerve were recorded in the L7 ventral root (or in single motoneurons) of decerebrated cats. Random stretches (mechanical noise) were applied to the lateral gastrocnemius plus soleus muscle by means of a closed-loop mechanical stimulator-transducer. In all cats we observed the SR phenomenon. The amplitude of the monosynaptic reflexes (or number of action potentials recorded in the motoneurons) evoked by the weak electrical stimuli applied to the medial gastrocnemius nerve were an inverted U-like function of the mechanical noise applied to the lateral gastrocnemius plus soleus muscle. A significant maximum value in the amplitude of the monosynaptic responses was reached with a particular noise amplitude value. Numerical simulations on a model of the monosynaptic reflex pathway qualitatively reproduce this stochastic resonance behavior. We conclude that the monosynaptic reflex response elicited by Ia afferents is optimized by the noisy stretching of a synergistic muscle. Our study provides the first direct demonstration that the motor system, and not only the sensory systems, exhibits the SR phenomenon.
INTRODUCTION

Stochastic resonance (SR) is commonly understood to be the enhancement, by noise, of the response of a non-linear system to a weak input signal (Wiesenfeld and Moss, 1995; Gammaitoni et al., 1998; Anishchenko et al., 1999; Ando and Graziani, 2000; Moss et al., 2004). The stochastic resonance is a counterintuitive phenomenon in which the response of the system develops an inverted U-like function versus the input noise level; the maximal enhancement of the response values occurs at an intermediate noise amplitude value. This phenomenon has been demonstrated in the central nervous system (Stacey and Durand, 2000, 2001; Gluckman et al., 1996; Manjarrez et al., 2002b). In sensory systems several SR type effects have been demonstrated in terms of the response amplitude or the signal-to-noise ratio of the output (Russell et al., 1999; Winterer et al., 1999; Hanggi, 2002; Manjarrez et al., 2002c,d, 2003; Mori and Kai, 2002; Ward et al., 2002; Collins et al., 1996b, 1997; Ivey et al., 1998; Richardson et al., 1998; Dhruv et al., 2002; Liu et al., 2002; Moss et al., 2004; Bahar and Moss, 2004; Ando, 2006, Manjarrez et al., 2007), however, there is no direct evidence about the existence of this phenomenon in the motor system.

The SR has been shown in electrophysiological experiments of human muscle spindles (Cordo et al., 1996), or in tendon organs and primary and secondary endings of cat muscle spindles (Fallon et al., 2004). Cordo et al. (1996) demonstrated that the sensitivity of muscle-spindle receptors to a weak movement signal is enhanced by introducing a particular level of noise through the tendon of the parent muscle. This means that a particular level of mechanical noise added to muscle spindles could enhance the muscle spindle sensory output. However, because experiments in humans offer certain limitations, it is not clear from these experiments whether the electrical...
activity of the motor spinal neurons also exhibits the SR behavior. In this context, the purpose of the present study was to extend the observation of Cordo et al. (1996) to the monosynaptic reflex actions of muscle spindle afferents on motoneurons of the cat spinal cord; i.e., to explore the presence of SR in the motor system counterpart. In the experiments reported here, we studied the effects of continuous noisy stretches (input noise) to the lateral gastrocnemius-soleus (LGS) muscle on the amplitude of monosynaptic reflexes (MSR) elicited by periodic stimuli to the medial gastrocnemius (MG) nerve. Thus the signal and the noise were not applied to the same muscle receptors. This protocol allowed that the signal and the noise were mixed not in the muscle spindle but in the motoneurons. In this context, the purpose of the present study was to substantiate whether SR occurs in the synaptic integration when two convergent synaptic inputs, one for the signal and another for the noise, are summated in the motoneurons of the monosynaptic reflex pathway. Disclosure of this phenomenon in the motor system is important because it shows that the motor system, and not only the sensory systems, also exhibits the SR phenomenon. Furthermore, our study shows that synaptic noise could be beneficial to enhance or to depress the monosynaptic reflexes, thus suggesting that the central nervous system could employ internal noise sources to modulate complex motor tasks.

MATERIALS AND METHODS

Preparation. Experiments were performed in 7 adult cats (weight range, 2.0-3.5 kg). Guidelines contained in the National Institutes of Health Guide for the Care and Use of Laboratory Animals (85-23, revised in 1985) were followed throughout. For surgery, gaseous anesthesia was induced and maintained with halothane (5 %) delivered in a mixture of 30 % oxygen and 70 % nitrous oxide. Atropine (0.05 mg kg-1) and
dexamethasone (2 mg kg\(^{-1}\)) were given at the beginning of the surgery. Radial vein was canulated to administer fluids and blood pressure was monitored from the carotid artery. A bicarbonate and glucose (5 \%) solution was delivered intravenously through the experiment at a rate of 5 ml h\(^{-1}\). A mechanical precollicular-postmammillary decerebration was performed with removal of both cortices and all tissue rostral to the transection. Dextran and saline solutions were given to maintain blood pressure between 80 and 120 mm Hg. After decerebration the anesthetic was discontinued. Animals were paralyzed with pancuronium bromide (Pavulon, Organon), and artificially ventilated.

