Dissociations between behavioural recovery and restoration of vestibular activity in the unilabyrinthectomized guinea-pig

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1. In the guinea-pig, a unilateral labyrinthectomy induces postural disturbances and an ocular nystagmus which abate or disappear over time. These behavioural changes are accompanied by an initial collapse and a subsequent restoration of the spontaneous activity in the neurones of the ipsilateral vestibular nuclei. Recently, it has been shown that the vestibular neuronal activity remained collapsed over at least 10 h whereas its restoration was complete 1 week after the lesion. The aims of this study were to determine when restoration of spontaneous activity in the partially deafferented vestibular neurones started and to compare the time courses of the behavioural and neuronal recoveries in guinea-pigs that had undergone a unilateral labyrinthectomy.

2. Neuronal discharge measurements were made using chronic extracellular recording of single unit activity. After a left labyrinthectomy, electrodes were placed on the site of the destroyed labyrinth to enable stimulation of the left vestibular nerve. Behavioural measurements included chronic recording of eye movements by the scleral search coil technique. After a left labyrinthectomy, lateral deviation of the head, twisting of the head, and eye velocity of the slow phases of the nystagmus were measured.

3. The neuronal activity of the rostral part of the vestibular nuclear complex on the lesioned side was recorded in alert guinea-pigs over 4 h recording sessions between 12 and 72 h after the lesion.

4. The criterion used to select vestibular neurones for analysis was their recruitment by an electric shock on the vestibular nerve. In addition, in order to explore a uniform population, we focused on neurones recruited at monosynaptic latencies (0·85–1·15 ms).

5. For each recording period, the mean resting rate was calculated animal by animal and the grand mean of these individual resting rate means was calculated. Previously, a deline in the grand mean resting rate from 35·8 ± 6·0 spikes s^{-1} (control state) to 7·1 ± 4·2 spikes s^{-1} during the first 4 h after labyrinthectomy had been shown. In the present study, the first sign of recovery was observed during the 12–16 h recording period when the resting rate grand mean increased to 16·3 ± 3·9 spikes s^{-1}. This grand mean activity did not change significantly during the following 12 h. Thereafter, restoration of neuronal activity improved and was complete 1 week after the lesion.

6. Although the abatement of the vestibular symptoms roughly paralleled the restoration of neuronal activity in the vestibular nuclei, some discrepancies between the time courses of both phenomena emerged. An important step in postural recovery (the animals managed to stand up) and a major part of the abatement of the nystagmus occurred before the recovery of vestibular neuronal activity. In addition, lateral deviation of the head disappeared while restoration of the neuronal activity was incomplete, but significant head twisting was still evident when vestibular resting rates had recovered completely.

7. We conclude that restoration of neuronal activity in the ipsilateral vestibular nuclei starts 12 h after the lesion and that restoration of neuronal activity in the ipsilateral vestibular nuclei is not the only mechanism underlying behavioural vestibular compensation.

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In mammals, unilateral labyrinthectomy results in a characteristic disturbance of spontaneous eye movements and body posture. These symptoms which are present in the absence of any elicited head movement are described as 'static'. They include a spontaneous nystagmus with its slow phases directed to the side of injury, a lateral deviation of the head and body towards the same side and a tilt of the head and neck in the frontal plane, also towards the side of injury (Precht, Shimazu & Markham, 1966; Azzena, 1969; Schaefer & Meyer, 1974; Jensen, 1979; Llinás & Walton, 1979; Lacour & Xerri, 1981; Fetter & Zee, 1988; de Waele, Graf, Josset & Vidal, 1989). All these symptoms progressively abate because of a process of behavioural recovery known as 'static' vestibular compensation (for a review, see Smith & Curthoys, 1989).

At the neuronal level, since the pioneering study of Precht *et al.* (1966), it has been repeatedly reported, on the basis of experiments performed in decerebrate or anaesthetized animals, that the resting discharge in the neurones of the ipsilateral vestibular nuclei collapses just after a unilateral labyrinthectomy and then recovers spontaneously (McCabe & Ryu, 1969; McCabe, Ryu & Sekitani, 1972; Pompeiano, Xerri, Gianni & Manzoni, 1984; Ried, Maioli & Precht, 1984; de Waele, Serafin, Mühlethaler & Vidal, 1988; Smith & Curthoys, 1988; Newlands & Perachio 1990; Zennou-Azogui, Borel, Lacour, Ez-Zaher & Ouaknine, 1993). In particular, from a recent study that we performed in the awake guinea-pig, we concluded that, at least in that species, restoration of the resting discharge of the partially deafferented vestibular neurones is complete 1 week after a unilateral labyrinthectomy (Ris, de Waele, Serafin, Vidal & Godaux, 1995).

However, the time course of the restoration of neuronal activity in the ipsilateral vestibular nuclei of the guinea-pig remains unknown. We decided to establish it for two reasons. (1) It is important to know the time at which restoration of neuronal activity starts for future studies intended to explore factors which could delay that restoration. (2) Since the work of Precht *et al.* (1966), it has been believed that the recovery of resting discharge rates in the vestibular nuclei is *the* mechanism of recovery from the behavioural symptoms related to the removal of one vestibular labyrinth. However, this postulate has never been subjected to a careful test. In this study, we aimed to do this by comparing the time course of recovery of resting discharge in the vestibular nuclei with that of amelioration of the behavioural symptoms in two groups of guinea-pigs that had undergone a unilateral labyrinthectomy performed under similar conditions (surgical procedure, operation timing, halothane anaesthesia).

METHODS

Experimental studies used twenty-four pigmented female guinea-pigs weighing between 400 and 800 g, obtained from an authorized supplier (Charles River, St Aubin les Elboeuf, France). Measurements of neuronal discharge were made in twelve of the animals and measurements of behavioural parameters were made in the other twelve.

Neuronal discharge measurements

Preliminary operation. During a preliminary operation, twelve guinea-pigs were prepared for chronic recording of the extracellular spikes of the neurones located in the rostral part of the left vestibular nuclear complex.

This operation was performed under halothane anaesthesia and aseptic conditions. We used halothane concentrations of 4% for the induction of anaesthesia and 2% for its maintenance. Halothane vapour was administered in a mixture of oxygen (1 l min^{-1}) and nitrous oxide (1 l min^{-1}). At the beginning of the induction, the unrestrained animal was placed in a small box (20 cm × 25 cm × 15 cm) where the gas was delivered. Once the animal was asleep, the volatile anaesthetic agent was given through a face mask. All skin incisions were made after subcutaneous injection of lidocaine (Xylocaine; 5 mg (solution, 20 mg ml^{-1}); Astra Pharmaceuticals, Bruxelles, Belgium). Each guinea-pig was fitted with a head holder cemented to the skull. A craniotomy was performed over the cerebellum (4 mm wide and 5 mm long, stereotaxic co-ordinates: L = 0–4 mm left, P = 5–10 mm). The dura mater was removed and a dental cement chamber constructed around the hole. Between recording sessions, the surface of the cerebellum was protected with a Silastic sheet (Dow Corning) and the chamber sealed with bone wax. About 30 min after stopping the gas delivery, the animal was fully awake. It immediately began to eat and drink, to explore its surroundings, and was apparently able to urinate and defaecate as normal.

Labyrinthectomy. One week later, a global left labyrinthectomy was performed. The animals were divided into two groups of six individuals. In the first group, a labyrinthectomy was performed at 8 p.m. and neuronal activity was recorded during two 4 h sessions beginning 12 and 18 h after the operation. In the second group, a labyrinthectomy was performed at 8 a.m. and neuronal activity was recorded during three 4 h sessions, beginning 24, 48 and 72 h after the operation. The labyrinthectomy was performed under halothane anaesthesia, using the same procedure as was used in the preliminary operation. In addition, lidocaine (2%, 10 mg) was injected into the subcutaneous tissue surrounding the left auricular meatus. During this second operation, halothane had to be administered for only 45 min. The lateral and anterior semicircular canals were approached via the dorsal bulla whereas the posterior semicircular canal and the cavity containing the utricule and saccule were reached via the mastoid bulla. The different parts of the membranous labyrinth were extirpated one after the other. Two stimulating electrodes (silver ball electrodes) were then placed over the round window and over the hole drilled in the horizontal and anterior semicircular ampullae, respectively. Terminal wires from stimulating electrodes were connected to a socket cemented to the holding system. At the end of the operation, antibiotic powder (virginiamycin and neomycin from Bencard, Genvel, Belgium) was poured onto the wound before suturing. The animal exhibited a severe imbalance, during the first hour after awakening. In order to minimize discomfort and to prevent the animal from hurting itself, it was allowed to recover in the corner of a small box (30 cm × 30 cm × 15 cm) the floor and walls of which were covered with cushions. In such circumstances, we observed that immediately after it awoke (that is 20 min after stopping the gas delivery), the animal began to eat the food pellets provided on the floor next to its head.

