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BACLOFEN AND VELOCITY STORAGE: A MODEL OF THE EFFECTS OF THE DRUG ON THE VESTIBULO-OCULAR REFLEX IN THE RHESUS MONKEY

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SUMMARY

1. Baclofen had a characteristic effect on vestibular and optokinetic nystagmus in rhesus monkeys. Each aspect of nystagmus that is dependent on the velocity-storage mechanism in the vestibulo-ocular reflex (v.o.r.) was altered by the drug: (a) Baclofen reduced the dominant time constant of the v.o.r. in a dose-dependent manner up to 5 mg/kg, the highest dosage used. The alteration in v.o.r. time constant began within 15 min of injection, was maximal between 1 and 4 h, and lasted for 14–18 h. This effect mirrors changes in plasma levels of baclofen after oral doses in humans (Faigle, Keberle & Agen, 1980). (b) Slow-phase velocities of steady-state nystagmus induced by rotation about axes tilted from the vertical (off-vertical axis rotation, o.v.a.r.) were reduced after baclofen and could not be maintained at previous levels. (c) There was a dose-dependent decline in the steady-state gain of optokinetic nystagmus (o.k.n.), and at the highest dosages little o.k.n. was induced. In parallel, the peak velocity and falling time constant of optokinetic after-nystagmus (o.k.a.n.) were reduced. Since baclofen is a GABA agonist, systems utilizing GABA and acting on $GABA_B$ receptors appear to produce inhibitory control of velocity storage.

2. The step gain of the v.o.r., measured at the beginning and end of constant-velocity rotation in darkness, was unaffected by baclofen, as were saccades, quick phases of nystagmus, and the ability to hold positions of fixation or to generate linear slow phases of nystagmus. This indicates that it is possible to use baclofen to manipulate the dominant time constant of the v.o.r. and of o.k.a.n. in relative isolation from effects on other oculomotor components.

3. Baclofen caused a dose-dependent reduction in the initial jump in eye velocity at the onset of o.k.n., suggesting that the initial jump is also under inhibitory control of $GABA_B$ receptors. However, there were still occasional slow phases with velocities up to 30–40 deg/s after baclofen, and animals were capable of visually suppressing the v.o.r. This indicates that pathways responsible for causing rapid changes in slow-phase velocity were capable of functioning, at least intermittently, in the presence of the drug.

4. The data were simulated by the model that predicts the v.o.r., o.k.n. and o.k.a.n. and visual–vestibular interactions (Raphan, Matsuo & Cohen, 1979; Waespe, Cohen

& Raphan, 1983). The effect of baclofen was reproduced by shortening the falling time constant of the velocity-storage integrator, reducing the gain of the direct visual–oculomotor pathway and modifying the structure of the non-linearity that couples the visual system to the indirect pathway and the velocity-storage integrator. Alterations in the non-linearity explain why the time course of the slow rise in o.k.n. and the rising time constant of o.k.a.n. were longer at low or moderate doses of baclofen and shorter at high doses.

5. The functional effect of inhibition of velocity storage would be to reduce the responsiveness of compensatory oculomotor reflexes to low frequencies of head rotation and high rates of retinal slip. Similar effects are produced by habituation and during rapid discharge of activity from the v.o.r. by visual suppression or by tilting the head. GABA and $GABA_B$ receptors may also be utilized in mediating these processes.

INTRODUCTION

Compensatory eye movements induced by the vestibulo-ocular reflex (v.o.r.) and visual system can be modelled by two processes (Cohen, Matsuo & Raphan, 1977; Raphan *et al.* 1979; Robinson, 1980; Waespe *et al.* 1983). One process has rapid dynamics and is able to produce rapid changes in eye velocity in response to head movement or movement of the visual surround. A second process has sluggish dynamics and produces slower changes in eye velocity. Called 'velocity storage' because it stores activity related to slow-phase eye velocity, it is primarily responsible for setting the long or dominant time constant of the v.o.r. and for producing o.k.a.n. (optokinetic after nystagmus; Cohen *et al.* 1977: Raphan *et al.* 1979). It is also utilized in mediating interactions between the visual and vestibular systems (Waespe & Henn, 1977; Raphan *et al.* 1979), the vertical and horizontal semicircular canals (Raphan, Cohen & Henn, 1981; Raphan, Cohen, Suzuki & Henn, 1983) and between the semicircular canals and otolith organs (Cohen, Suzuki & Raphan, 1983; see Raphan & Cohen, 1985, for review).

As yet transmitters utilized in generating the various components of nystagmus are not well understood. Glycine and GABA were implicated early on as inhibitory transmitters in the v.o.r. (Curtis, Duggan & Felix, 1967; Obata, Ito, Ochi & Sano, 1967; Obata & Highstein, 1970; Precht, Baker & Okada, 1973), and aspartate and glutamate have been proposed as excitatory transmitters in vestibular, cerebellar and oculomotor systems (Dememes & Raymond, 1982; Dememes, Raymond & Sans, 1984; Ito, 1984*a*; Raymond, Nieoullon, Dememes & Sans, 1984). A knowledge of how these transmitters modulate the v.o.r. in the alert animal could shed light on the organization of the system and provide tools for manipulating it experimentally or clinically.

Baclofen (Lioresal, β-*p*-chlorophenyl-γ-aminobutyric acid) is a GABA agonist which has been employed mainly as an anti-spastic agent (Hattab, 1980; Davidoff, 1985). Baclofen has a weak action on synapses that are blocked by bicuculline and respond to muscimol ($GABA_A$ receptors). Fox, Krnjevic, Morris, Puil & Werman (1978) showed that there was a decrease in excitatory amino acids in the supernatant when brain slices were stimulated in the presence of baclofen. They and others

(Potashner, 1979; Johnston, Hailstone & Freeman, 1980; Lanthorn & Cotman, 1981) have suggested that baclofen acts presynaptically as a selective inhibitor of the release of excitatory amino acids. It is postulated that this action is mediated by a separate class of GABA receptors, known as $GABA_B$ receptors (Hill & Bowery, 1981). In addition to its presynaptic action, baclofen also produces more conventional post-synaptic inhibition in the hippocampus (Newberry & Nicholl, 1984*a*, *b*). $GABA_B$ receptors are widely distributed in the central nervous system, including the spinal cord and the granule cell layer of the cerebellum (Price, Wilkin, Turnbull & Bowery, 1984). Although GABA is the major transmitter of the massive Purkinje cell output that ends in the vestibular nuclei (see Ito, 1984*b*, for review), to date $GABA_B$ receptors have not been described in the vestibular nuclei.