The lumbo-sacral and low thoracic spinal segments were exposed and the dura mater removed. After the surgical procedures, the animal was restrained in a stereotaxic apparatus using spinal and pelvic clamps. The ventral roots L4-S2 were dissected and sectioned. The L7 ventral root was placed in a pair of electrodes for recording. Pools were made with the skin around the exposed tissues and filled with mineral oil (after placement of the electrodes). The animal was maintained at a constant temperature (37 °C) by means of a heating pad and radiant heat. The left MG nerve was cut and placed in pair of electrodes for stimulation. With the LGS nerves intact the left LGS muscles were freed from the skin and surrounding tissue as completely as possible without disturbing their blood supply. The tendon of Achilles was longitudinally attached to the mechanical stimulator-transducer. Transmission of mechanical noise through the bone was avoided by removing a 1 cm section of the left femur.

**Test stimuli (input signal).** Test stimuli (electrical pulses) were applied on the MG nerve (Figure 1A). Such stimuli consisted of single pulses with a total duration of 0.1 msec delivered at a constant frequency of 2.5 Hz. Figure 1B shows the input-output curve for the L7 MSR amplitude versus the test stimulus strength and Figure 1C shows
the power spectrum of the MSRs, indicating a frequency of response of 2.5 Hz. The asterisk in Figure 1B indicates the weak intensity of the periodic stimuli used to evoke the MSRs.

**Input noise.** Mechanical noise was applied with a closed-loop mechanical stimulator-transducer that allowed measures of the displacement. The output of a function generator [Wavetek (San Diego, CA) 132] provided input to the stimulator-transducer and supplied the input noise (Figure 1A). In the protocol of stimulation we employed 5 or 6 levels of noise; but because we used a non-digital-Wavetek function generator (Figure 1A) the increments in the intensity level of noise were exactly not equally spaced. Noise with a power spectrum ranging from 0.1 to 200 Hz was applied on the tendon of the LGS muscle (Figure 1A). Figure 1D shows the power spectrum of a typical noisy stimulus. The inset in Figure 1D shows the amplitude distribution (Gaussian) of the typical noisy stimulus. The magnitude of the input noise was quantified by means of the standard deviation of the input stretching ($\sigma_n$ of input noise, displacement expressed in $\mu$m). All noise applications were made longitudinally with the LGS muscle stretched by 500 $\mu$m.

**Protocol of stimulation.** To access the effects of mechanical noise (local tendon-displacements) to the LGS muscle on the amplitude of the MG MSRs, 64 periodic pulses were applied to the MG nerve and the evoked MSRs were averaged. The effects of different levels of noise on the MSR amplitude were measured with respect to averages over 64 MSRs in control conditions. We applied five or six sequences, each with a different mechanical noise intensity level. The presentation order of the different noise levels was varied randomly to remove possible serial effects. We waited a period of about 1 or 2 minutes to apply a control sequence after every noise level. Because in
long lasting recordings of MSRs we observed stability in the MSR amplitude sequence (see Figure 1E) we used 64 samples of MSRs. We observed that the statistical significance of the data (student’s t-test) was successfully accessed with these 64 samples in control conditions versus other 64 samples for each level of noise. Every change in the mean MSR amplitude produced by each level of noise was compared with their own control (i.e., the mean MSR elicited by 64 electrical pulses applied to the MG nerve).

**Electrophysiological recordings.** Spinal cord potentials (output afferent volleys; see Figure 2D) were recorded from the surface of the L7 dorsal horn with a silver ball electrode against an indifferent electrode placed on the near paravertebral muscles. Furthermore, dorsal root potentials were recorded with two electrodes, one placed distally on the central end of a sectioned L6 or L7 dorsal rootlet, and the other close to, but not touching, the spinal cord. Monosynaptic reflexes were recorded from the L7 ventral root (Figures 1A and 2D). In our experiments we observed that the application of mechanical noise on the LGS muscle did not produce a significant change in the mean amplitude of the dorsal root reflexes (black circles) or the afferent volleys (white squares) elicited by electrical stimuli applied to the MG nerve (see Figure 2E).

In other series of experiments intracellular recordings were obtained from motoneurons receiving synaptic inputs from LGS and MG afferents (Figure 3B). These recordings were made by means of 3M potassium acetate-filled micropipettes (tip diameter 1-2 μm) connected to high-impedance DC amplifier. Motoneurons were identified by their antidromic response to ventral root stimulation. Data acquisition was performed with a sampling rate of 10 kHz.
**Data analysis.** Data acquisition of the input noise and of the spinal potentials was performed with a sampling rate of 10 kHz. Frequency filters were set to 0.3 Hz and 30 kHz. We estimated effects of mechanical noise (applied to the LGS muscle) on monosynaptic reflexes directly from the averaged amplitude of monosynaptic reflexes elicited by stimulation to the MG nerve. The mechanical noise alone applied to the LGS muscle did not produce MSRs. We averaged 64 monosynaptic reflexes for each level of noise or absence of noise. The monosynaptic reflex amplitudes were expressed as a percentage of control (100%) ± standard deviation (error bars in Figures 2F-H). Control was considered as the monosynaptic reflex response in absence of noise. A student’s t-test (p<0.05) was used to test for significant changes of the maximal amplitude value for an intermediate level of noise respect to the mean control amplitude.