Recording of neuronal activity. At the beginning of each experimental session the animal's head was attached to a holding bar located in the centre of a turntable and adjusted in such a way that the plane defined by the two horizontal semicircular canals was coincident with the earth horizontal plane (head pitched 40 deg nose down) (Curthoys, Curthoys, Blanks & Markham, 1975). Care was taken to avoid any discomfort to the animals throughout the experimental sessions. In particular, the body of the animal was wrapped in a light cover and kept still using small cushions. The effect of this procedure on the animal was assessed by monitoring the heart rate and respiratory rhythm. The heart rate was recorded with electrodes positioned on the skin of the thorax. Respiratory rhythm was recorded by means of a thermal probe located near a nostril which detected changes in air temperature as air was expired and inspired. Our immobilization procedure did not affect heart rate or respiratory rate. We also arranged two 15 min pauses during each 4 h recording session, in order to avoid the animal being immobilized continuously. The cranial opening was cleaned with sterile saline and antibiotics. Local anaesthetic (lidocaine, 2%, 4 mg) was also used to irrigate the cement chamber to prevent any pain.

The first step in the recording procedure consisted of localizing the vestibular nuclei. A glass microelectrode (1–5 MΩ impedance at 1000 Hz) guided by a micromanipulator was lowered vertically through the cranial opening towards the left vestibular nuclei. The field potential, evoked by stimulation of the vestibular nerve, was used to map out the location of the rostral part of the vestibular complex.

To record neuronal activity in the vestibular nuclei, a glass micropipette was passed through the cerebellum until it reached the region where the vestibular field potential had been previously localized. It is important to realize that, after labyrinthectomy, many vestibular neurones became silent and thus could only be detected by applying a search stimulus. Hence, since this work intended to study the time course of the recovery of the spontaneous discharge of the vestibular neurones, the neurones to be studied were selected using the same criterion for each animal, i.e. they had to be orthodromically recruited by stimulation of the ipsilateral vestibular nerve. The left vestibular nuclei were thus explored during stimulation of the left vestibular nerve. The intensity of the square pulses used as a search stimulus was between 2 and 3 times the threshold intensity required to obtain an N1 potential (Shimazu & Precht, 1965; Wilson & Felpel, 1972; de Waele, Vibert, Baudrimont & Vidal, 1990; Newlands & Perachio, 1990). At that intensity and at the frequency used ($2\ s^{-1}$), stimulation of the vestibular nerve did not appear to stress the animal. There was not the slightest sensitive movement in response to electric shocks and we verified that neither the heart rate of the animal nor its respiratory rhythm were changed as a result of the stimulation. The small amplitude of the field potential obtained with such pulses did not obscure evoked single action potentials. Once a unit was recruited, its threshold was determined to be the shock level at which the neurone responded to about 50% of the pulses. The latent period of the neurone was then measured with a stimulation of twice the unit threshold. Since we wished to compare the vestibular nuclear activity at different time points on separate animal populations, we always ensured that the density of the tracts was distributed uniformly throughout the entire region where a field potential could be recorded. The activity of the neurones that we identified was then recorded in complete darkness. The alertness of the animals was maintained by producing unexpected sounds. When an animal was alert, it constantly made jaw or leg movements that we could hear.

In order to establish the full time course of the recovery of the vestibular neuronal activity after a unilateral labyrinthectomy, the data from the present study were combined with other data recorded in a previous work (Ris *et al.* 1995). In the latter study, neuronal activity was recorded in the same way as in the present experiments in six control animals, in six animals during two 4 h sessions beginning 1 and 6 h after, and in six animals 1 week after, unilateral labyrinthectomy.

Data analysis. Neuronal activity was analysed off-line on PC/486 IBM compatible computers, after storage on disk from digital audiotape recordings. The spontaneous activity of each neurone studied was obtained by measuring the mean firing rate of the spikes occurring over 1 min while the animal was in complete darkness.

As far as the measurement of resting activity is concerned, it must be stressed that the method used in the present study was different from that used in our previous work (Ris *et al.* 1995). In the latter study, the activity of each identified neurone was recorded in complete darkness during sinusoidal rotation of the animal. The instantaneous firing rate was plotted against head velocity and submitted to linear regression analysis. The *Y*-intercept of the regression line was interpreted as the spontaneous firing rate (resting discharge) and its slope as the sensitivity of the neurone to head velocity. Since we had demonstrated that sensitivity to head velocity collapsed immediately after labyrinthectomy and remained collapsed 1 week after the lesion (Ris *et al.* 1995), we did not measure the sensitivity to head velocity between 12 and 72 h after the injury and therefore could not interpolate the resting discharge as we did in the previous study. Instead, we chose to monitor a value representing true spontaneous discharge at rest, i.e. the mean firing rate of the spikes occurring over 1 min. To maintain consistency between the studies, we used the same value monitored, but not published, for the neurones recorded in the previous study. It is worth noting that the values obtained by either method were close. The correlation between the two types of values was high ($r = 0{\cdot}79$).

Histology. After completion of the recording sessions, three small electrolytic lesions 1 mm apart (30 μA for 10 min) were induced under the vestibular nuclei using a glass microelectrode (see Fig. 3 in Ris *et al.* 1995). Animals were deeply anaesthetized with pentobarbitone (60 mg (1 ml) I.P.; Sanofi, Libourne, France) and were then killed by the transcardial perfusion of 0·9% saline followed by 10% formaldehyde. Once the formaldehyde perfusion had finished, a brainstem slice was cut at a 40 deg angle with respect to the vertical plane. The slice was then coated with paraffin and cut into 20 μm transverse sections which were stained with Cresyl Fast Violet. In the living animal, we determined the location of each recorded neurone and of the electrolytic lesions with respect to the tip of a reference needle fixed to the head holder. The co-ordinates of the locations of the brainstem units where then recalculated with respect to the electrolytic lesions so that the anatomical location of each recorded neurone could be determined on the histological sections.

Behavioural measurements

Preliminary operation. During a preliminary operation, twelve guinea-pigs were prepared for chronic recording of eye movements.

The anaesthetic procedure was the same as that used for neuronal recordings. A coil 9 mm in diameter made from three turns of Teflon-coated seven-stranded stainless-steel wire was implanted subconjunctivally on the right eye (Judge, Richmond & Chu, 1980;

de Waele *et al.* 1990). This was performed after having poured local anaesthetic (lidocaine) over the cornea and the conjunctiva. A head holder was cemented to the skull. The leads from the coil were passed subcutaneously towards the head region where they were soldered onto a socket cemented to the holding system. Thirty minutes after stopping the gas delivery, the animal was fully awake and its behaviour was as normal as that observed after the preliminary craniotomy (see above).

Labyrinthectomy. One week later, a global left labyrinthectomy was performed. The animals were divided into two groups of six individuals. In the first group, the labyrinthectomy was performed at 8 a.m. and the parameters characterizing the vestibular syndrome were measured 2, 4, 6, 8, 10, 24, 48 and 72 h and then 1 week after the operation. Spontaneous nystagmus was also measured 1 h after labyrinthectomy. In the second group, the animals were operated on at 8 p.m. and the parameters characterizing the vestibular syndrome were measured 12, 14, 16, 18, 20 and 22 h after labyrinthectomy.

