Use of galvanic vestibular feedback to control postural orientation in decerebrate rabbits

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Zelenin PV, Hsu L-J, Orlovsky GN, Deliagina TG. Use of galvanic vestibular feedback to control postural orientation in decerebrate rabbits. J Neurophysiol 107: 3020–3026, 2012. First published March 7, 2012; doi:10.1152/jn.00042.2012.—In quadrupeds, the dorso-side-up body orientation during standing is maintained due to a postural system that is driven by feedback signals coming mainly from limb mechanoreceptors. In caudally decerebrated (postmammillary) rabbits, the efficacy of this system is considerably reduced. In this paper, we report that the efficacy of postural control in these animals can be restored with galvanic vestibular stimulation (GVS) applied transcutaneously to the labyrinths. In standing intact rabbits, GVS causes a lateral body sway towards the positive electrode. We used this GVS-caused sway to counteract the lateral body sway resulting from a mechanical perturbation of posture. Experiments were performed on postmammillary rabbits that stood on the tilting platform with their hindlimbs. To make the GVS value dependent on the postural perturbation (i.e., on the lateral body sway caused by tilt of the platform), an artificial feedback loop was formed in the following ways: 1) Information about the body sway was provided by a mechanical sensor; 2) The GVS current was applied when the sway exceeded a threshold value; the polarity of the current was determined by the sway direction. This simple algorithm allowed the “hybrid” postural system to maintain the dorsal-side-up orientation of the hindquarters when the platform was tilted by ± 20°. Thus, an important postural function, i.e., securing lateral stability during standing, can be restored in decerebrate rabbits with the GVS-based artificial feedback. We suggest that such a control system can compensate for the loss of lateral stability of various etiologies, and can be used for restoration of balance control in patients with impaired postural functions.

posture; balance; sensory feedback; galvanic vestibular stimulation; rabbit

MAINTENANCE of the basic body posture, upright in humans and dorsal-side-up in quadrupeds, is a vital motor function. Efficient control of the basic posture is equally important for standing and during walking as well as for providing support of voluntary limb movements (Horak and Macpherson 1996; Macpherson et al. 1997; Massion 1998). The basic posture is maintained due to the activity of a closed-loop control system driven by sensory feedback signals coming mainly from limb mechanoreceptors, although vestibular and visual inputs can also contribute (Beloozerova et al. 2003; Macpherson et al. 2007; Talbott and Brookhart 1980). The system compensates for any deviations from the stabilized body position by producing corrective motor responses.

Different diseases and traumatic injuries of CNS result in impairment of the system controlling body posture and balance (see e.g., Maynard et al. 1990; Sommerfeld et al. 2004). In a number of these cases, the spinal pathways transmitting supraspinal commands for postural corrections remain mostly undamaged (see e.g., Tator et al. 1993), and a possible reason for postural deficits is insufficient value and/or incorrect timing of these commands addressed to the spinal cord.

The goal of our study was to improve these commands by means of an artificial feedback affecting the brainstem-spinal descending systems. The study was performed on decerebrate rabbits, with the brainstem transection at the postmammillary level. These animals cannot maintain the dorsal-side-up body posture and balance (Musienko et al. 2008). Our objective was to improve the lateral stability in these rabbits by means of an artificial feedback based on galvanic vestibular stimulation (GVS).

The GVS is a type of transcranial direct current stimulation that affects vestibular afferents (Been et al. 2007), and, thus, through the brainstem-spinal descending systems, exerts influences on the subject’s posture. The response to binaural GVS in humans includes reciprocal changes in the activity of trunk and limb muscles on the two sides, resulting in a lateral body sway towards the anode (see e.g., Séverac Cauquil et al. 2000). A similar reaction to GVS (a sway towards the anode) was observed in intact rabbits (Beloozerova et al. 2003; Gorguladze 2004). Recently we have found that GVS strongly affects postural limb reflexes in decerebrate rabbits as well (Hsu et al. 2011). The idea to make use of GVS for elicitation of corrective postural responses was first proposed by Scinicariello et al. (2001). These authors have demonstrated that, in standing healthy humans, the lateral body sway caused by GVS could be used for counteracting the sway caused by a mechanical perturbation of body posture (lateral translation of the supporting platform), thus improving the lateral stability. The timing and value of the injected current were calculated on the basis of information about the imposed platform movement (a feedforward mode of postural control). In a similar study (Orlov et al. 2008), the timing and value of the injected current were determined by the feedback, which allowed responding to unpredicted postural perturbations. In the present study, we also used artificial feedback. The timing and polarity of the injected GVS current were determined by the mechanical sensor signaling a postural perturbation (the lateral body sway). It has been found that this “hybrid” GVS-based control system can secure the dorsal-side-up body orientation in the postmammillary rabbit whose innate postural mechanisms were badly damaged.