Baclofen also affects the vestibular and oculomotor system. Halmagyi, Rudge, Gresty, Leigh & Zee (1980) observed that periodic alternating nystagmus, which follows some brain-stem or cerebellar lesions in humans, was abolished by the drug in about two-thirds of cases. Baclofen also blocked periodic alternating nystagmus produced in monkeys by surgical lesions of the nodulus and ventral uvula (Waespe, Cohen & Raphan, 1985*b*). Presumably, the function of systems that stabilize the vestibulo-ocular reflex (Leigh, Robinson & Zee, 1981) was restored by this GABA-ergic agonist. Nevertheless, the locus of action of the drug on the oculomotor and vestibular systems is unknown.

The purpose of this study was to examine the effects of baclofen on the v.o.r., on o.k.n. (optokinetic nystagmus) and o.k.a.n. and on saccades of the normal monkey. The study was initiated when we noted that baclofen caused the dominant time constant of the v.o.r. to become shorter in normal monkeys. The data will show that GABA, acting on $GABA_B$ receptors, is probably utilized in inhibiting velocity storage.

METHODS

Baclofen, obtained in powder form in a racemic mixture, was reconstituted in bacteriostatic water at a concentration of 20 mg/ml. The bacteriostatic water alone had no effect on the oculomotor system. When testing the dose–response relationship of baclofen, animals received 0·2–5 mg/kg of the drug intramuscularly no more often than every other day, with the response on alternate days serving as a control. The effect of the drug was generally determined 1–3 h after the animal had received the medication, at a time when the drug effect was at its maximum (see Fig. 3).

Eye movement recording

Eight juvenile rhesus monkeys (*Macaca mulatta*) of 3–5 kg were prepared for eye movement recording under anesthesia. Bolts embedded in acrylic resin cement on the skull were used to restrain the head during recordings. In initial experiments silver–silver chloride electrodes were implanted in the bone around the eyes to record the electrooculogram (e.o.g.) (see Cohen *et al.* 1977, for details). Later, magnetic search coils were attached to the sclera of the left eye in the frontal plane for measurement of horizontal and vertical eye position, using the technique of Judge, Richmond & Chu (1980) (see also Robinson, 1963; and Fuchs & Robinson, 1966).

Voltages related to eye position and eye velocity in the vertical and horizontal planes were displayed on an oscillograph and recorded on FM magnetic tape along with various parameters of the stimulus. The recording system had a bandpass from d.c. to 35 Hz. Slow-phase eye velocity and saccadic velocities were determined by differentiating eye position. Eye movement recordings were calibrated by normalizing them with reference to the eye velocity induced by rotation about

a vertical axis in light at 30 deg/s. The gain of the v.o.r. (slow-phase eye velocity/stimulus velocity) was assumed to be close to unity under these circumstances (Skavenski & Robinson, 1973).

Animals generally received up to 0·2 mg/kg of amphetamine sulphate 30 min before testing to maintain a constant level of alertness. Recordings taken when animals were alert but unmedicated were not different from those taken after receiving amphetamine (D. Helwig & B. Cohen, unpublished data). In this paper we consider only horizontal nystagmus as well as saccadic eye movements in all directions. In the Figures eye movements to the right caused upward trace deflections in both eye position and eye velocity traces.

Techniques of stimulation and data analysis

The animals or the surrounding visual field were rotated at constant velocities in a three-axis vestibular and optokinetic stimulator (Raphan *et al.* 1981) to elicit per- and post-rotatory nystagmus, o.k.n. and o.k.a.n. Accelerations at the beginning and end of rotation were in excess of 1000 deg s^{-1} s^{-1}, approximating a step in stimulus velocity. O.k.n. was induced by movement of the shell of the stimulator which constituted the animal's visual surround. It was a closed cylinder, 88·9 cm in diameter and 61 cm high, with alternating 10 deg black and white stripes. When the visual surround was stationary with regard to the animal, it was called a subject-stationary surround whether the animal was moving or at rest. This condition was used for visual suppression of vestibular nystagmus or o.k.a.n..

Peak velocities and time constants of decline of slow-phase velocity were used to characterize per- and post-rotatory nystagmus. For o.k.n. and o.k.a.n., important parameters included the initial jump in eye velocity at the onset of stimulation, steady-state eye velocity, the velocity of o.k.a.n. measured 1 s after the end of stimulation, and the rising and falling time constants of o.k.a.n. Falling v.o.r. and o.k.a.n. time constants were calculated by integrating the area under the slow-phase velocity envelope and dividing it by the slow-phase velocity at the height of the response. This produces a time constant for the envelope of slow-phase velocity which is the same as that of an exponential of the same area (Cohen *et al.* 1977). The rising or 'charging' time constant of o.k.a.n. was established by giving full-field motion for varying durations and determining the time course of the rise in o.k.a.n. to a steady state (Cohen *et al.* 1977). Using the technique described above the curves were reversed to obtain the rising time constant of o.k.a.n. charge data. Since the duration of optokinetic stimuli can affect the falling time course of o.k.a.n. (Buettner, Waespe & Henn, 1976), the period of exposure to the rotating visual surround was fixed at 30 s when determining falling o.k.a.n. time constants.

Animals were also rotated about axes tilted from the vertical (off-vertical axis rotation, o.v.a.r.) to produce continuous nystagmus (Guedry, 1965; Benson & Bodin, 1966; Raphan *et al.* 1981; Cohen *et al.* 1983; see Raphan & Cohen, 1985, for review). Saccades were elicited while the animal viewed the stationary optokinetic drum. Amplitudes, maximum velocities and durations of saccades were calculated and plotted by computer programs.

To test for visual suppression the monkey and the lighted visual surround were rotated together at the same velocity, or the animal viewed a stationary visual surround during post-rotatory nystagmus. Under these conditions the vestibular system signals movement, but the visual system indicates that the subject is stationary. The usual result is that nystagmus is suppressed. The ratio of slow-phase velocity at the onset or end of rotation in the stationary surround to that in darkness gives a measure of the suppression (Raphan *et al.* 1979; Waespe *et al.* 1983).