Data collection and analysis. After destruction of the left labyrinth, the following parameters were measured: (1) lateral deviation of the head, (2) longitudinal twisting of the head, and (3) spontaneous ocular nystagmus. At each selected recording time, the following recordings were made, always in the same sequence. The animal was videotaped using a top view (10 min), and a front view (2 min). Eye movements were then recorded over 5 min in the light and 5 min in complete darkness. Video recordings were performed while the animal was not restrained at all. Eye movements were recorded while the animal's head was attached in the same position as for neuronal discharge measurements.

Conventional video recording was done with a Panasonic VHS NV-R11 portable camera (25 frames s^{-1}) and a Panasonic VHS NV-HD90EC recorder. The camera was positioned either over the animal or facing the animal standing on a small turntable which could be moved manually to keep the head of the guinea-pig in front of the camera. Videotapes were examined off-line. Individual frames were captured and stored on the disk of a PC with a Video Maker card (Vitec, Paris). The images could then be analysed using Corel Draw software.

Eye movements were measured using the scleral search coil technique (Fuchs & Robinson, 1966). The measurement system had a bandwidth of 1000 Hz and a sensitivity of 0·25 deg. Calibration was obtained by rotating both magnetic fields ± 5 deg around the horizontal and vertical axes with the guinea-pig's head kept still in space. Eye movements were recorded on an 8-track digital audiotape recorder (Teac RD-180T; DC–5000 Hz bandwidth). Eye velocity was obtained by calculating the derivative of the eye position signal digitally off-line.

RESULTS

General characteristics of the recorded neurones

In order to be included in this study on the restoration of the resting activity in the vestibular nuclei, a neurone had to be activated by an electric stimulation of the ipsilateral vestibular nerve. Furthermore, in order to study the behaviour of a more uniform population of neurones, we focused our attention on the monosynaptically recruited (second-order vestibular) neurones. The criterion used to establish monosynaptic recruitment was based on the following considerations. In other studies, the peak latency of the N1 wave of the field potential evoked in the vestibular nuclei of the guinea-pig by a stimulation of the ipsilateral nerve has been consistently found to be 1 ms. On the other hand, in our group, the shortest observed peak latency of the unitary potentials was 0·85 ms. This value was 0·15 ms lower than the latency of the N1 wave peak which was assumed to correspond to the mean monosynaptic latent period (Precht & Shimazu, 1965). Hence, we considered neurones to be monosynaptically recruited when they were activated at latencies between 0·85 and 1·15 ms. Figure 1 shows two samples of vestibular neurones activated at monosynaptic latencies (Fig. 1*A* and *D*). One of them was a spontaneously active neurone (Fig. 1*B* and *C*). The other one was a silent neurone (Fig. 1*E*).

In this study, recordings were made from 909 monosynaptically recruited neurones between 12 and 76 h after a unilateral labyrinthectomy. The spiking behaviour of the vestibular neurones was measured at various times after labyrinthectomy during 4 h sessions. The spiking parameters of the neurones recorded in the same 4 h session were combined. The 12–16 h and the 18–22 h recording sessions on the one hand and the 24–28 h, 48–52 h and 72–76 h recording sessions on the other hand were performed on two distinct groups of six individuals. In addition, in order to present the full time course of the restoration of the resting discharge, we have complemented the data of the present study with data previously obtained from 424 monosynaptically recruited neurones recorded in six control animals, six animals examined during the first 10 h after a unilateral labyrinthectomy and 6 animals examined 1 week after such a lesion (Ris *et al.* 1995).

Recordings were made from neurones in the anterior part of the vestibular nuclear complex. Figure 2*A–D* shows the areas of the vestibular nuclear complex that were explored. These included the superior vestibular nucleus (S), the rostral pole of the parvocellular part of the medial vestibular nucleus (Mp), the magnocellular part of the medial vestibular nucleus (Mm), the lateral vestibular nucleus (L) and the rostral pole of the descending vestibular nucleus (D). Figure 2*E–M* presents, for each recording session, the relative densities of recordings from each area. These distributions showed that recordings from neurones were made in each of the explored vestibular nuclei, with a higher density in the Mp and Mm areas. However, a small disparity was present during the 12–16 h and the 18–22 h recording sessions (Fig. 2*H* and *I*) when a higher proportion of neurones was obtained from the descending vestibular nucleus (see Discussion).

Restoration of the resting activity in the vestibular neurones

A first approach to monitoring the restoration of activity in the neurones in the rostral part of the vestibular complex is presented in Figs 3 and 4. For each 4 h recording session, the data from neurones in the different parts of the vestibular complex in six animals were pooled. Figure 3 shows the

distribution of the resting discharges of the monosynaptically recruited neurones in the control animals and in the labyrinthectomized animals at different time intervals after the lesion. In addition, in each histogram, the number of silent neurones is indicated by a filled column. Finally, for each histogram, the mean firing rate, its standard deviation and the percentage of silent neurones are indicated. In control animals, there were no silent units and the mean resting discharge was $36{\cdot}0 \pm 21{\cdot}2$ spikes s^{-1} (mean $\pm$ S.D., $n = 103$ units) (Fig. 3*A*). From 1 to 5 h after the lesion, the majority of the neurones (73%) were silent while the mean resting discharge was as low as $6{\cdot}7 \pm 17{\cdot}0$ spikes s^{-1} (mean $\pm$ S.D., $n = 97$ units) (Fig. 3*B*). From 6 to 10 h after the lesion, the mean resting rate remained collapsed ($7{\cdot}5 \pm 11{\cdot}7$ spikes s^{-1}, $n = 76$ units) (Fig. 3*C*). From 12 to 16 h after the lesion, the mean resting rate started to increase ($15{\cdot}7 \pm 20{\cdot}2$ spikes s^{-1}, $n = 222$ units) (Fig. 3*D*). As the hours went by, the percentage of silent units diminished while the mean resting rate increased (Fig. 3*E–H*). One week after the lesion (not illustrated), there were no longer any silent units and the mean resting rate was $40{\cdot}8 \pm 23{\cdot}7$ spikes s^{-1} ($n = 148$ units).

In the preceding section, the mean resting firing rates were calculated by combining both silent and active neurones because this was the best way to assess the global neuronal activity of a nucleus (Fig. 4*A*). However, it was also of interest to analyse the evolution of the mean firing rate of the active neurones. This is shown in Fig. 4*B*. In contrast to the mean firing rate of silent and active neurones combined (Fig. 4*A*), the mean firing rate of the active neurones alone remained roughly constant between 1–5 h and 72–76 h after labyrinthectomy ($25{\cdot}4 \pm 25{\cdot}2$ spikes s^{-1} and $30{\cdot}7 \pm 18{\cdot}4$ spikes s^{-1}, respectively; Fig. 4*B*).

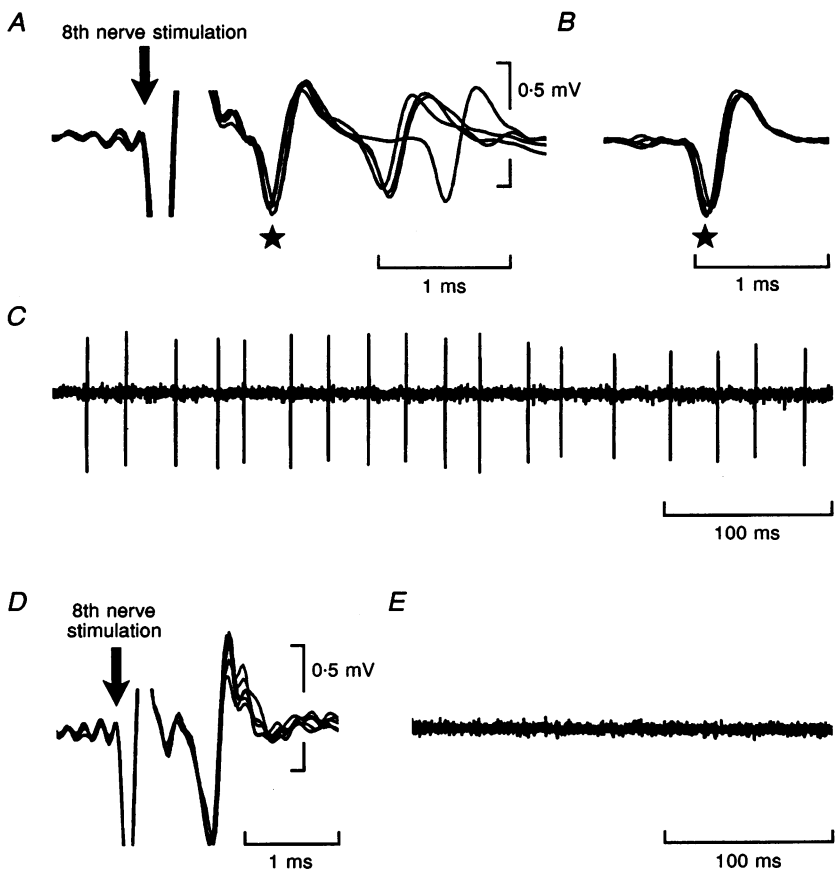

Figure 1. Illustration of the criterion for selection of the vestibular neurones studied: their responsiveness to a stimulation of the vestibular nerve at a monosynaptic latency