A brief account of part of this study has been published in abstract form (Zelenin et al. 2011).
METHODS

Experiments were carried out on five adult New Zealand rabbits (weighing 2.5–3.5 kg). All experiments were conducted with approval of the local ethical committee (Norra Djurförsöksnämnden) in Stockholm.

Surgical procedures. The animal was injected with propofol (average dose 10 mg/kg iv) for induction of anesthesia, which was continued on isoflurane (1.5–2.5%) delivered in O2. The trachea was cannulated. For all subsequent procedures, the animal was positioned in a metal frame, and the head was rigidly fixed. The electrodes for galvanic stimulation (0.5 cm² silver-silver-chloride) were covered by a current-conducting paste and inserted into the right and the left ear. They were fixed in the external canals by small pieces of cotton. The impedance of electrodes was 1–3 kΩ. The ground electrode was positioned on the back of the animal, and the left electrode was placed on the right side of the head. The currents could be regulated between the ground and the right electrode, another one between the ground and the left electrode. These currents were not less than 1 h after cessation of anesthesia.

Experimental design. As shown in Fig. 1A, the head of the rabbit was rigidly fixed and the forequarters were suspended in a hammock. The hindlimbs were positioned on a platform (inter-feet distance, 11 cm); they provided support for the posterior part of the body and could perform corrective movements in response to tilts of the platform (Fig. 1B–D). A time profile of tilting the platform (Fig. 1E) was trapezoidal and symmetrical in relation to the horizontal platform position. Each extreme position was maintained for ~2.5 s, and the transition between them lasted ~0.5 s. These movements of the platform were repeated periodically (period ~6 s). The tilt angle of the platform was monitored by a mechanical sensor. The lateral displacements of the top point of the posterior trunk were monitored by another mechanical sensor (S). Signals from this sensor were used to control parameters of GVS (see RESULTS).

In this study, two configurations of GVS were used (Séverac Cauquil et al. 2000). In open-loop experiments, we used binaural configuration of GVS with one source of stimulating current. The current was passed between the two electrodes, which were positioned in the right and left ears (see Surgical procedures). This current activated vestibular fibers on the cathode side and inhibited those on the anode side (Minor and Goldberg 1991). In closed-loop experiments, we used double monaural configuration of GVS with two independent sources of stimulating currents. One current was passed between the ground and the right electrode, another one between the ground and the left electrode. These currents could be regulated separately to compensate for possible asymmetry in GVS responses (see RESULTS).

Recordings and data analysis. Signals from EMG electrodes and from position sensors were amplified, digitized with a sampling frequency of 5 kHz (EMGs) and 1 kHz (sensors), and recorded on a computer disk using the data acquisition and analysis system (Power1401/Spike2; Cambridge Electronic Design, Cambridge, UK). In most experiments, EMG signals were rectified and smoothed. The smoothed output at time t was the average value of the input from time \( t-\tau \) to \( t+\tau \); the value of \( \tau \) was 50 ms. All quantitative data in this study are presented as means ± SD. Student’s t-test was used to characterize the statistical significance when comparing different means; the significance level was set at \( P = 0.05 \).

RESULTS

Open-loop condition. Each tilt of the platform caused a body sway towards the side moving downward. The excursions of the top body point between the left and right tilted positions (trace S in Fig. 2A) were large (6–7 cm). On average, this value was 6.3 ± 2.1 cm (means ± SD, \( n = 17 \)). The body configuration of the tilted rabbit (without the GVS-based feedback) is shown schematically in Fig. 1C. Tilts of the platform elicited reflex responses in limb muscles. The extensors were activated on the side moving downward and inactivated on the opposite side (Fig. 2A). These reflexes prevented the animal from the sideward falling, but they were not sufficient to considerably reduce the lateral body sway.

The effects of GVS in the same rabbit were then tested on the stationary (horizontal) platform (Fig. 1B). As shown in Fig. 2B, the reversal of GVS at point 1 (from ~2 mA to +2 mA in relation to the right labyrinth) caused activation of extensors in the left limb and their inactivation in the right limb, as well as the body sway (S) towards the anode. The switch of GVS to the initial polarity (point 2) caused opposite effects. The lateral excursions of the top body point, caused by reversal of GVS, were very large (7–8 cm). This value of sway was close to that observed in the tilting animal without the GVS-based feedback (Fig. 2A), suggesting that the GVS-evoked body sway would be sufficient for counteracting the body sway caused by tilts (see below). The latency of motor effects of GVS was estimated when standing on a horizontal platform. The moment of GVS reversal was taken as the onset of stimulation (as in Fig. 2B). The latency of EMG responses in Gast and Vast (mea-
sured on the cathode side) was 32 ± 9 ms (means ± SD; n = 19). The latency of the GVS-induced body sway was 60 ± 24 ms (n = 11).