**Mathematical formulas and model parameters used in computer simulations.** To model our experimental results we considered a pool of independent but slightly different motoneurons. The pool received convergent afferent synaptic inputs from sources generating signal and noise (see figure 4F). The amplitude of the selected signal was weak enough not to produce a spike in the absence of noise.

Because there is experimental evidence that approximately 60 MG Ia-afferents project to each of the 300 alpha-motoneurons (Mendel and Henneman, 1968) in our model we only considered a pool of 300 motoneurons. Furthermore, because the proportion of possible direct excitatory connections between motoneurons is low (Gogan et al., 1977) and there is controversy that there are electrical connections between neighboring motoneurons in adult cats (Hinckley and Ziskind-Conhaim, 2006) we have not considered couplings between them. Moreover, we do not expect that our model yield qualitatively different results after including either electrical or excitatory connection between motoneurons.
To describe the motoneuron activity, we used the Morris-Lecar model (Morris and Lecar, 1981):

\[
\frac{dV_i}{dt} = \frac{1}{C_m} \left( I_{\text{app}}^{\text{ext}} - I_i^{\text{ion}} - I_i^{\text{syn}} \right) + I_i^{\text{rand}} 
\]

(1)

\[
\frac{dW_i}{dt} = \phi \Lambda (V_i) \left[ W_i (V_i) - W_i \right] 
\]

(2)

where \(i=1,\ldots,N\) index the neurons, and \(V_i\) and \(W_i\) represent the membrane potential and the fraction of open potassium channels, respectively. \(C_m\) is the membrane capacitance per unit area. \(I^{\text{app}}\) is an external bias current. The ionic current is given by

\[
I_i^{\text{ion}} = g_{Ca} M_\infty (V_i) (V_i - V_{Ca}^0) + g_K W_i (V_i - V_K^0) + g_L (V_i - V_L^0) 
\]

(3)

where \(g_a\) and \(V_a^0 (a = Ca,K,L)\) are the conductance and the resting potentials of the calcium, potassium and leaking channels, respectively. \(\phi\) is the decay rate of \(W_i\) and we define the following functions of the membrane potential:

\[
M_\infty (V) = \frac{1}{2} \left[ 1 + \tanh \left( \frac{V - V_{M1}}{V_{M2}} \right) \right] 
\]

(4)

\[
W_\infty (V) = \frac{1}{2} \left[ 1 + \tanh \left( \frac{V - V_{W1}}{V_{W2}} \right) \right] 
\]

(5)

\[
A_\infty (V) = \tanh \left( \frac{V - V_{W1}}{2V_{W2}} \right) 
\]

(6)
where $V_{M1}, V_{M2}, V_{W1}$ and $V_{W2}$ are constant values. The synaptic current is defined as

(Destexhe et al., 1994):

$$I_{i}^{\text{syn}} = \sum_{j \in \text{neigh}(i)} g_{i}^{\text{syn}} r_{j} (V_{i} - E_{j}) \quad (7)$$

where $g_{i}^{\text{syn}}$ is the conductance of the synaptic channel. $r_{j}$ represents the fraction of bound receptors described as:

$$r_{j} = (1 - e^{-\alpha t}) \quad \text{for } t \leq t_{\text{on}} \quad (8)$$

$$r_{j} = (1 - e^{-\alpha t_{\text{on}}}) e^{-\beta (t-t_{\text{on}})} \quad \text{for } t > t_{\text{on}}$$

where $\alpha$ and $\beta$ are rise and decay time constants respectively. Here “$t_{\text{on}}$” represents the time at which the synaptic connection is activated.

The value of the parameters we used (Balenzuela and Garcia-Ojalvo, 2005) are specified in the following table:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{m}$</td>
<td>5(\mu)F/cm²</td>
</tr>
<tr>
<td>$I_{\text{app}}$</td>
<td>65 mV</td>
</tr>
<tr>
<td>$g_{K}^{0}$</td>
<td>8(\mu)S/cm²</td>
</tr>
<tr>
<td>$g_{L}^{0}$</td>
<td>2(\mu)S/cm²</td>
</tr>
<tr>
<td>$g_{Ca}^{0}$</td>
<td>4.4(\mu)F/cm²</td>
</tr>
<tr>
<td>$V_{K}$</td>
<td>−80 mV</td>
</tr>
<tr>
<td>$V_{L}$</td>
<td>−60 mV</td>
</tr>
<tr>
<td>$V_{Ca}$</td>
<td>120 mV</td>
</tr>
</tbody>
</table>
It has been recently shown that diversity might play an important role in forced excitatory systems, equivalent to the one played by noise in the stochastic resonance phenomena (Tessone et al. 2006). Tessone et al. (2006) demonstrated that the response of a system to an external weak periodic signal can be optimized by an intermediate level of diversity between the elements composing the system, even in the absence of any other noise source. Consequently, diversity (represented by a quenched noise) and stochastic noise seem to play qualitatively the same role. Since diversity is intrinsic in nature, we included it in our model assuming that it plays the same role as the internal noise sources.