A, responses of a vestibular neurone to ipsilateral vestibular nerve stimulation at 2 s^{-1}. Four traces are superimposed. This neurone was recruited at a monosynaptic latency (0·94 ms). *B*, superimposition of 4 individual spikes recorded during spontaneous discharge with the same micropipette located at the same place as for the recordings illustrated in *A*. The fact that the shapes of the spikes (indicated by the stars) illustrated in *A* and *B* are nearly identical shows that these spikes are generated by the same neurone. *C*, spontaneous activity of the neurone whose electrical recruitment is illustrated in *A*. *D*, four superimposed responses of another neurone to ipsilateral vestibular nerve stimulation at 2 s^{-1}. This neurone was recruited at a monosynaptic latency (0·92 ms). *E*, absence of spontaneous activity in the neurone whose electrical recruitment is illustrated in *D*. Amplitude calibrations are the same in *A–C* and in *D–E*, respectively.

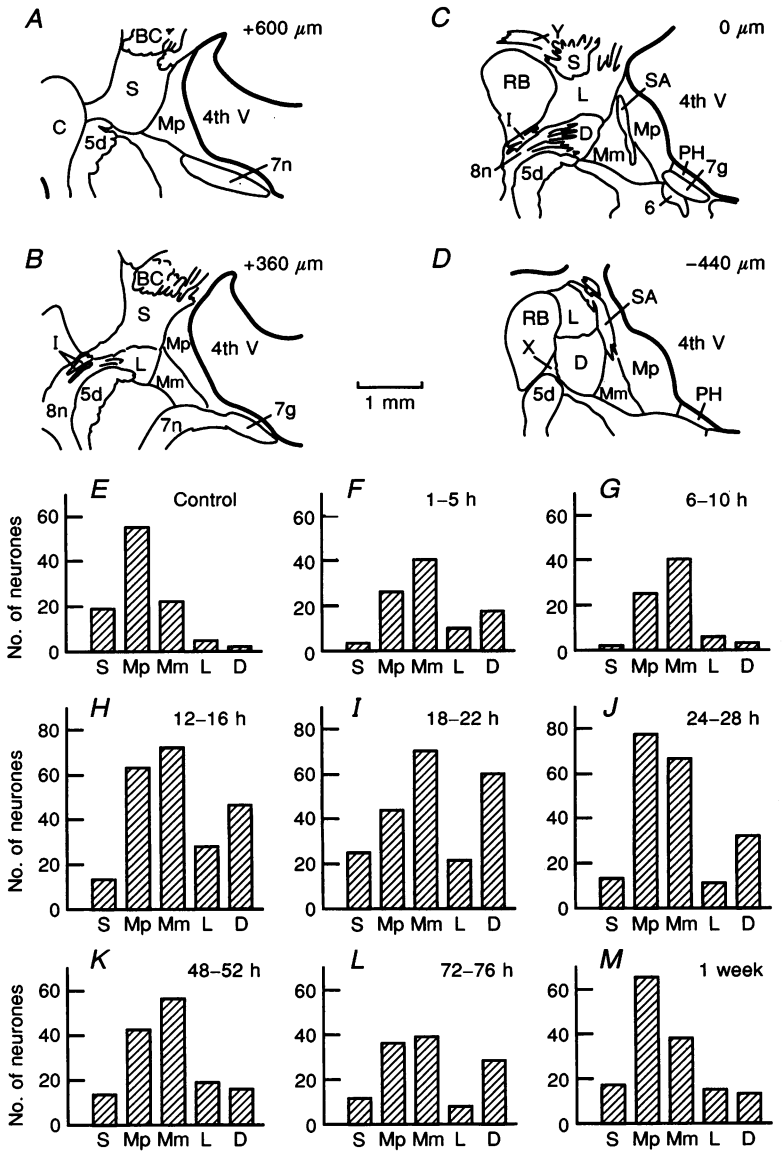

Figure 2. Locations of the neurones recorded in this study

A–D, subdivisions of the rostral part of the vestibular nuclear complex. The plane of the illustrated sections is tilted 40 deg posteriorly with respect to the vertical stereotaxic plane as defined by Rapisarda & Bacchelli (1977). The reference point is the centre of the abducens nucleus, which has a diameter of only 0·25 mm in the guinea-pig. Section in *A* is 600 μm anterior to the centre of the abducens nucleus. Section in *B* is 360 μm anterior to the reference point. Section in *C* passes through the reference point. Section in *D* is 440 μm posterior to the reference point. S, superior vestibular nucleus; Mp, parvocellular part of the medial vestibular nucleus; Mm, magnocellular part of the medial vestibular nucleus; L, lateral vestibular nucleus; D, descending vestibular nucleus; 8n, vestibular nerve; I, interstitial nucleus of the vestibular nerve; X, X group; Y, Y group; 4th V, fourth ventricle; 7n, facial nerve; 7g, genu of the facial nerve; BC, brachium conjunctivalis; C, cochlear nucleus; 5d, descending root of the trigeminal nucleus; RB, restiform body; SA, stria acustica; PH, nucleus prepositus hypoglossi; 6, abducens nucleus. This map was established by combining Nissl staining with acetylcholinesterase differential staining (authors' unpublished observations). *E–M*, distribution of the recorded neurones in the S, Mp, Mm, L and D subdivisions during the different recording periods. In each panel *F–M*, the time interval indicated at the top right corresponds to the period after the labyrinthectomy during which recordings were made.

Because the highest densities of neuronal recordings were obtained from the Mm and Mp subdivisions of the vestibular nuclear complex (see Fig. 2*E–M*), it was interesting to consider separately the mean resting rates of the neurones (both silent and active) from these two vestibular nuclei. The time courses of the restoration of neuronal activity in the Mp and Mm subdivisions are presented in Fig. 4*C* and *D*, respectively. They were similar to that of the pooled neurones (compare *C* and *D* in Fig. 4 with *A*).

Another approach to monitoring the restoration of activity in the pool of neurones in the rostral part of the vestibular complex is presented in Fig. 5. For each recording period, the mean resting rate was calculated animal by animal. Figure 5*A* shows the evolution of the mean of these individual means (grand mean; $n = 6$ animals) as a function of the time elapsed after labyrinthectomy. Interestingly, the low variability of the means indicates that the time course of the resting discharge restoration did not differ much from one animal to another. In control animals, the resting rate grand mean was $35{\cdot}8 \pm 6{\cdot}0$ spikes s^{-1} (mean ± S.D., $n = 6$ animals). In the first 4 h recording session after labyrinthectomy, it fell to a value as low as $7{\cdot}1 \pm 4{\cdot}2$ spikes s^{-1}. The resting rate grand mean did not change significantly during the next recording session (6–10 h post-operative; Wilcoxon matched-pairs signed-rank test, $P = 0{\cdot}60$). The first significant sign of recovery was observed in the 12–16 h recording session when the resting rate grand mean was $16{\cdot}3 \pm 3{\cdot}9$ spikes s^{-1} ($n = 6$ animals). There was a significant difference between the