Closed-loop condition. In these experiments, the body height in the standing position, i.e., the distance of the top pelvis point from the support surface, depended on the extensor tone in the hindlimbs. Body configuration with a higher extensor tone (observed in 2 rabbits) is shown schematically in Fig. 1, A and B. Usually, the extensor tone decreased over time after the limbs had been mounted on the platform and loaded, which resulted in a gradual reduction of the body height (from 14–15 to 11–12 cm).

In three other rabbits, the extensor tone was lower, and both limbs were considerably flexed when standing. In one of these rabbits, application of GVS caused extension of the limbs until the rabbit adopted a normal body configuration, as well as exhibited normal postural reactions to tilts. To enable normal limb configuration and normal operation of postural mechanisms in these rabbits, we suspended the hindquarters by means of a long elastic rope (Fig. 1A) and thus reduced the hindlimb load by 25–50%. Under these conditions, the GVS-based postural system was able to maintain balance and compensate for tilts.

A representative example of the effects of GVS-based feedback on the lateral trunk oscillations is shown in Fig. 3A (a rabbit with low extensor tone). Before the feedback loop was closed, tilts of the platform (tilt cycles 1–5) caused large lateral oscillations of the trunk, with a peak-to-peak value of 5–6 cm. During this period, EMG responses in limb extensors (Vast and Gast) were small.

When the feedback loop was closed, the GVS current was determined by signals coming from the sensor monitoring lateral deviations of the top point of the trunk from the sagittal plane (S in Fig. 1C). In these experiments, we used the double monaural configuration of GVS, with opposite currents passed through the right and left electrodes (see Methods). The GVS was initiated (or changed its polarity) when the lateral deviation of the rabbit exceeded the threshold level (S₀ or Sₚ in Fig. 3B). The polarity of current applied to each electrode depended on the direction of deviation: the current was negative (cathodal) with deviations toward the side of electrode, and positive (anodal) with opposite deviations.

Closing the feedback loop (ON in Fig. 3A) resulted in 1) a significant increase in the EMG responses in limb extensors, and 2) a significant decrease in the lateral oscillations of the trunk (S) (Fig. 3A, tilt cycles 6–12). The reduction of lateral trunk oscillations demonstrates that the GVS-based system is capable to maintain the dorsal-side-up trunk orientation.

Augmenting the feedback by increasing the value of stimulating current (Fig. 3A) resulted in 1) a further increase in EMG responses, and 2) a further decrease of lateral body oscillations (cycles 13–17). These changes demonstrate an increase of the efficiency of postural mechanisms. When the feedback loop was opened (OFF in Fig. 3A), large trunk oscillations reappeared (cycles 18–23). Similar results were obtained in all five rabbits studied with a closed feedback loop.
A characteristic feature of the GVS-based control system was presence of peaks of body sway (lasting for 0.5–1.0 s) that followed each change of the tilt angle (Fig. 3, A and B). This phenomenon was due to the particular feedback scheme used in this study (threshold-based activation of GVS) and the reaction time of postural mechanisms. Between these peaks, the sway value was relatively constant and much smaller than without feedback. It was reduced on average from 6.3 ± 2.1 cm to 1.4 ± 0.6 cm. The latter value was even smaller than the magnitude of oscillations (2–4 cm peak-to-peak) observed in similar tests of intact rabbits (Beloozerova et al. 2003; Musienko et al. 2008; Zelenin PV, unpublished data).

In three out of five rabbits tested under closed-loop condition, the extensor tone in the right and left limbs was substantially different, resulting in the right-left asymmetry of the stabilized body position. To make this position more symmetrical, we used different values of current for stimulating the right and the left side (illustrated in Fig. 4A).

Improvement of postural control with GVS-based feedback was due to a specific pattern of EMG activity. In Fig. 4A, the
mean values of body sway and Vast EMGs are plotted against time for two conditions, with feedback loop closed and opened. The EMG patterns were qualitatively similar in both conditions, with a peak in the second half of the period of ipsilateral tilting (intervals 2–3 and 5–6), but this peak was two to three times larger when feedback loop was closed. This finding suggests that impairment of postural control in this particular rabbit was caused by reduced peaks of extensor EMGs, while the phasing of these peaks was correct. Similar results were obtained in two other rabbits. Finally, in two more rabbits, the EMG responses with the opened feedback loop were not only considerably reduced but also had incorrect phasing. Extensors were activated during ipsilateral tilts with the feedback loop closed, but during contralateral tilts with the feedback loop opened (Fig. 4B).