To account for the natural heterogeneity existing in spinal motoneurons, we introduced diversity in the conductance channel parameters: $g_k = (A \cdot w_k + 1) g^0_k$, $g_L = (A \cdot w_L + 1) g^0_L$ and $g_{Ca} = (A \cdot w_{Ca} + 1) g^0_{Ca}$ also in the synaptic amplitude $g^{syn} = (A \cdot w_{syn} + 1) g^{syn}_0$, being $w_j$ ($j = K, L, Ca, syn$) a Gaussian distributed random number of zero mean and unit variance. $A=0.1$ is the unitary percent of heterogeneity.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_{M1}$</td>
<td>$-1.2 \text{ mV}$</td>
</tr>
<tr>
<td>$V_{M2}$</td>
<td>$18 \text{ mV}$</td>
</tr>
<tr>
<td>$V_{W1}$</td>
<td>$2 \text{ mV}$</td>
</tr>
<tr>
<td>$V_{W2}$</td>
<td>$30 \text{ mV}$</td>
</tr>
<tr>
<td>$\varphi$</td>
<td>$1/25 \text{ s}^{-1}$</td>
</tr>
<tr>
<td>$\alpha$</td>
<td>$0.33 \text{ ms}^{-1} \text{ mM}^{-1}$</td>
</tr>
<tr>
<td>$\beta$</td>
<td>$0.2 \text{ ms}^{-1}$</td>
</tr>
<tr>
<td>$g^{syn}_0$</td>
<td>(specified in each case)</td>
</tr>
<tr>
<td>$\tau_{syn}$</td>
<td>$3 \text{ ms}$</td>
</tr>
<tr>
<td>$E_s$</td>
<td>$0 \text{ mV}$</td>
</tr>
</tbody>
</table>

Table 1. Parameters used in the numerical simulations.
we considered. In our simulations we took $I_{i_{\text{syn}}}$ as periodic synaptic pulses every 400 ms (i.e., 2.5 Hz as in the experiments) with time “$t_{\text{on}}$” equals to 3 ms and amplitude $g_{\text{syn}}$. “

RESULTS

Experimental Results

All animals that we examined exhibited a SR behavior in the amplitude of monosynaptic reflexes (MSRs) elicited by electrical stimulation to the MG nerve when different levels of continuous random stretches (input noise) on the LGS muscle were applied. We observed the SR-like effect when a weak electrical stimulus was applied to the MG nerve. Figure 1B illustrates with an asterisk the weak intensity used to produce MSRs of about 20 µV in one typical experiment. We computed the mean amplitude of successive MSRs in control conditions (elicited by electrical stimuli to the MG nerve) and during the application of different levels of noise applied to the LGS muscle. Figure 1E shows in circles the amplitudes of successive MSRs (at 2.5 Hz) for the three levels of noise indicated (low, intermediate and high). The MSR amplitude in control conditions is indicated with black circles. Note that the amplitude of the successive MSRs was significantly increased ($p<0.05$) when an intermediate level of mechanical noise was applied to the LGS muscle (as is illustrated in Figure 1A) and was decreased when a high level of such mechanical noise was added.

Figures 2A-C show examples of successive recordings of the input signal (Figure 2A), input noise (Figure 2B), and the corresponding output afferent volleys and output MSRs (Figure 2C) for three different levels of input noise as is indicated (“low”,...
“intermediate” and “high”). MSRs were elicited by periodic stimulation to the MG nerve (1.2xT) at a frequency of 2.5 Hz. The input noise consisted of random stretches applied to the LGS muscle (see methods and Figure 1A). Figure 2C illustrates that the amplitude of the MSRs was facilitated for an intermediate level of noise applied to the LGS muscle. Note that in this example individual MSRs increased their amplitude for an intermediate level of noise. This observation was confirmed statistically after averaging over 64 MSRs for different levels of noise in six different decerebrated cats (Figures 2F, G and H). The maximal point in each graph of Figures 2F to 2H and the corresponding control value were used for the statistical Student’s t-test. We observed that in these animals the mean MSR amplitude was significantly enhanced (p<0.05, Student’s t-test) at an intermediate noise level (see asterisks in graphs of Figures 2F-H). We observed significant maximal changes (p<0.05, Student’s t-test) in the mean MSR of 108.1 %, 110.2 %, 115.2 %, 141.5 %, 114.4 % and 110.6 %, respectively, for the six different experiments. The mean percentage increase in the MSR amplitude respect to control for all the animals was statistically significant 117 ± 12 % (p<0.05, Student’s t-test). We observed that the graphs of MSR amplitude versus input noise exhibited different profiles between animals. While in some cases a low level of input noise was enough to produce an enhancement of the MSR amplitude, in other cases a high level of input noise was required. This fact reflects not only the intrinsic diversity between the different cats, but also that the internal level of noise is different in each animal.