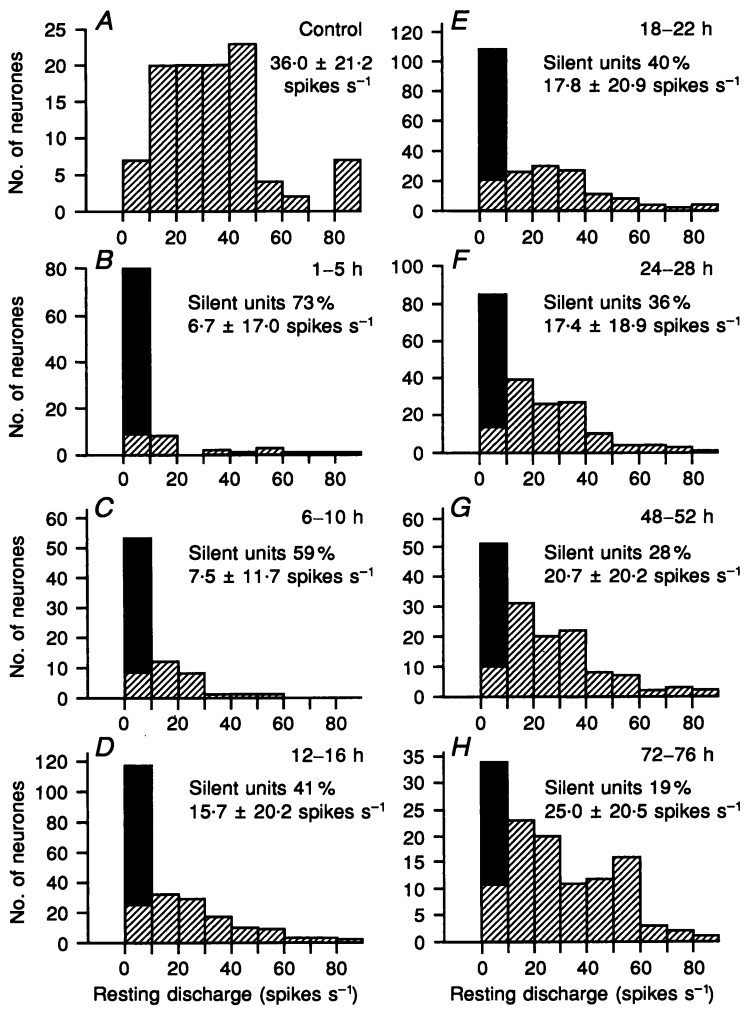

Figure 3. Histograms of the resting discharges of monosynaptically recruited vestibular neurones recorded in control animals and during 4 h sessions at various time points following a unilateral labyrinthectomy

In each histogram, the recording period is indicated at the top right, the filled column represents the number of silent neurones and the hatched columns correspond to spontaneously active neurones. All data from neurones whose resting rate exceeded 80 spikes s^{-1} are combined in one column. In each histogram, the percentage of silent units, the mean firing rate and its standard deviation are indicated.

resting rate grand means measured during the 6–10 h recording on the one hand and during the 12–16 h recording period on the other hand (Mann–Whitney U test, $P < 0{\cdot}05$). The grand mean activity did not change significantly during the following 12 h (Kruskal–Wallis H test, $P > 0{\cdot}05$). Thereafter, restoration of neuronal activity improved and was complete 1 week after the lesion ($41{\cdot}9 \pm 8{\cdot}7$ spikes s^{-1}, $n = 6$ animals) (Kruskal–Wallis H test, $P < 0{\cdot}05$).

Figure 5*B* illustrates a similar interindividual mean approach for the percentage of spontaneously active (not silent) neurones. For each recording period, the mean percentage of spontaneously active neurones was calculated animal by animal. Then, the mean of these individual percentages was calculated. The evolution of that mean value as a function of the time elapsed after labyrinthectomy is shown in Fig. 5*B*. The time course of the mean of the percentage of spontaneously active neurones was roughly parallel to that of the grand mean of the resting rate (compare Fig. 5*B* with Fig. 5*A*). Interestingly, the percentage of spontaneously active neurones also showed a small interindividual variability. This fact demonstrated, once again, that the recovery process did not differ much from one animal to another.

Recovery from postural disturbances

The time courses of the abatement of the static symptoms induced by a unilateral labyrinthectomy (see Fig. 6) are presented in Fig. 7. In order to make the comparison between the time courses of recovery of neuronal and behavioural features easier, recovery of the resting rate grand mean was replotted in this figure as an inverted curve (Fig. 7*A*) and this was then superimposed on each of the static symptom recovery curves (see Fig. 7*B–D*).

Twenty minutes after cessation of halothane delivery, each animal that had undergone a complete left labyrinthectomy recovered a normal state of alertness. The animals first lay on their left side and their attempts to stand up gave rise to episodes of violent rolling towards the left side. During that 'critical' stage, the total absence of balance prevented any measurement of body posture. After a time, varying from one animal to the other of between 45 and 90 min, the

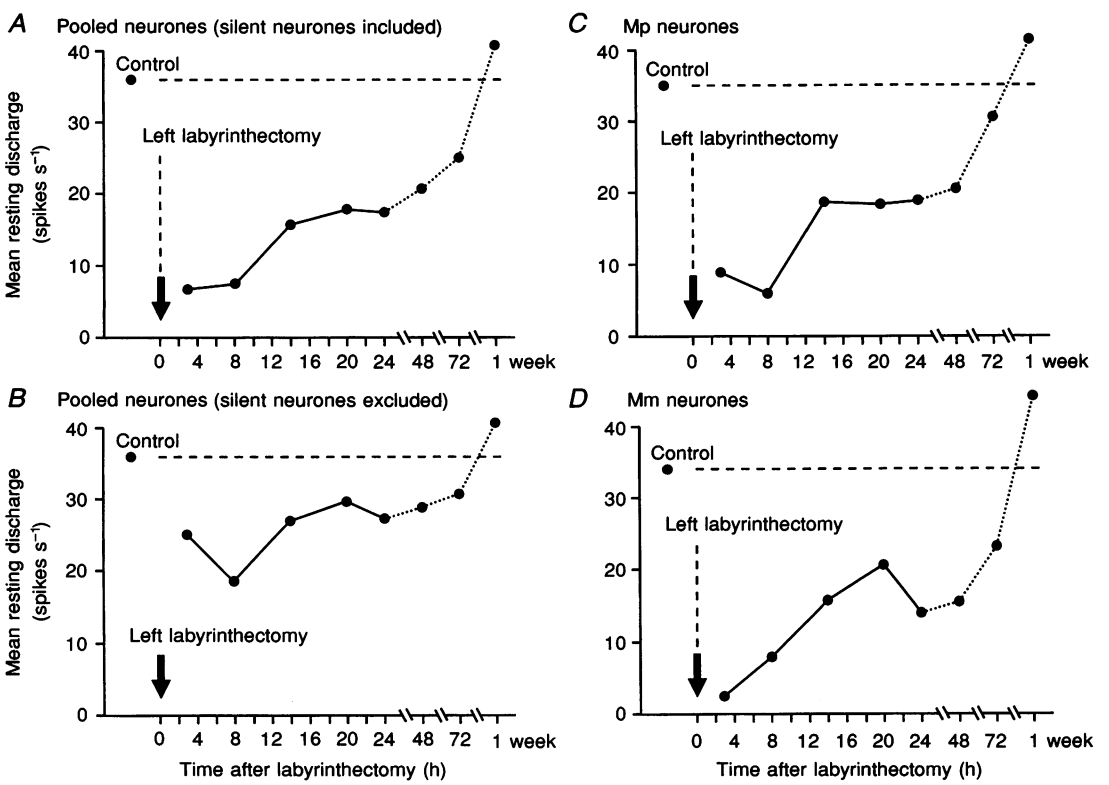

Figure 4. Time course of the restoration of the resting activity in the vestibular neurones after a unilateral labyrinthectomy

In this figure, the neuronal recordings were pooled independently of the animals in which they had been made. The abscissa of each point is the mid-point of a 4 h recording period and the recorded activity from each 4 h recording session was combined as if each recording had been made at the mid-point of the recording session. Note the breaks on the time scale after the 24th h following the lesion. *A*, the mean resting rate of our overall neurone sample (including the silent neurones) is plotted as a function of the time elapsed after the lesion. *B*, plot similar to that presented in *A* for the spontaneously active neurones only in the overall sample. *C* and *D*, plots similar to that shown in *A*, for the neurones recorded either in the Mp area (*C*) or in the Mm area (*D*).

animals managed to maintain their balance. We therefore began measuring their postural deviations from the second hour after the lesion.