In all rabbits, an increase of GVS current could cause body oscillations in the frontal plane (when standing on the tilting or stationary platform) at a frequency of ×1 Hz, and with the EMGs in the right and left limbs alternating (Fig. 5). These auto-oscillations could be abolished by reducing the value of GVS current (not illustrated).

Successful postural control, with lateral oscillations smaller than those in intact animals, was observed in all five rabbits tested under the closed-loop condition. For each rabbit, optimal parameters of the feedback loop were determined experimentally using the following procedure. First, we set up thresholds $S_R$ and $S_L$, thus defining the range of tolerable body sway. Second, we determined the current causing auto-oscillations and reduced this value by 20–30%. Third, we determined the proportion of anodal and cathodal current to compensate for the left-right asymmetry in the responses to GVS. The optimal parameters remained valid with repeated trails or needed minor adjustment if excitability of the preparation changed between the trails.

**DISCUSSION**

For studying normal functioning of postural mechanisms, as well as their damage and repair, we employ a convenient model, the decerebrate rabbit. This animal is able to maintain the basic (dorsal-side-up) body posture, provided decerebration was done at the premammillary or more rostral level. With a more caudal (postmammillary) decerebration, the capacity to maintain the dorsal-side-up body orientation is considerably reduced, which can be explained by a decreased value of reflex responses to postural perturbations, as well as by abnormal phasing of these responses (Musienko et al. 2008, 2010).

The goal of our study was the restoration of normal postural control in the hindquarters of postmammillary rabbit, first by increasing the gain of postural reflexes, and second by proper phasing of these reflexes in relation to postural perturbations. For this purpose, we supplemented a part of the control system (the sensory feedback) with an artificial feedback (Fig. 6). Previously, such hybrid systems were successfully used for the analysis of postural mechanisms in simpler animals, mollusks (Deliagina et al. 1998) and lampreys (Zelenin et al. 2000).

To activate postural mechanisms, we used a technique of GVS. As shown in numerous studies on humans, this technique allows exerting specific influences on the subject’s posture through the vestibulo-spinal and other descending systems (Goldberg et al. 1984; Wardman and Fitzpatrick 2002). The GVS results in activation of limb extensors on the cathode side, and in their inactivation on the anode side. This asymmetry causes a lateral body sway towards the anodal stimulus (see, e.g., Coats and Stoltz 1969; Britton et al. 1993; Séverac Cauquil et al. 2000). In intact rabbits, GVS also results in a lateral body sway towards the anode (Beloozerova et al. 2003). A detailed analysis of GVS effects in decerebrate rabbits has been recently performed (Hsu et al. 2011).

We took advantage of the fact that the motor response to GVS is a lateral body sway and used this response to counteract the sway caused by a postural perturbation, i.e., by lateral tilt of the support surface. The idea of using the GVS-caused motor response for postural corrections was first proposed by Scinicariello et al. (2001) and later used by Orlov et al. (2008). These authors have demonstrated that in standing healthy humans, a properly timed GVS can reduce the body sway caused by postural perturbations.

When tested under open-loop conditions, tilts of the platform caused body sways three to four times larger than in intact rabbits (Beloozerova et al. 2003; Musienko et al. 2008; Zelenin PV, unpublished data), indicating that postural control was considerably impaired. We compared the lateral body sway...
caused by tilts with that caused by GVS (Fig. 2) and found that, in all rabbits, the GVS-evoked body sway was sufficient for counteracting the body sway caused by tilts.

The artificial feedback loop was formed in the following way. First, the lateral body sway was taken as a regulated variable of the control system. This signal was provided by a mechanical sensor (S in Figs. 1 and 6). Second, the signal S was used to determine characteristics of the injected current (S-signal processing in Fig. 6) according to the following algorithm: the current was turned on when S reached the right or the left threshold level (S_R or S_L), the polarity of current being opposite for S_R and S_L. This algorithm was very simple. The value of injected current was constant and did not depend on the magnitude and speed of the body sway.

This newly formed control system was examined by tilting the platform under the rabbit. The system was able to considerably reduce the lateral body sway caused by tilts (Fig. 3A). Thus, an important postural function, maintenance of the dorsal-side-up body orientation, which was considerably impaired in postmammillary rabbits, could be restored by means of the GVS-based external feedback. However, for optimal operation of the control system with such a simple algorithm, it was necessary to roughly adjust its characteristics to different patterns of postural perturbations (e.g., by changing the value of injected current, as in Fig. 4A). If the value of current was made dependent on the sway magnitude, it would still be necessary to define the gain of the feedback.