The effect of single doses of baclofen on the time constant of per- and post-rotatory nystagmus was determined over a 24 h period. This experiment was done in two stages. Baseline values were established for nystagmus induced by steps of angular velocity of 30–120 deg/s. Animals were tested frequently in the first 60 min after receiving the drug, and then hourly for 12 h. Then they were returned to their cages and were tested for recovery on the next day. That evening they received a single injection of the drug, and 12 h later were tested hourly for the second 12 h period. On the following day a control value was taken again. The animals received a single dose of amphetamine just before beginning testing on each day. During the two 12 h test periods the animals were frequently taken from the vestibular stimulator and allowed to move freely in a chair or in their cages. The small doses of amphetamine that were given would not be expected to produce continuous alerting after 4 h. However, frequent handling of the animals was effective in keeping them awake during testing, and the time constant of vestibular nystagmus was approximately the same at the end as at the beginning of testing (Fig. 3).

RESULTS

General effects

Baclofen is widely used in humans and, aside from weakness, produces relatively few side-effects (Brogden, Speight & Avery, 1974). In monkeys there was little observable behavioural effect of the drug at lower dosage levels (0·7–3 mg/kg). At higher dosages (4–5 mg/kg) the monkeys appeared weak, somewhat fearful and could be found, on occasion, lying in their cages. Nevertheless, they were roused

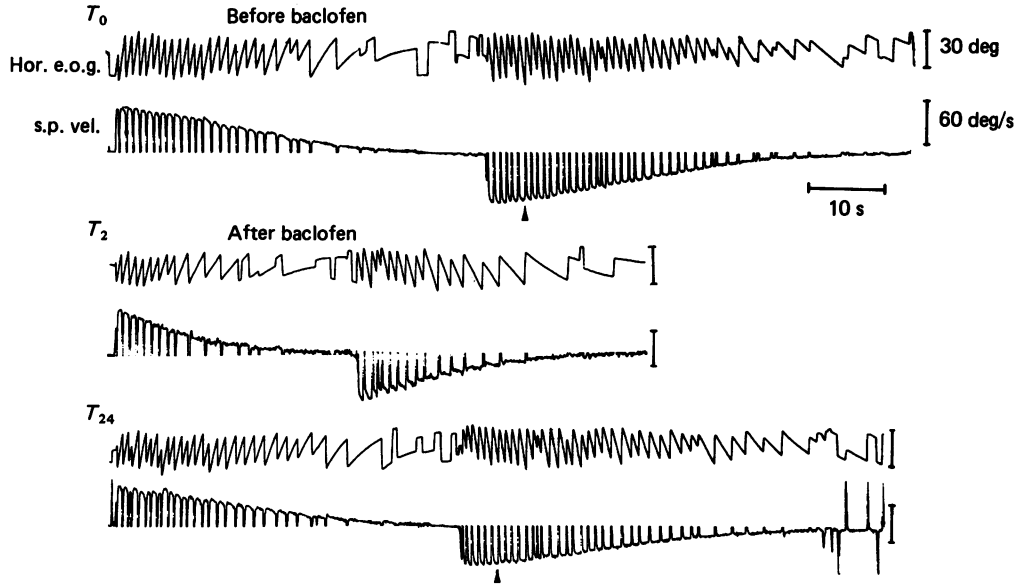

Fig. 1. Per- and post-rotatory nystagmus before (T_0), 2 h after (T_2), and 24 h after (T_{24}) administration of 4 mg/kg of baclofen. The monkey was upright in darkness receiving constant-velocity rotation about a vertical axis. Eye movements were recorded with e.o.g. Each panel shows horizontal eye position (Hor. e.o.g.) and rectified slow-phase velocity (s.p.vel.). Calibrations are shown by the vertical bars at the right of the traces and the time base by the horizontal bar under the top panel. The arrows point to the plateau in the step response at T_0 and T_{24} h. Note that the time course of per- and post-rotatory nystagmus was considerably shorter 2 h after administration of baclofen (T_2), but that the size of the initial step in velocity at the onset and end of rotation was unaffected. The time constant of the v.o.r. returned to its normal value 24 h later.

easily, could move about in their cages normally and were able to jump to their perches. Several animals vomited 3–4 h after receiving medication. Because of weakness we did not use dosage levels above 5 mg/kg.

Effects of baclofen on the vestibulo-ocular reflex

Baclofen had no effect on the gain of the initial jump in slow-phase eye velocity induced by rotation at a constant velocity about a vertical axis in darkness, i.e. by steps of velocity (Fig. 1). The linear relationship of eye velocity to stimulus velocity was maintained up to 180 deg/s for dosages as high as 5 mg/kg (Fig. 2*A*). Despite its lack of effect on the initial jump in eye velocity, there was a striking effect of baclofen on the time course of the induced nystagmus. In response to an intra-