For each animal and at given time intervals postsurgery, the deviation of the head towards the injured side was measured on twenty individual frames taken randomly from the corresponding videorecording. Lateral deviation of the head was defined as the angle between the longitudinal body axis and the line joining the centre of the guinea-pig's snout to the point halfway between its ears (Fig. 6*A*). Figure 7*B* shows the abatement of the lateral deviation of the head over time. The lateral deviation of the head was 82·0 ± 30·3 deg (mean ± S.D., $n = 6$ animals) 2 h after the lesion. Thereafter, it decreased progressively. Twenty-four hours after the lesion it was 42·5 ± 16·2 deg and at 72 h post-labyrinthectomy it ceased to be significantly different from the corresponding control value (Wilcoxon matched-pairs signed-rank test, $P > 0{\cdot}05$).

For each animal and at different time intervals, the tilt of the head in the frontal plane (towards the lesioned side) was

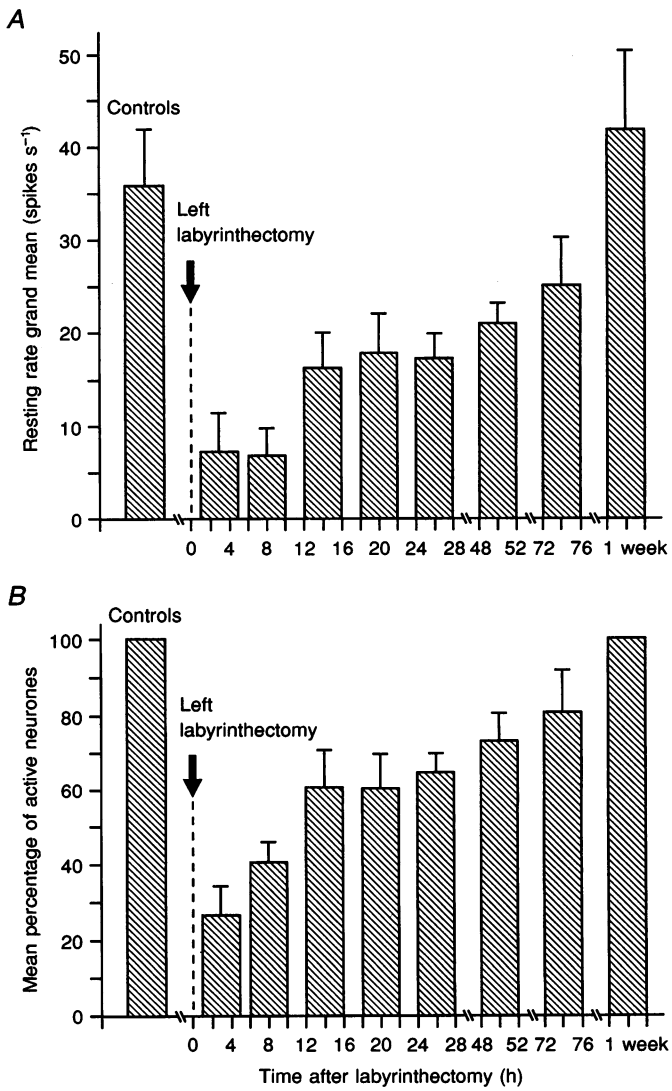

Figure 5. Time course of the restoration of the resting activity in the vestibular neurones after a unilateral labyrinthectomy

This figure presents an interindividual approach of the phenomenon. For each 4 h recording session, the mean resting rate (*A*) and the percentage of spontaneously active neurones (*B*) were calculated animal by animal. *A*, the mean of the individual resting rate means (grand mean; $n = 6$ animals) is plotted as a function of the time elapsed after the lesion. The resting activity recorded in each 4 h recording session is represented by a column whose height is the grand mean of the spontaneous firing rates of the recorded neurones and whose left and right limits correspond to the start and cessation of the recording period, respectively. Each column is surmounted by an error bar corresponding to the standard deviation of the resting rate grand mean. Note the breaks on the time scale after the 24th hour following the lesion. *B*, the mean percentage of spontaneously active neurones is plotted as a function of the time elapsed after the lesion. The characteristics of the display are similar to those used in *A*.

also measured on twenty individual frames taken randomly from the corresponding video recording. Head tilt was defined as the angle between the horizontal axis and the line passing through the centres of both eyes (Fig. 6*B*). In a normal animal, this angle was near zero and only showed sporadic variations. The control values of our two groups of guinea-pigs were 0·1 ± 1·7 deg (mean ± S.D., $n = 6$ animals) and −1·5 ± 1·0 deg (mean ± S.D., $n = 6$ animals). Two hours after the lesion, the head tilt was 34·4 ± 12·7 deg (mean ± S.D., $n = 6$ animals). Thereafter, it diminished gradually (Fig. 7*C*). However, 1 week after the labyrinthectomy, it remained abnormal. In the animal group in which it was measured at that time point, its value (12·4 ± 5·0 deg) was then significantly greater than in the control state (0·1 ± 1·7 deg) as confirmed by the Wilcoxon matched-pairs signed-rank test ($P < 0·05$).

Recovery from ocular nystagmus

In the guinea-pig, unilateral labyrinthectomy caused a nystagmus whose slow phases, separated by quick resetting phases, were curved and directed towards the lesioned side (Fig. 6*C*). One hour after the lesion, a severe nystagmus, mainly horizontal, was observed both in the light and in complete darkness. Thereafter, the nystagmus abated. Forty-eight hours after the lesion, the nystagmus was weak but still persistent both in the light and in complete darkness in all animals. Seventy-two hours after the lesion, a faint nystagmus was present in all animals when tested in complete darkness and in two out of six animals when observed in the light. One week after the lesion, the eye movements had returned to normal.

Normally, both vestibular nerves show the same tonic activity. When one of those tonic input activities becomes smaller than the other, there is a vestibular imbalance that causes a sustained deviation of gaze towards the weaker side, interrupted by quick resetting phases. The slow phases thus form the primary phenomenon of the nystagmus. The intensity of the nystagmus occurring in complete darkness was thus quantified by the mean velocity of the right eye during the horizontal component of the slow phases (Fig. 7*D*). One hour after the lesion, the mean eye velocity was 15·9 ± 8·2 deg s^{-1} (mean ± S.D., $n = 6$ animals). Afterwards, it diminished first rapidly and then more slowly (Fig. 7*D*). The mean eye velocity was 1·3 ± 0·7 deg s^{-1} 48 h after the lesion and 0·4 ± 0·2 deg s^{-1} 72 h after the lesion.

To allow comparison with other studies published in the literature, we also measured the number of nystagmic beats per minute (occurring in complete darkness) as a function of the time elapsed since labyrinthectomy. The pattern was similar to that of the eye velocity of the slow phases. In complete darkness, the number of nystagmic beats per minute diminished rapidly from 100 ± 35 (mean ± S.D.) 1 h after the lesion to 51 ± 15 10 h after the lesion. The nystagmic beating was as low as 6 ± 3 beats min^{-1} 72 h after the lesion and had completely disappeared 1 week after labyrinthectomy. The correlation between the eye velocity of the slow phases and the number of nystagmic beats per minute was good ($r = 0·77$, $P < 0·05$).

DISCUSSION

A unilateral labyrinthectomy induced severe vestibular symptoms which progressively abated, and a collapse of the resting discharge of the vestibular neurones followed by a subsequent recovery. We studied both phenomena in animals that had undergone a unilateral labyrinthectomy using the same protocol. The major results can be summarized as follows. (1) After a unilateral labyrinthectomy, spontaneous activity in the partially deafferented second-order vestibular neurones began to recover approximately 12 h after the lesion. (2) The almost complete disappearance of the static vestibular symptoms and the complete restoration of the resting discharge in the second-order vestibular neurones occurred over a similar period of time. (3) However, close comparison of the time courses of both phenomena reveals some disparities.