The patterns of EMG activity, generated when the feedback loop was closed, were similar in all rabbits. The extensors were activated during ipsilateral tilts and inactivated during contralateral tilts (Figs. 3 and 4). With an open loop, the amplitude of extensor EMGs was considerably reduced in all rabbits, and, in some of these rabbits, the EMG phasing in certain muscles was incorrect (Fig. 4B). These specific changes in the motor pattern could explain the profound deficits in postural performance observed in postmammillary rabbits (Musienko et al. 2008, 2010).

In the present study, a considerable improvement of postural control due to the artificial GVS-based feedback was demonstrated for only one type of postural perturbations, i.e., for tilting of the support surface in the transverse plane. We believe that the control system with the artificial GVS-based feedback can also compensate for other postural perturbations, provided these perturbations result in a lateral body sway. This class of perturbations, besides the tilts of the support surface considered here, also includes the lateral translation of the support surface (see, e.g., Scinicariello et al. 2001) and the lateral force (push) applied to the subject (Karayannidou et al. 2009). It is likely that the range of perturbations that can be compensated by the system can be widened by using more sophisticated algorithms of sensory-motor transformation (e.g., with the value of injected current depending on the value and speed of perturbation).

Normally, numerous mechanoreceptors in the limbs (muscle spindles, Golgi tendon organs, etc.) provide feedback signals for the postural control system (see, e.g., Duyssens et al. 2000; Deliagina et al. 2000, 2006). In the GVS-based control system, the feedback signals were provided by a single mechanical sensor, which monitored the lateral body sway (Fig. 1). Our reason for this choice was based on the assumption that the S value well reflects the position of the center of mass, which was suggested to be one of the regulated variables in the postural system (Massion 1994, 1998). Due to the proper choice of feedback signals, the phasing of all EMGs in relation to postural perturbations was correct, i.e., similar to that in intact rabbits (Beloozerova et al. 2003). Other sensors could also be used for providing feedback signals on the condition that they contain the sway-related information. For instance, a difference between the contact forces under the right and left limbs reflects the position of the center of pressure and can therefore be used as the feedback signal.

Testing the GVS-based control system by trapezoidal tilts (Fig. 2B) revealed a delay (60 ± 24 ms) between the injection of GVS current and the elicited motor response. This is one of the reasons why compensation for rapid tilts was not immediate (Fig. 3B). Another reason is the particular feedback scheme used in this study (threshold-based activation of GVS). One way to improve this characteristic is to increase the GVS current, but such increase could easily cause auto-oscillations in the system (Fig. 5). Similar body oscillations were observed in humans in the conditions of increased gain in the feedback loop (Peterka and Loughlin 2004). Another way to decrease the reaction time to platform tilt is to use a more sophisticated feedback scheme, with complex profiles of injected current, or to supplement the GVS-based control system with a predictive component, to deal with the dynamics of postural perturbations (for discussion see Scinicariello et al. 2001).

We suggest that the control system, with the artificial GVS-based feedback, can compensate for the loss of postural orientation of different etiology, including the loss caused by an incomplete spinal cord injury (SCI) in humans. It was shown that normal reaction to GVS (the lateral body sway) persisted in a part of SCI patients (Iles et al. 2004; Liechti et al. 2008; Wydenkeller et al. 2006). This finding implies that the spinal pathways responsible for the effect of GVS (which descend in the ventral part of the spinal cord, Muto et al. 1995) were not damaged in these patients. We suggest that the noninvasive technique developed for the rabbit and described in this paper can be transferred onto the patients with incomplete SCI to improve their postural control. Thus, the hybrid model of postural system may have not only theoretical importance but also clinical applications. For these applications, however, a highly simplified scheme of sensory-motor processing used in rabbit experiments would not be practical (e.g., once GVS is turned on, it would never be turned off) and would need to be replaced by a more sophisticated scheme.

To conclude, a principal result of the present study has been a demonstration that an important postural function, i.e., maintenance of the dorsal-side-up body orientation during standing, which was significantly impaired because of brain damage (decerebration), can be restored. To restore this function, we formed a new control system in which some nervous mechanisms (constituting the feedback loop) were supplemented with their synthetic homologs (Fig. 6). We suggest that such a hybrid system can compensate for the loss of lateral stability of different etiology. The goal of our future studies is to test this hypothesis on subjects with incomplete SCI, and to reveal optimal parameters of the control system for each particular case.
REFERENCES