Furthermore, we observed that when a supra-threshold stimulus was applied to the MG nerve the amplitude of MSRs significantly (p<0.05; t-test) decreased as a function of the level of noise applied to the LGS muscle (Figure 2I).

In contrast, it is important to note that in all the experiments the noisy stretching of the LGS muscle did not produce SR-like effects in the MG dorsal root potentials or
in the afferent volleys. Figure 2E illustrates a graph of the mean amplitude of the afferent volley (white squares) and dorsal root potentials (black circles) for the experiment illustrated in Figure 2G (black lines). Note that no significant changes in the amplitude of the afferent volleys were observed for the different levels of noise. Similar results were obtained in all the experiments. This suggests that in our experimental conditions (and the noise range employed) the SR observed in the monosynaptic reflexes was mediated by postsynaptic actions on the motoneurons. This fact justifies the use of postsynaptic connections in the model that we used to explain our experimental results, as described in the next section (numerical simulations).

To further investigate in detail the effects of noise on the motor responses, in other series of experiments intracellular recordings were obtained from motoneurons. However, only in one cat we obtained successful recordings in two motoneurons (-55 and -65 mV of resting potential) and with stable recordings during all the stimulation protocol (the same used for MSRs recorded from the L7 ventral root; see methods). The only difference was that in this case we defined one weak (i.e., sub-threshold) stimulus as the stimulus that no produces an action potential. With this assumption, we applied a sequence of 64 stimuli to the MG nerve with an intensity to produce a sub-threshold monosynaptic response. Figure 3A shows the raster displays and the corresponding histograms of the number of action potentials evoked in one motoneuron for five different levels of noise. Figure 3A shows the effect produced by increased levels of mechanical noise applied to the LGS muscle. Figure 3C shows in black circles the maximum peak of the successive histograms illustrated in Figure 3A. Note that the number of action potentials in the motoneuron was increased for a particular level of mechanical noise applied to the LGS muscle. A similar result was obtained for another motoneuron recorded in the same experiment (see white circles in Figure 3C).
Horizontal lines in Figure 3C represent the magnitude of a 95 % confidence interval, which provides a scale against which to assess the significance.

**Numerical simulations**

Recently it was shown that the total conductance resulting from a sum of thousands of synaptic inputs has a power spectrum that approximates a Lorentzian shape, i.e., which decays as $\exp(-t/\tau)$. This was demonstrated in a detailed physiological model of cortical neurons subject to stochastic synaptic inputs (Destexhe et. al, 2001). The Gaussian nature of the Orstein-Uhlenbeck process and its Lorentzian spectrum qualitatively match the conductances underlying synaptic noise, thus providing an effective stochastic representation that captures the amplitude of the conductances, their standard deviation and the spectral structure. This motivates the use of the Orstein-Uhlenbeck process as a valid description of synaptic noise (Destexhe et. al, 2001) that would match our experimental conditions. Following the Destexhe et al. (2001) idea, for the case of motoneurons, we assumed that external noise $I^{\text{rand}}$ that enters the pool of neurons through the synaptic connections is modeled as an Orstein-Uhlenbeck process, i.e. as a colored noise source, with a correlation time of $\tau = 0.5$ ms. Integration was made by using a stochastic Runge-Kutta method (known as the Heun method) following ref. (San Miguel et al. 1999).

As we said before, we initially verified that no neuron fired a pulse under the solely presence of the periodic signal or noise for the subthreshold value of $g_{\text{syn}}^{\text{cm}} = 1 \mu\text{S/cm}^2$. For the other value of $g_{\text{syn}}^{\text{cm}} = 1.4 \mu\text{S/cm}^2$ the signal is suprathreshold and induces pulsations even in the absence of noise. In the subthreshold case, we combined the two inputs and fed the 300 neurons with both the signal and noise. To account for
the global response we averaged the membrane potential generated by all of the neurons.

Figure 4 contains similar information to that shown in the experiments. As in Figure 2B the black (white) triangle in Figure 4A indicates the weak (strong) intensity of the periodic stimulus used to evoke the simulated responses of the motoneurons. Figure 4B illustrates the power spectrum of the input signal while Figure 4C illustrates the power spectrum of the colored noise. In Figure 4D we plot the monosynaptic response amplitude, computed as the number of spikes generated in a small time window by the combination of the signal and the noise (where the number of responses generated only by the noise has been subtracted) versus the noise level, normalized to the number of spikes generated under the control noise value, as in Figures 2F-H, of 25 in this numerical case. Closed symbols stand for a sub-threshold signal while open symbols stand for the response of the system to a supra-threshold signal (see discussion below). For the sub-threshold signal a peak at intermediate noise level can be clearly seen. This indicates that the modeled response of the system also exhibits the SR effects for the combination of a sub-threshold signal and noise as seen in the experiment. Figure 4E shows a graph for the collective evoked amplitude response to a sub-threshold signal of the 300 motoneurons, as a simulation of the monosynaptic reflex response, versus the input noise intensity. The values in the ordinates have been again calculated by averaging over 700 periods of the input signal. A clear maximum at intermediate noise levels that decays for smaller or larger noise strengths can be seen, in agreement with the experiments. Error bars indicate a small dispersion of the maximum values over the evoked potentials for the 700 input pulses. Although the comparison is only qualitative, the results agree very well with the experiments, showing that a simple model including pools of motoneurons receiving convergent synaptic inputs from
sources generating the periodic signal and the noise is sufficient to explain the experimental observations.