Sampling problems

This study consisted of a comparison of nine neuronal populations (control and different times post-operative) and

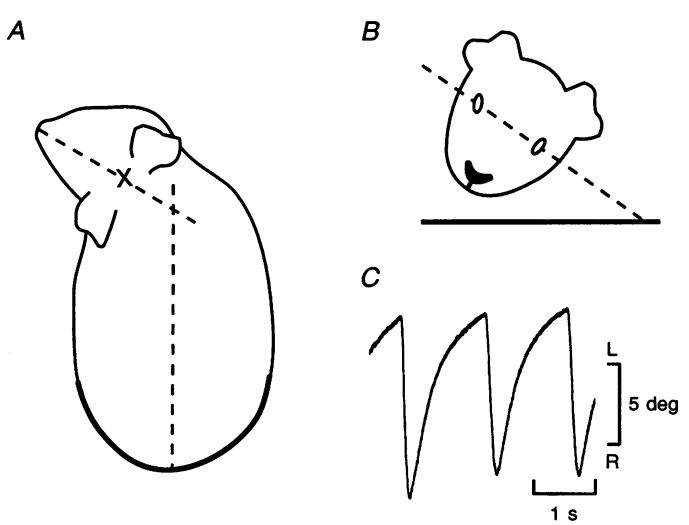

Figure 6. Assessment of the static vestibular symptoms in the guinea-pig

A, lateral deviation of the head was defined by the angle between the longitudinal body axis and the line joining the centre of the guinea-pig's snout to the point halfway between its ears. *B*, head twisting was defined as the angle between the horizontal axis and the line going through the centres of both eyes. *C*, sample of nystagmic beats recorded 1 h after a left labyrinthectomy. The intensity of the nystagmus was quantified by the mean velocity of the horizontal component of the slow phases.

therefore had to be designed carefully in order to avoid possible bias. As explained in detail in a previous study (Ris *et al.* 1995), we have sampled the neurones on the basis of their activation by electric shocks applied to the vestibular nerve. This procedure has the major advantage of giving silent neurones (especially after labyrinthectomy) the same probability of being picked up as spontaneously active neurones. Among the sampled neurones, we focused our attention on the monosynaptically recruited neurones (second-order vestibular neurones). The advantage of using this criterion was that it allowed comparison of neuronal populations which were uniform. This prevented a bias which might have arisen if the ratio between the neurones receiving a mono- or a polysynaptic vestibular input had varied from one neuronal population to another. Finally, it is important to note that during the different recording sessions recordings were made from neurones in the same vestibular areas (Fig. 2). The fact that an important anatomical bias has been avoided is attested by the distribution of the locations of the recorded neurones presented in Fig. 2*E–M*. Furthermore, it has been verified that the higher density of recordings from neurones in the descending nucleus (D), obtained during the 12–16 h and the 18–22 h sessions (Fig. 2*H* and *I*), did not introduce a bias due to a particular behaviour pattern of these neurones. When the data from all the neurones were combined, the resting rate grand mean was 16·3 ± 3·9 spikes s^{-1} during the 12–16 h recording session and 17·9 ± 4·2 spikes s^{-1} during the 18–22 h recording session. When the neurones from the D subdivision were excluded from the computation, the resting rate grand means observed in these two successive recording sessions were 17·3 ± 3·2 and 19·7 ± 5·9 spikes s^{-1}, respectively.

Recovery from neurological symptoms and restoration of neuronal activity

After unilateral labyrinthectomy, the partially deafferented vestibular neurones of the guinea-pig remained silent for

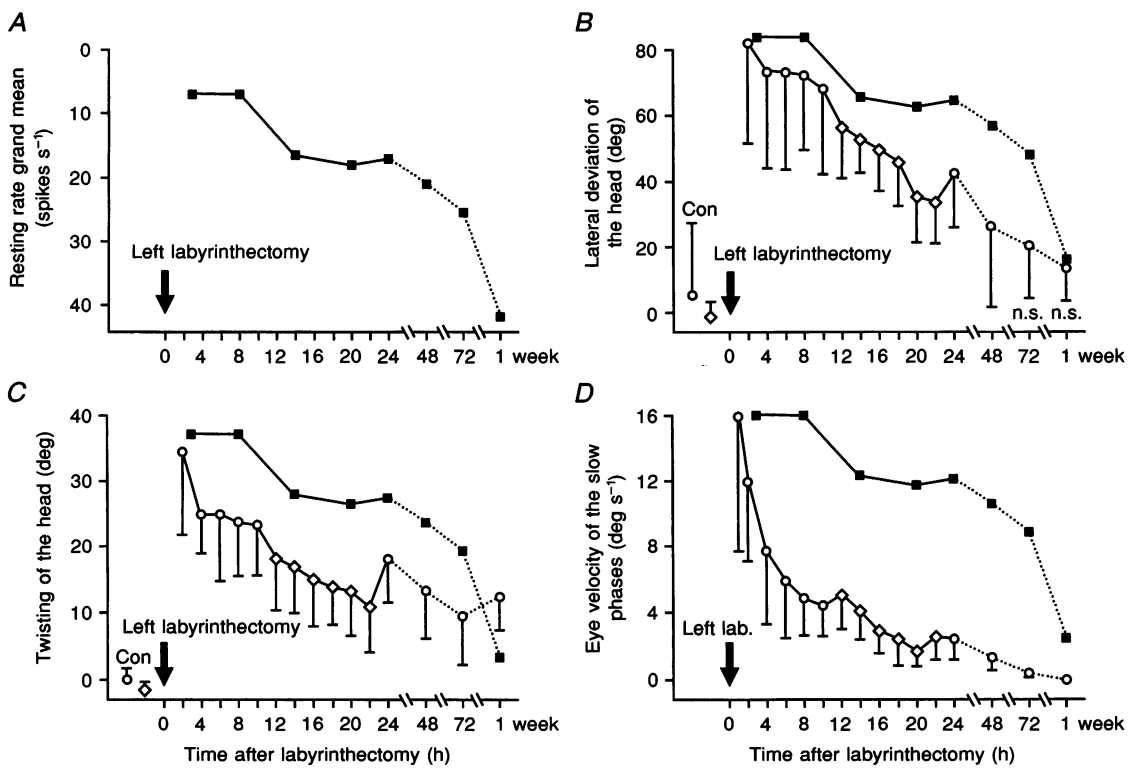

Figure 7. Comparison of the time course of the restoration of resting activity in the vestibular nuclei with the time courses of the amelioration of the static vestibular symptoms following a unilateral (left) labyrinthectomy in the guinea-pig

A, the restoration of the resting rate grand mean shown in detail in Fig. 5*A* is presented here as a single inverted curve (recovery downwards), in order to allow a comparison with the other curves. The curve is superimposed on each of the graphs *B–D*. Note the breaks in the time scale after the 24th hour following the labyrinthectomy. *B*, time course of recovery from lateral head deviation. n.s. indicates a non-statistically significant difference with respect to the corresponding control values (Wilcoxon matched-pairs signed-rank test, significance assumed at $P < 0{\cdot}05$). Con, control values. *C*, time course of recovery from head twisting (head tilt in the frontal plane). *D*, time course of recovery from ocular nystagmus. In *B–D*, at each selected time after unilateral labyrinthectomy, a symbol and its associated error bar corresponds to the mean ± the related standard deviation of the studied parameter measured on 6 animals. ○ and ◇ indicate measurements made on different groups of 6 guinea-pigs.

about 10 h. They began to be active again from the 12th hour after the lesion. Thereafter, restoration of the spontaneous neuronal activity progressed and 1 week after the lesion, the resting discharge of the vestibular neurones had reached a level similar to the control rate.

Comparison of Fig. 7*A*, which summarizes the time course of the recovery of the resting neuronal discharge, with Fig. 7*B–D*, which summarize the time courses of the abatement of the vestibular symptoms, shows that there is a good parallel between both phenomena. Restoration of resting activity in the vestibular nucleus is obviously a factor that could contribute to the behavioural vestibular compensation. Our results demonstrate that it occurs at an appropriate time to play an active and important role.

However, there are a few noticeable discrepancies between the time course of recovery from the behavioural symptoms and that of the restoration of the resting activity in the vestibular nuclei.