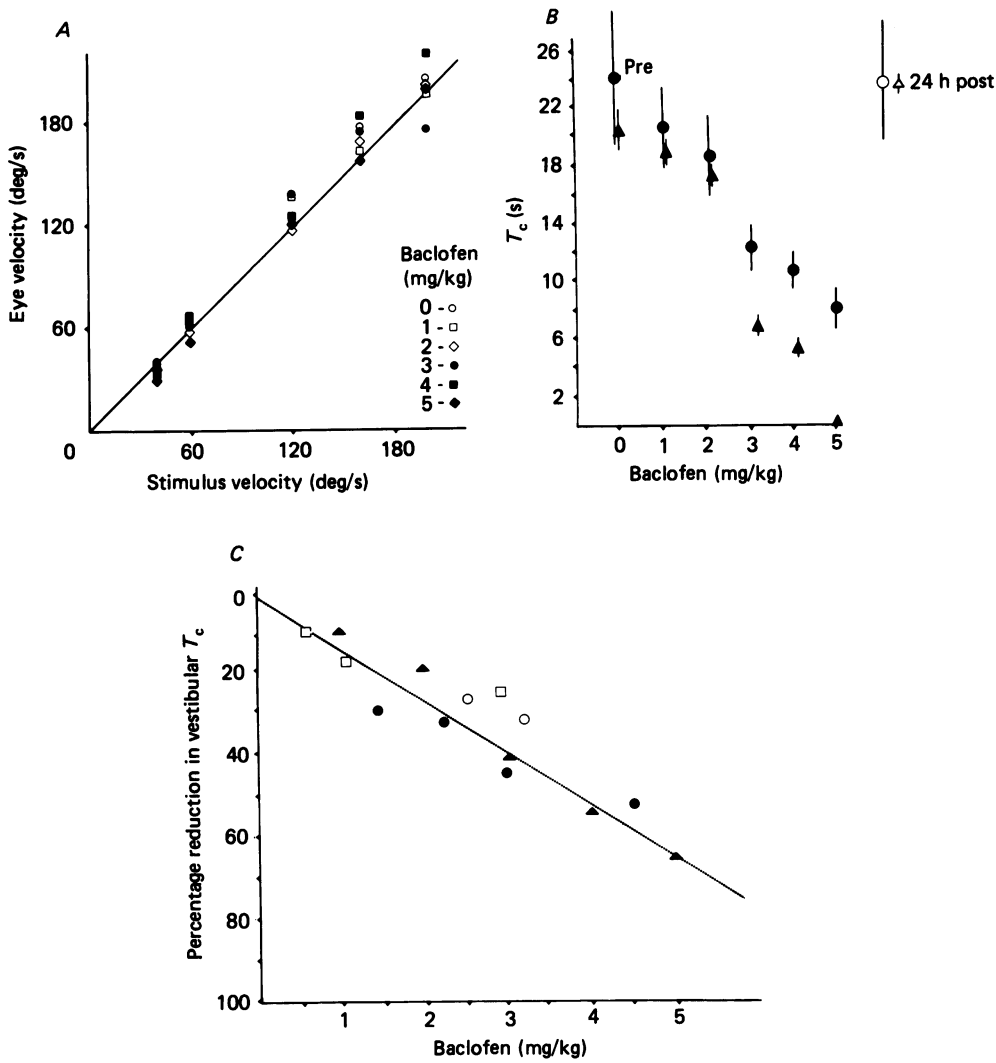

Fig. 2. *A*, relationship between initial jump in slow-phase eye velocity (ordinate) during steps of rotational velocity about a vertical axis in darkness (abscissa) at different dosages of baclofen, shown by the symbols at the right of the graph. Each point is constituted from the mean of four tests at each velocity. Responses to the right and left are averaged together. The continuous line shows unity gain. Baclofen had no effect on the step gain of the v.o.r. *B*, time constants (ordinate) of per- and post-rotatory nystagmus (●) and o.k.a.n. (▲) in one animal as a function of dose of baclofen (abscissa). The symbols are mean values and the vertical bars show two standard deviations. Each value for the v.o.r. represents sixteen samples from tests at 30–120 deg/s. Values for o.k.a.n. represent four samples for tests at 60 and 120 deg/s. On the left (Pre) are control values taken just before receiving the drug, and on the right (24 h post, ○ and △) are values for the tests done 24 h later. Both v.o.r. and o.k.a.n. time constants fell with increasing doses of baclofen. The o.k.a.n. time constant, tested concomitantly, was always shorter than the v.o.r. time constant (see text for explanation). *C*, relationship between dose of baclofen (abscissa) and percentage reduction in time constant of per- and post-rotatory nystagmus (ordinate) for four animals. Each point is the mean of twelve time constants taken from nystagmus induced by velocities of 30–120 deg/s. The filled triangles are from the animal whose data are shown in Figs 2*B* and 5*A*. The data were approximated by a least-squares straight line with a slope of about 11 % reduction in time constant for each 0·5 mg/kg of baclofen ($r = 0{\cdot}91$).

muscular dose of 4 mg/kg, the v.o.r. time constant fell from 25 s in one monkey (Fig. 1, T_0) to about 11 s 2 h later (T_2). This was accompanied by a loss of the plateau in slow-phase velocity that frequently occurs just after the initial step (Fig. 1, T_0, arrow). The duration of the plateau is dependent on the length of the v.o.r. time constant and becomes shorter or non-existent for short time constants and at higher velocities (Raphan *et al.* 1979). On the following day the time constant had reverted

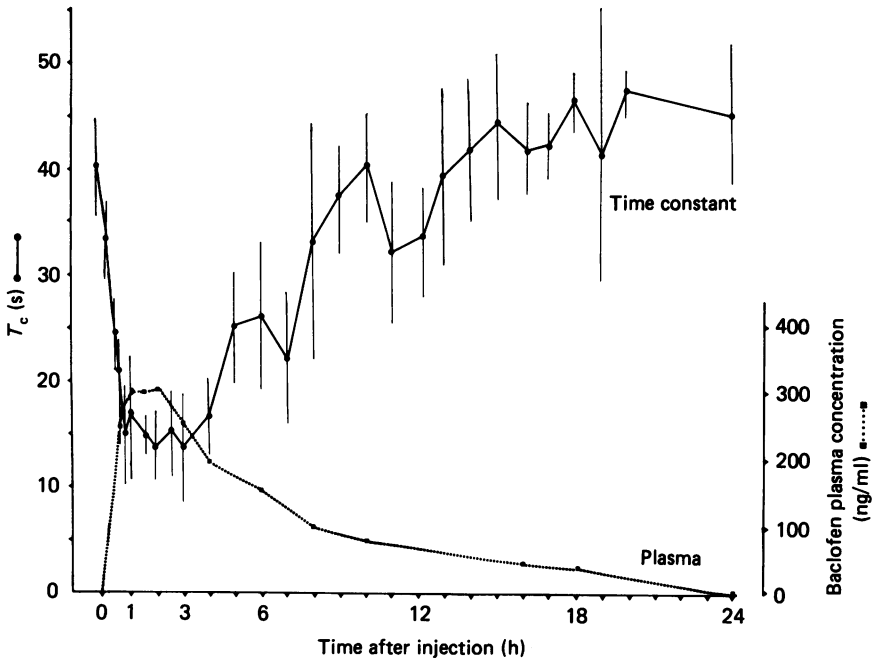

Fig. 3. Upper curve (continuous line) shows time constants of per- and post-rotatory nystagmus after a single injection of 10 mg baclofen (3·3 mg/kg). Each dot is the mean of four time constants induced by velocity steps of 60 deg/s. The vertical bars show two standard deviations. The abscissa is time after injection. The ordinate on the left is the time constant of the nystagmus in seconds. The lower curve (dotted line) is taken from Faigle *et al.* (1980), and shows plasma concentrations of baclofen, determined in a human after a single oral dose of 20 mg at various times after ingestion (abscissa). The levels in ng/ml are shown on the ordinate on the right. Note the correspondence between the time course of the fall in the v.o.r. time constant in the monkey and the rise in baclofen plasma levels in the human.

to its original level, and the plateau was again present (T_{24}). The reduction in time constant occurred within 15 min after injection, peaked in the first 3 h and lasted for about 14–18 h (Fig. 3, continuous line). The decline in v.o.r. time constant mirrored the rise in plasma baclofen levels after an oral dose in humans. An example from Faigle *et al.* (1980) is shown in Fig. 3 by the dotted line.