To go further in our numerical predictions we considered a supra-threshold signal for the stimulus ($g_{syn} = 1.4 \ \mu S/cm^2$, see white triangle symbol in Figure 4A) to check whether SR still holds under this condition. The result is shown in Figure 4D with open circles. It can be clearly seen that the maximum disappeared; as expected supra-threshold signals are not amplified and the response degrades for increasing noise level, as it was also observed in the experiment.

**DISCUSSION**

Our results show that the monosynaptic reflex pathway exhibits the stochastic resonance behavior, a phenomenon that can be qualitatively reproduced in a realistic model of synaptic integration on a pool with a relatively small number of motoneurons with diversity.

SR was first proposed in 1981 as a possible explanation for the apparent periodicity of Earth’s ice ages (Benzi et al. 1981). A variety of nonlinear systems physical and biological exhibit this phenomenon; in particular, sensory systems. Some examples related with the present study, but in the peripheral nervous system, have been reported: in tactile sensations (Collins et al. 1996), in muscle spindle receptors (Cordo et al., 1996) or in afferents from Golgi tendon organs and primary and secondary endings of the cat muscle spindles (Fallon et al., 2004). However, although the study of Fallon et al (2004) was performed in cats they did not provide evidence about the existence of the SR phenomenon in the motor system, in particular in the Ia-monosynaptic reflex pathway of the cat spinal cord.
**Stochastic resonance in the motor system**

We demonstrated experimentally that a particular level of noise applied to the stretching of the LGS muscle can produce an enhancement of the MSRs evoked by a periodic stimulus to the Ia afferent fibers of a synergistic muscle (MG). We obtained a similar result in the intracellular monosynaptic reflex responses of motoneurons, thus providing support to the monosynaptic ventral root responses. These results demonstrate that the SR is not exclusive of the sensory systems and can be exhibited in the output of the motor system, within the central nervous system. This is consistent with previous reports in sensory systems, visual (Mori and Kai, 2002) and somatosensory (Manjarrez et al., 2003), in which the SR has been observed as a result of the synaptic integration of signal and noise within the central nervous system.

Our study extends observations of Cordo et al. (1996) by showing that the SR occurs in the central nervous system, specifically in the spinal motoneurons, and not only in the peripheral nervous system at the muscle spindle stage. To our knowledge our study presents the first direct demonstration that the SR can also be exhibited by the motor system.

The idea that noise has an effect on the motor system was first indirectly suggested by Priplata et al. (2002, 2006), who demonstrated that the addition of tactile noise to the feet of quietly standing subjects can lead to an enhanced balance control. However, because tactile noise was applied to the feet they can not discard that the stochastic resonance phenomenon was also produced by the somatosensory system (Collins et al. 2003; Priplata et al., 2006). In this context, we consider our study in cats as a direct evidence of the stochastic resonance in the motor system because we did not
stimulate the skin and instead we exclusively activated the motoneurons by stimulation of group I muscle afferents.

Furthermore, we consider that our experimental method allowed a selective stimulation of the primary endings of muscle spindles by applying small noisy changes of length (noisy stretching) to a muscle. In fact, the effective range of noisy stretching that enhanced the MSR amplitude in our experiments was similar to the amplitude range (<60 µm) of sinusoidal stimulation (i.e., vibration) which produces selective activation of primary muscle spindles without activating secondary endings and Golgi tendon afferents (Brown et al., 1967). This finding provides additional support to the hypothesis that the interactions between the input signal and the input noise associated to the enhancement of the MSRs were at the postsynaptic level on the motoneurons (see also Figure 2E to support the fact that no presynaptic effects were detected).

**The model and its justification**

Our model qualitatively agree very well with the experiments, showing that a simple simulation including pools of motoneurons receiving convergent synaptic inputs from sources generating the noise and the periodic signal is sufficient to explain the experimental observations. Other models of neural networks, as Hodgkin-Huxley (Liu et al., 2006), leaky integrator models (Kohn, 1998) or Izhikevich (2003, 2004) could be implemented, however the Morris-Lecar (1981) method offers a simple system of equations to simulate neuronal networks from the spinal cord (Skinner and Mulloney, 1998). Furthermore the natural diversity we introduced in the synaptic and conductance channel parameters makes the model more realistic, still retaining the most relevant features of the SR-phenomenon. This point is original because to our knowledge there are not models in the literature that consider diversity in the parameters of the equations
modeling the monosynaptic reflex pathway, in the context of the stochastic resonance. Our model is supported by recent theoretical studies in the context that diversity might play an important role in SR phenomena (Tessone et al. 2006).