During the first 90 min following the lesion, a major improvement in the labyrinthectomy-induced postural syndrome occurred: the animals managed to stand up and maintain their balance. It is important to note that this step in the recovery process occurred while the resting discharge of the vestibular neurones was still absent ($7{\cdot}1 \pm 4{\cdot}2$ spikes s^{-1} during the 1–5 h post-operative recording).

A second difference concerned the ocular nystagmus. From the first to the tenth hour after unilateral labyrinthectomy, the resting rate grand mean remained low and did not change significantly from the first (1–5 h post-operative) to the second (6–10 h post-operative) recording period, as attested by the Wilcoxon matched-pairs signed-rank test ($P > 0{\cdot}05$; Figs 5*A* and 7*A*). By contrast, during the same period from the first to the tenth hour after unilateral labyrinthectomy, the intensity of the nystagmus measured at different time intervals on the same animals diminished markedly, as confirmed by the Friedman test ($P < 0{\cdot}001$; Fig. 7*D*).

A third discrepancy concerned parameters measured after the 48th hour following labyrinthectomy (compare measurements made 48 h, 72 h and 1 wk after the lesion in Fig. 7*A* and *B*). From 48 h to 1 wk after the lesion, the resting rate grand mean increased significantly (Kruskal–Wallis H test, $P < 0{\cdot}05$) by a factor of 2 (from 20·9 to 41·9 spikes s^{-1}) (Fig. 7*A*). During the same period of time, the mean lateral deviation of the head diminished from $26{\cdot}4 \pm 24{\cdot}6$ to $13{\cdot}6 \pm 10{\cdot}1$ deg (Fig. 7*B*), but this modification was not statistically significant (Friedman test, $P > 0{\cdot}05$). In other words, recovery from lateral deviation of the head was almost complete 48 h after the lesion while a significant part of the restoration of the neuronal activity still occurred after that period.

A fourth discrepancy concerned the fact that 1 week after labyrinthectomy, the guinea-pig exhibited a significant twisting of the head of 12·4 deg at a time when vestibular resting rates had recovered completely (compare Fig. 7*A* with Fig. 7*C*).

Recovery from the nystagmus

Amongst the disparities pointed out in the preceding section, that concerning the ocular nystagmus is the most obvious (Fig. 7*D*). However, it is possible that our overall neurone sample contained a subsample of vestibulo-ocular projection neurones that recovered their resting rate more rapidly than the other neurones in the sample. We think that this is unlikely. The precise location of the second-order vestibular neurones projecting on to the abducens motoneurones is unknown in the guinea-pig. However, in the cat and the squirrel monkey, this class of neurone has been found to be located in areas corresponding to the Mp and Mm areas of the vestibular nuclear complex of the guinea-pig (McCrea, Strassman, May & Highstein, 1987; Ohgaki, Curthoys & Markham, 1988). Interestingly, comparison of Fig. 4*C* and *D* with Fig. 4*A* shows that the subsamples of neurones recorded from either the Mp or the Mm areas did not recover more rapidly than the overall sample of recorded neurones.

Our observation that the major part of the recovery from ocular nystagmus occurred within the first 10 h of labyrinthectomy (Fig. 7*D*) was not reported by Smith, Darlington & Curthoys (1986). However, these authors performed the labyrinthectomy under anaesthetic drugs and measured nystagmus at times when interference caused by these drugs could not be avoided. The early recovery of the nystagmus was not observed in studies using drug anaesthesia where ocular movement was only measured from the 10th hour after the lesion (Smith & Darlington, 1988; Jerram, Darlington & Smith, 1995). However, it has been reported in several studies in which labyrinthectomy was performed under gas anaesthesia (Schaefer & Meyer, 1974; Jensen, 1979; Masumitsu & Sekitani, 1991; Pettorossi, Della Torre, Grossi, Zampolini, Capocchi & Errico, 1992).

Recovery from postural disturbances

In this work, we selected the neurones according to their input pathway but we did not make any attempt to divide the samples of recorded neurones according to their output pathways. Amongst the second-order vestibular neurones, some are involved in gaze control whereas others play a role in posture control. The probability that we did not analyse the firing behaviour of a significant number of the gaze-control neurones was low (see preceding paragraph), but could be a factor when considering posture-control neurones. Indeed, the vestibular neurones involved in posture are more scattered throughout the vestibular nuclear complex than the vestibulo-ocular neurones. Retrograde tracer studies have shown that the lateral vestibulospinal tract descends ipsilaterally and originates from the L and Mm nuclei whereas neurones in the M and D nuclei and some cells in the S nucleus contribute to the medial vestibulospinal tract which descends bilaterally (Kuypers & Maisky, 1975; Epema, 1990). As a result, the possibility

that we failed to obtain recordings from a subsample of posture-control neurones whose recovery rate was different from that of our neurone sample cannot be excluded. Our observation of the absence of complete recovery from head twisting at a time (1 week after labyrinthectomy) when the recovery of the resting rate was complete in our overall sample of neurones could perhaps be explained in this way. It could be that we did not record from a subsample of neurones which did not recover spontaneous resting activity. By contrast, it is difficult to explain the initial major step in the postural recovery (when the animal managed to stand up) as being due to an especially rapid (less than 90 min) recovery of the resting rate in one subsample of neurones that we failed to select. Interestingly, another discrepancy between the time course of restoration of neuronal activity and that of recovery from posture disturbance has been observed by others in another species (the frog), using another method of assessment of neuronal activity (the deoxyglucose uptake technique; see Dieringer, 1995). In the frog, the key symptom after a unilateral labyrinthectomy consists of a severe posture disturbance without any concomitant spontaneous nystagmus of the eyes (Bienhold & Flohr, 1980; Precht & Dieringer, 1985). There is a tilt of the head and trunk towards the operated side while the forelimbs are flexed on the ipsilateral side and extended on the contralateral side. Normalization of posture proceeds exponentially over a period of 60 days (Bienhold & Flohr, 1980). In that species, the evolution of the resting activity of the ipsilateral vestibular nucleus has been studied by Flohr, Bienhold, Abeln & Macskovics (1981) and by Flohr, Burt, Will & Ammelburg (1989) who used the uptake of ^{14}C-labelled 2-deoxy-D-glucose as an indicator for neuronal activity. Deoxyglucose uptake was found to be considerably reduced on the operated side a few days after unilateral labyrinthectomy and considerably restored 3 months after the lesion. However, the onset of the restoration of the neuronal activity in the ipsilateral vestibular nucleus was delayed with respect to the recovery from the postural disturbances. One month after unilateral labyrinthectomy, the activity in the vestibular nuclei (ipsi- and contralateral) was still as asymmetric as during the first few days after the lesion, which contrasted with the significant abatement of the postural symptoms observed during that time.

Restoration of resting neuronal activity

It is important to know why there is a spontaneous restoration of the resting discharge in the vestibular neurones. One possibility is that some *intrinsic* modification of the deafferented neurones makes them either endogenous pacemakers, or more sensitive to neuromediators which act on them in the control state (denervation supersensitivity). Another possibility is that some modifications *extrinsic* to the vestibular neurones play a role. These could consist of a change in the synaptic efficacy of the axons ending on the deafferented neurones and/or of a firing rate increase in the extravestibular excitatory neurones, resulting in a more powerful stimulation of the deafferented neurones. For the time being, there is no clear evidence favouring one or the other key mechanism. The present study has not been designed to investigate these mechanisms. However, we made an interesting observation, illustrated in Fig. 4. We found that the mean resting rate of the active neurones was relatively high ($25{\cdot}0 \pm 25{\cdot}2$ spikes s^{-1}) just after labyrinthectomy and did not change much during the following 72 h. In our opinion, this indicates that the vestibular neurones of the intact animal can be subdivided into two categories. There are neurones which are endogenous pacemakers and are therefore relatively little susceptible to deafferentation and there are non-pacemaker neurones which become silent after the lesion.

Conclusion

Restoration of activity in the deafferented vestibular neurones is obviously involved in the recovery of the behavioural symptoms. However, the lack of complete agreement between the time courses of recovery of the resting rates and the behavioural symptoms indicates that mechanisms other than restoration of activity in the vestibular neurones deprived of their labyrinthic input play a role in the behavioural vestibular compensation.

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