Using rotation in darkness to induce nystagmus the relationship between the dosage of baclofen and the dominant time constant of the v.o.r. was studied in four animals. The intensive testing required to perform the experiment caused the v.o.r. to habituate in three of the monkeys, and values were not obtained for a full range of dosages. In the fourth animal no trend towards habituation was present; its data

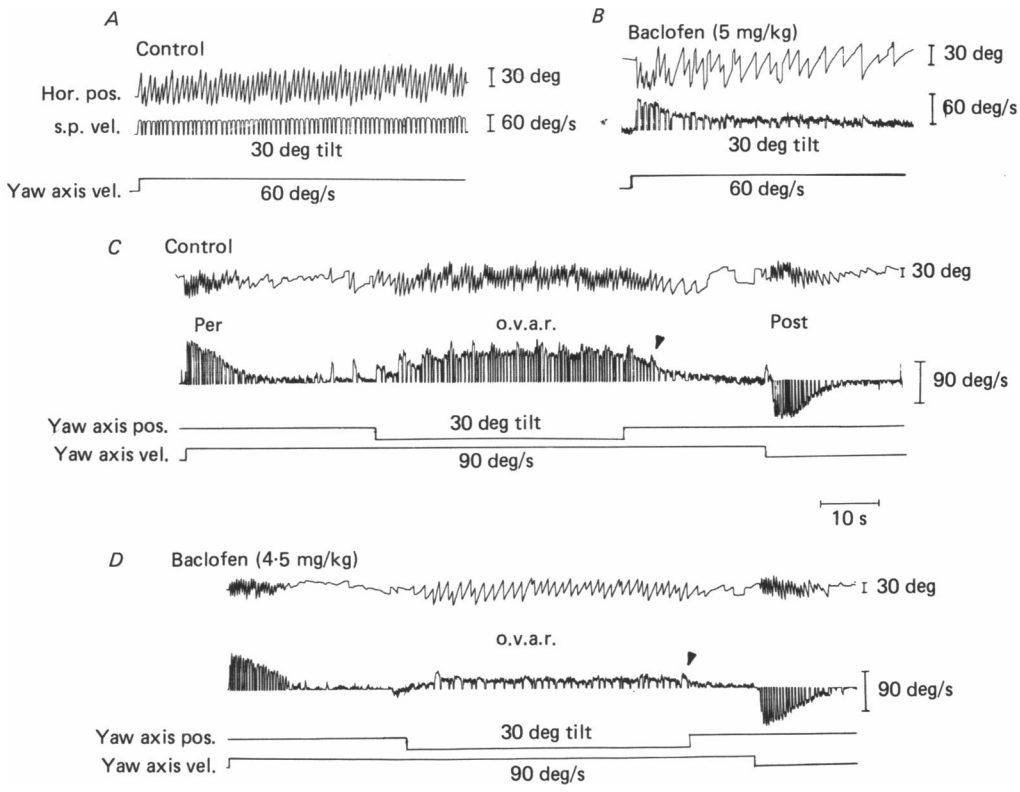

Fig. 4. Nystagmus induced by off-vertical axis rotation in darkness before (*A* and *C*), and 2 h after (*B* and *D*) receiving baclofen. *A* and *B*, during a step of velocity in darkness about an axis tilted 30 deg from the vertical, slow-phase velocity was maintained before (*A*) but not after baclofen (*B*). *C* and *D*, the monkey received a step of velocity about the vertical axis until the nystagmus had disappeared (Per). The axis of rotation was then tilted 30 deg (o.v.a.r.). Nystagmus reappeared and built to a steady-state level. The axis of rotation was then brought back to the vertical and nystagmus declined over the dominant time constant of the v.o.r. (arrows) before the animal was stopped, producing post-rotatory nystagmus (Post). Steady-state slow-phase velocity during o.v.a.r. was much lower after (*D*) than before the drug (*C*). The dominant time constant of the velocity-storage integrator was also shorter after than before the drug (arrows). Eye position was recorded in *A* and *B* with e.o.g. and in *C* and *D* with an eye coil.

are shown in Fig. 2*B*. The v.o.r. time constant declined monotonically with increasing dosages of baclofen (●). The time constant fell from an initial value of 25 s in the untreated state to 8 s at 5 mg/kg of the drug, a decline of about 3 s mg^{-1} kg^{-1} of baclofen. Twenty-four hours later the time constant had recovered (○). Time constants from all four animals 2 h after receiving baclofen were normalized to control values taken 24 h before and after testing. There was a linear relationship between dose of baclofen and percentage reduction in time constant of the v.o.r. (Fig. 2*C*, dotted line, $r = 0{\cdot}91$) with a reduction of about 11% in the time constant for each mg/kg of the drug.