Furthermore, the modeling of monosynaptic reflexes and their modulation by noise could have some relevance in, e.g., robots development. In this context, the present study could have important implications in robotics and neural motor prosthetics (Friehs et al., 2004; Ando, 2006).

To account for the natural heterogeneity existing in spinal motoneurons we introduced diversity in the synaptic input and in the conductance channel parameters. We consider that the modeling of a group of heterogeneous neurons is interesting because the main difference between homogenous and inhomogenous arrays is that the response of a homogeneous array without interaction is equivalent to the response of a single neuron. In this context, the modeling of a homogeneous network without interactions does not represent the behavior of natural neurons. On the contrary, an inhomogeneous array (diversity) is intrinsic in neuronal systems and the purpose of including it was to show that the stochastic resonance phenomenon is very robust. Moreover, it has been recently shown that diversity plays a similar role as the internal noise (as shown by Tessone et al. 2006) in which the stochastic resonance behavior can be even favored by the presence of the otherwise natural diversity.

Regarding our simulations, because we considered a large number of motoneurons with diversity we assume that an additional source of internal noise should not change the results qualitatively. Therefore, in our computer simulations we have not included internal noise sources. The addition of internal noise may produce an effect that could be quantitatively but not qualitatively different.
**Noise sources and functional implications**

Because in our experiments the levels of noisy stretching of the LGS muscle did not produce significant effects in the amplitude of MG dorsal root potentials or in the amplitude of afferent volleys (Figure 2E) we suggest that the SR observed in the monosynaptic reflexes was mediated by noisy postsynaptic actions on the motoneurons. However, we can not exclude the possibility that for higher levels of noise in the stretching of the LGS muscle, relative to the range ($\sigma_n = 0$ to $160 \, \mu$m) explored in the present study, some presynaptic effects could also contribute to the SR of the monosynaptic reflexes. Although in this circumstance we should also consider the opposed fact that electrical stimulation to extensor group Ia muscle afferents produces a relative very small primary afferent depolarization in extensor group Ia muscle afferents (Eccles et al., 1962). Therefore, further experiments will be necessary to explore in detail this issue. In this context, a discussion of the possible noisy sources participating in the enhancements of the amplitude of the monosynaptic reflexes merits a discussion.

Our results suggest that the monosynaptic reflex pathway uses a stochastic resonance-type mechanism to increase the monosynaptic reflexes via a noisy synaptic input on the motoneurons. Such noisy synaptic input could be originated from descending pathways (Brouwer and Ashby 1992), from dorsal horn neurons producing spontaneous cord dorsum potentials (Manjarrez et al., 2005), or from propriospinal neurons (Swinnen and Duysens, 2004). There is evidence that propriospinal neurons provide a linkage between cervical and lumbar neuronal circuits of the spinal cord that act in the interlimb coordination of leg and arm movements during human locomotor activities (Swinnen and Duysens, 2004). Therefore, stretch reflexes in the lower limbs of humans can be affected by alterations in arm postures, thus suggesting that there
might be interlimb reflex modulation with movement (Delwayde et al., 1977). We suggest that random properties of propriospinal neurons could provide the stochastic input required to produce a stochastic resonance mechanism in the Ia-motoneuron reflex pathway. This means that propriospinal neurons could serve as a beneficial intrinsic noise source for the monosynaptic reflex pathway. Enhancements of the monosynaptic reflexes could be mediated by an intermediate level of input noise on the motoneurons provided by the internal noise of the propriospinal system. There are studies supporting the idea that “internal noise” plays a role in information transmission within the central nervous system, via the “internal stochastic resonance” phenomenon (Manjarrez et al., 2002b). This phenomenon has been examined in detail in diverse nonlinear systems (Gailey et al., 1997; Lee et al., 1998; Balazsi et al. 2001; Li and Li, 2003; Li et al., 2004; for review see Lindner et al., 2004) and could be an interesting issue to explore in the cat spinal cord in the context of the motor output.

The possibility that the application of noise could improve the motor performance of stroke-survivors has been considered recently in an empirical study (Rogers et al., 2006). Such study was motivated by the fact that 75% of stroke-survivors have sensorimotor deficits such as hemi-paresis and proprioceptive losses, with resulting change to both muscle activation patterns and reflex modulation during movement. Rogers et al. (2006) suggested that noise can be used as a potential method for eliciting functional neuroplastic change post-stroke, via the stochastic resonance phenomenon. While pedaling a motorized cycle ergometer, soleus H-reflexes were recorded alone (in control conditions), or during noise, presented to either the Hamstrings or Quadriceps of the ipsilateral paretic limb. Electrical noise, in the form of sub-sensation Gaussian white noise, was delivered to the target muscle via surface electrodes. Rogers et al (2006) found that for noisy stimulation to either the Quadriceps
or Hamstrings muscles there was a significant change between the mean normalized soleus H-reflex amplitudes relative to the control condition (p<0.01), with an increase in soleus H-reflex with noise. We consider that the present study in cats provides support to these empirical observations in persons with post-stroke hemiparesis.