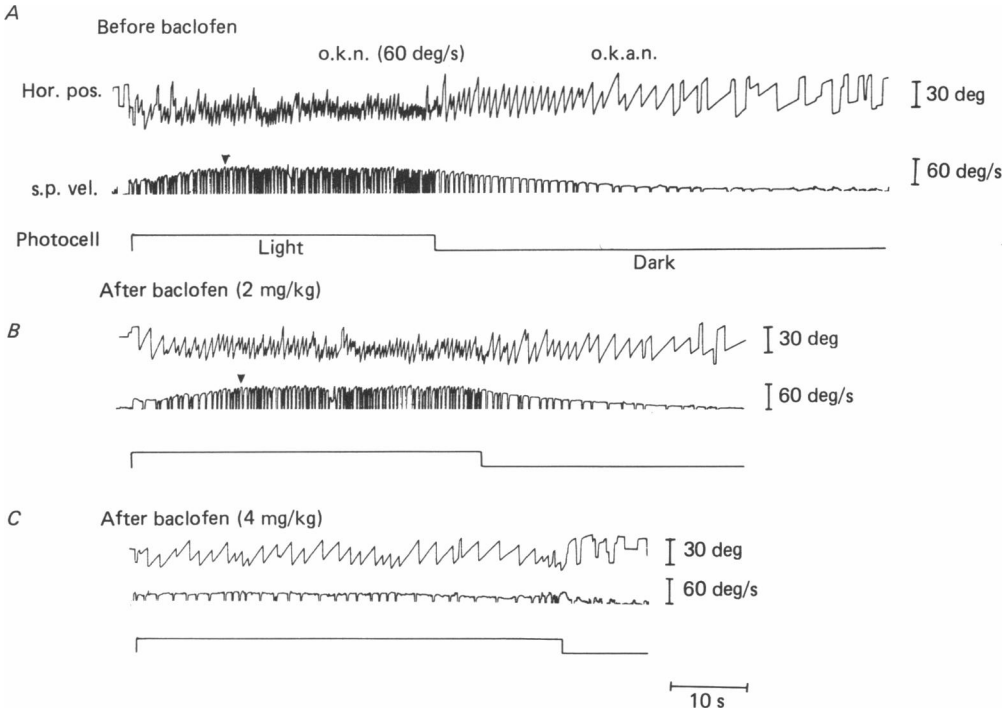

Fig. 5. O.k.n. and o.k.a.n. induced by surround rotation at 60 deg/s before (*A*) and after receiving 2 mg/kg (*B*) and 4 mg/kg of baclofen (*C*). The initial and steady-state levels of o.k.n. and o.k.a.n. were lower after receiving baclofen, and the falling time constants of o.k.a.n. were shorter. The arrows in *A* and *B* indicate the point at which the slow rise in o.k.n. culminated. It was about 2 s longer in *B* than in *A*. Data from this animal is shown in Fig. 2*B*.

Off-vertical axis rotation (*o.v.a.r.*)

Rotation at a constant velocity in darkness about an axis tilted from the vertical (off-vertical axis rotation, o.v.a.r.) induces nystagmus whose slow-phase velocity is maintained for as long as rotation continues (Guedry, 1965; Benson & Bodin, 1966). Peak steady-state velocities during o.v.a.r. are proportional to rotational velocity up to approximately the saturation velocity of o.k.a.n. (Raphan *et al.* 1981). The steady-state response is generated by activation of the velocity-storage integrator by a signal arising in the otolith organs (Correia & Money, 1970; Raphan *et al.* 1981; Cohen *et al.* 1983). Typical nystagmus during a step of velocity about a tilted axis is shown in Fig. 4*A*. After baclofen the initial step of velocity, which is produced by the semicircular canals, was unaffected. The steady-state response could not be maintained, however (Fig. 4*B*).

To demonstrate the separate effects of baclofen on nystagmus produced by the semicircular canals and the otolith organs during o.v.a.r., animals were rotated about a vertical axis in darkness until per-rotatory nystagmus had subsided (Fig. 4*C*, Per). The axis of rotation was then tilted 30 deg to initiate a rotating gravity vector that excited the otolith organs (o.v.a.r.). Before baclofen when the axis of rotation was

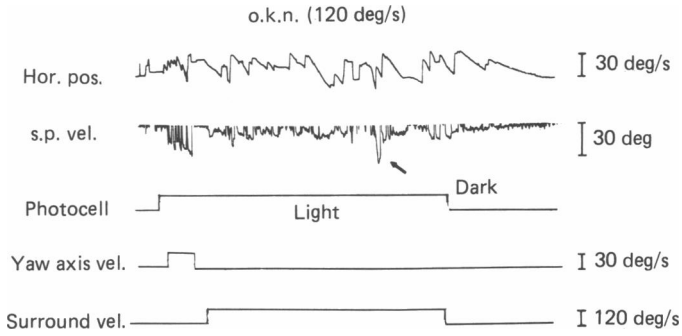

Fig. 6. O.k.n. and o.k.a.n. in another animal after receiving 4·5 mg/kg of baclofen. The animal was first rotated at 30 deg/s in light. It then received surround rotation at 120 deg/s. Although initial and steady-state o.k.n. levels were low, occasionally the animal generated a slow phase with a velocity of 30–40 deg/s (arrow).

tilted, nystagmus reappeared and climbed to a steady-state level of about 60 deg/s. When the axis of rotation was tilted back to the upright, nystagmus slow-phase velocity declined over the characteristic time constant of the storage integrator (arrow). After baclofen (Fig. 4*D*) the same stimulus to the otoliths produced only about 20 deg/s of steady-state nystagmus. Consistent with the shorter time constants of per- and post-rotatory nystagmus after baclofen, the time constant of decline in slow-phase velocity was shorter when the axis of rotation was returned to the upright after the drug (arrow).

Optokinetic nystagmus and optokinetic after-nystagmus

Baclofen also altered o.k.n. and o.k.a.n. (Fig. 5), reducing the initial and steady-state velocity of o.k.n. and causing o.k.a.n. to be of lower velocity and to decline more rapidly. After 4 mg/kg of baclofen the steady-state response was only about 10–15 deg/s, and the after-nystagmus was brief, disappearing within several seconds (Fig. 5*C*). Reduced slow-phase velocities of o.k.n. and o.k.a.n. after 4·5 mg/kg of baclofen in response to surround rotation of 120 deg/s in another animal (Fig. 6) can be contrasted to the eye velocities induced by angular rotation at 30 deg/s, shown at the beginning of the trace. Before baclofen the animal could easily achieve eye velocities close to 120 deg/s during o.k.n.

The alteration in each component of o.k.n. and o.k.a.n. was dose dependent (Fig. 7*A–C*). Peak velocities of both steady-state o.k.n. and o.k.a.n. fell by about 15 deg s^{-1} mg^{-1} kg^{-1} of drug (Fig. 7*B* and *C*). Comparative effects on o.k.a.n. and v.o.r. time constants produced by the same dosages are shown in Fig. 2*B* (▲ *vs.* ●, respectively) for the animal whose data are shown in Fig. 5. The changes in the time constants were similar, although the v.o.r. time constant was always somewhat longer. The longer vestibular time constant is probably due to continued activation of the central vestibular system by cupular deflection that persists after the beginning or end of a step of velocity (Goldberg & Fernandez, 1971). This would keep the integrator from discharging as rapidly during rotation as it does during o.k.a.n. (Raphan *et al.* 1979).

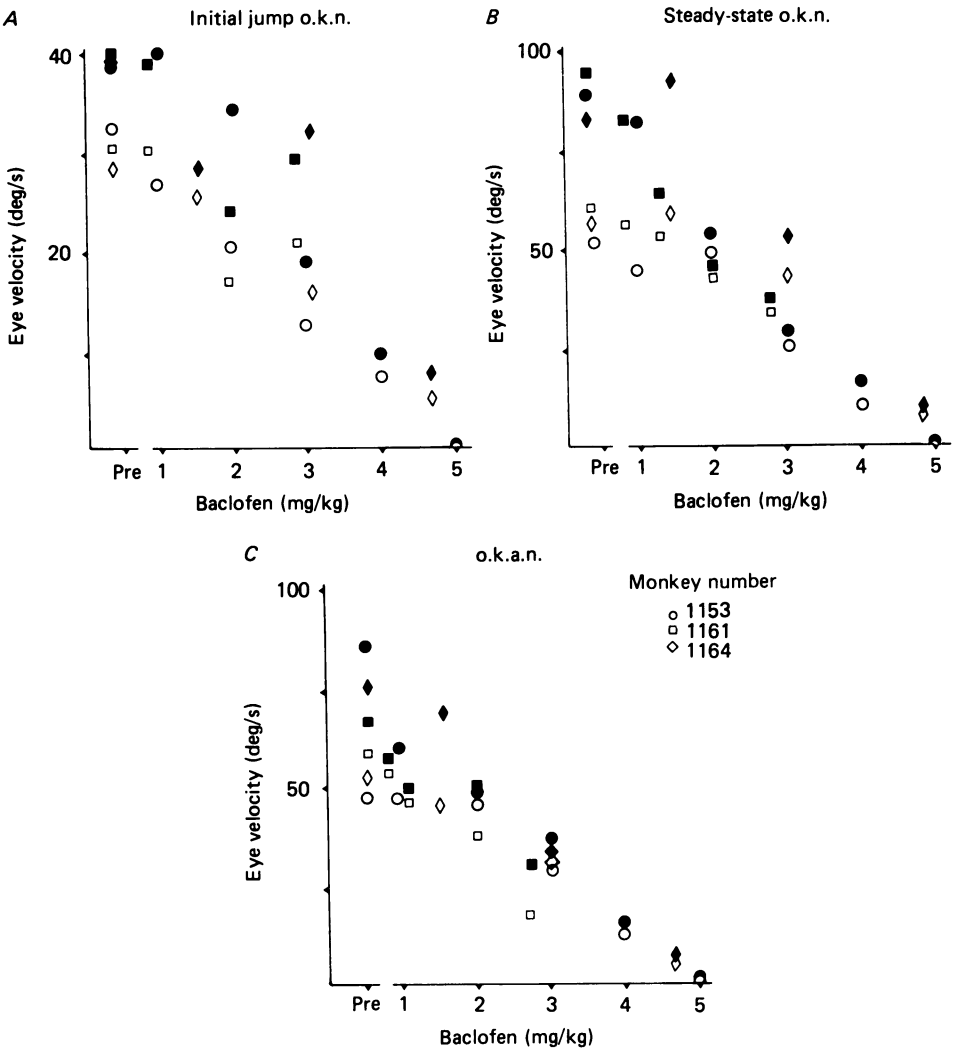

Fig. 7. *A–C*, relationship between initial jump in o.k.n. velocity (*A*), steady-state o.k.n. eye velocity (*B*), and peak velocity of o.k.a.n. (*C*) shown on the ordinates and the dosage level of baclofen (abscissa). Two stimulus velocities were used (60 deg/s, open symbols; 120 deg/s, filled symbols). Each symbol is the mean of four tests. There was a dose-dependent decline in each component of o.k.n. and o.k.a.n. after baclofen.

The charge time of o.k.a.n., which is responsible for the slow rise in o.k.n. to its steady-state level (Cohen *et al.* 1977), was tested after baclofen, and the data were fitted with exponentials (Fig. 8). In accordance with the data of Fig. 7*C*, the peak velocity of o.k.a.n. (V_{max}) was reduced after baclofen (Fig. 8*B* and *D*). Of interest was the finding that the time constant of the rise of o.k.a.n. (T_r) depended on the dose of baclofen. Doses of baclofen that produced small or moderate decreases in the falling time constant of o.k.a.n. caused the charging time constant of o.k.a.n. to be somewhat longer. Typical values were 4·7 s before baclofen at 30 deg/s (Fig. 8*A*) *vs.* 5·5 s after