In general, it is tempting to suggest that in physiological conditions adjustments in the level of intra-spinal noise sources could contribute to control the size of monosynaptic reflexes via the stochastic resonance phenomenon. For an intermediate level of noise a desirable enhancement of MSRs could occur; however, for higher levels of noise a desirable decrease could be produced depending of the requirements for the motor task. This last point could also be of importance in clinics if we consider that some pathological conditions of the motor system involve spastic states, in which, is desirable the attenuation of MSRs in certain muscles. In this context, our study provides support to examine in future studies the levels of noise that could be beneficial in humans to control the amplitude of MSRs by means of noise applied to the Achilles tendon, via the stochastic resonance phenomenon. Therefore, our study is important because suggest that certain levels of mechanical noise could be employed in rehabilitation interventions in order to improve the performance of motor task requiring an enhancement of monosynaptic reflexes.
REFERENCES


FIGURE LEGENDS

Figure 1. A, Scheme of the experimental arrangement. B, Amplitude of Monosynaptic reflexes (MSR) versus intensity of the electrical stimuli (input signal, expressed as times threshold, xT) applied to the medial gastrocnemius nerve (MG). The asterisk indicates the weak intensity employed to produce the MSRs in control conditions and during continuous noise applied to the lateral gastrocnemius plus soleus muscle (LGS). C, Power spectrum of the MSRs elicited at 2.5 Hz. D, Power spectrum of the random stretches (mechanical input noise) applied to the LGS muscle by means of a close-loop mechanical stimulator-transducer. All noise applications were made longitudinally with the LGS muscle stretched by 500 µm. Inset in Figure 1D shows amplitude distribution for the random stretches around this 500 µm. E, Amplitude of successive monosynaptic reflexes in the conditions indicated. Note that the mean amplitude of the MSRs was significantly enhanced (p<0.05, t-test) for an intermediate level of mechanical noise.

Figure 2. The amplitude of the monosynaptic reflexes evoked by the electrical stimuli to the medial gastrocnemius (MG) nerve was an inverted U-like function of the mechanical noise (σ_m) applied to the lateral gastrocnemius plus soleus (LGS) muscle. A, Continuous recordings of the input signal (periodic electrical stimuli applied to the MG nerve at 2.5 Hz) for the three conditions indicated (low, intermediate and high levels of noise). B, Continuous recordings of the mechanical input noise (random stretches applied to the LGS muscle) for the same conditions indicated above. C, Continuous recordings of the output afferent volleys and of the output monosynaptic reflexes (MSRs) for the same conditions of noise indicated above. D, The same scheme illustrated in Figure 1A indicating how the afferent volleys were recorded. E, Typical graph of afferent volley (open squares) and dorsal root potential (black circles)
amplitude versus input noise intensity for one animal. **F-H**, MSR amplitude versus input noise intensity for six cats, respectively, when input signal was weak. Dashed horizontal line indicates the control. Error bars indicate the standard deviation obtained from the averaging of 64 MSRs for each level of noise. Asterisks indicate points for which the difference between the effect and the control was statistically significant and the MSR amplitude was increased (p<0.05, Student’s t-test). **I**, The same as F-H, but for MSRs elicited by supra-threshold stimulus in one animal.

**Figure 3.** A particular level of mechanical noise to the LGS muscle increases the probability of response of motoneurons to a weak electrical stimulus applied to the MG nerve. **A**, Raster displays and peri-stimulus time histograms of action potentials evoked in one motoneuron for different levels of noise applied to the LGS muscle, 11.3, 16.5, 33.1, 45.7 and 57.9 µm, respectively. **C**, Black circles indicate the maximal amplitude of the histograms in figure 3A (counts). White circles, show the corresponding graph obtained from a second motoneuron. A 95% confidence interval is indicated in gray line for the graph in white circles, and in dashed line for the graph in black circles. **B**, Scheme of the experimental arrangement for the intracellular recording of spinal motoneurons.

**Figure 4.** The model considers diversity in the parameters of the equations that generate postsynaptic potentials in the simulated motoneurons, and diversity in the synaptic conductance. That means that each simulated motoneuron receives synaptic input with a different synaptic weight (w_j, see text for details), which is a random number. Furthermore, each simulated motoneuron receives Gaussian synaptic noise, indicated by I^{rand}. This synaptic-like noise source is modeled as an Orstein-Uhlenbeck process, as a colored noise with correlation time of τ=0.5 ms (according to Destexhe et al., 2001). **A-**
B, Same format as Figures 1B-C. D, Collective summated evoked response of 300 motoneurons (300 M) versus the input noise intensity, i.e., the simulated MSR amplitude versus input noise. The graph in black circles was obtained when the signal was evoked by a sub-threshold stimulus and the graph in white circles when the signal was elicited by a supra-threshold stimulus. E, The same as D (black circles). The values in the ordinates have been calculated by averaging over 700 periods of the evoked responses. Note the qualitative similitude between these graphs and the experimental results. F, Scheme of the model
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FIGURE 4
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Table 1. Parameters used in the numerical simulations.