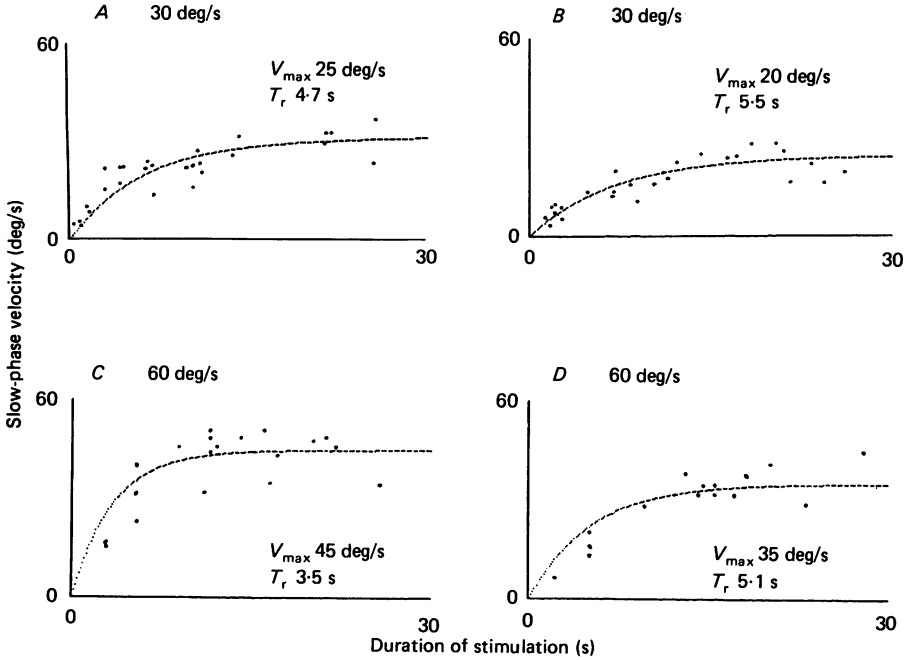

Fig. 8. Build-up of o.k.a.n. (ordinate) as a function of duration of stimulation during o.k.n. (abscissa) before (*A* and *C*) and after baclofen (*B* and *D*). The abscissa is 30 s long and the ordinate 60 deg/s. The data in *A*, *B* and *C*, *D* are from different animals. The steady-state gain of o.k.a.n. (V_{max}) was less and the rising time constants (T_r) were longer after the drug.

baclofen (Fig. 8*B*). In another animal at 60 deg/s they were 3·5 s before baclofen (Fig. 8*C*) *vs.* 5·1 s after baclofen (Fig. 8*D*). The same type of increase was found for stimulation at 15 deg/s. The slower rise time of o.k.n. at low doses of baclofen can also be seen in Fig. 5*A* and *B* where the time to peak velocity, shown by the downward arrows, was about 2 s longer after 2 mg/kg of baclofen than in the untreated state. Larger doses of the drug, which caused greater decreases in the falling time constant of o.k.a.n., were associated with shorter rising time constants of o.k.n. (Figs 5*C* and 6). Before baclofen the slow rise in o.k.n. took 15–20 s to reach culmination in the animal whose data is shown in Fig. 6.

Baclofen also reduced the size of the initial jump in slow-phase eye velocity at the onset of o.k.n. in a dose-dependent fashion (Figs 5, 6 and 7*A*), but there were almost always occasional single beats of nystagmus whose slow-phase velocities were as high as 30–40 deg/s (Fig. 6, arrow). This suggests that although the animal's ability to generate rapid changes in eye velocity through visual–oculomotor pathway had been diminished by baclofen, it could mobilize these pathways under some circumstances. It is postulated that an internal signal related to ocular pursuit (Lisberger & Fuchs, 1978) and to the rapid component of o.k.n. (Waespe *et al.* 1983) is used during visual–vestibular conflict to suppress the v.o.r. The animal's ability to suppress the v.o.r. after baclofen was tested with steps of velocity and with sinusoidal rotation in

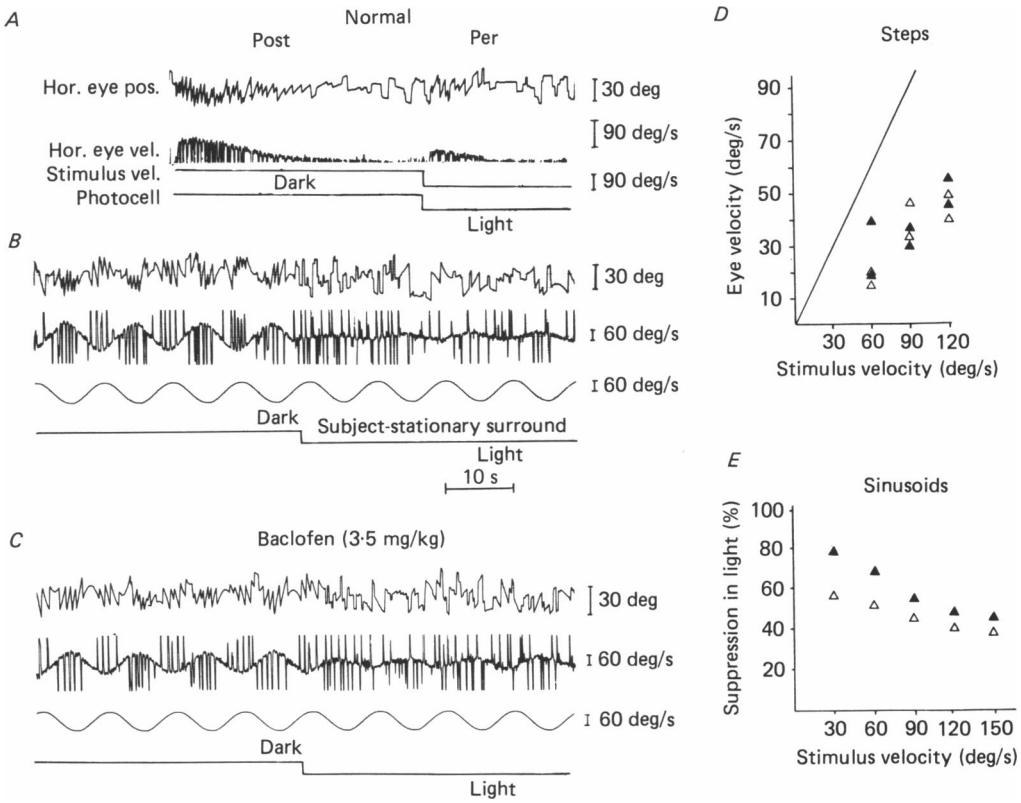

Fig. 9. *A*, nystagmus during a velocity step in darkness (left) and in a lighted, subject-stationary visual surround (right). The subject-stationary surround was produced by mechanically coupling the o.k.n. drum to the rotating chair in light. The recording was from a normal monkey using an eye coil. Note the reduction in the initial jump in eye velocity and the short duration of nystagmus in the subject-stationary surround. *B* and *C*, eye position and eye velocity during sinusoidal rotation at 0·1 Hz and a peak rotational velocity of 60 deg/s in dark (left) and in a subject-stationary visual surround (right) before (*B*) and after (*C*) baclofen. The traces are as labelled in *A*. Note the suppression of the v.o.r. regardless of administration of baclofen. *D*, visual suppression of nystagmus during steps of velocity before (▲) and after 3·5 mg/kg of baclofen (△). The continuous line indicates unity gain which was close to the response in darkness. *E*, percentage suppression of the v.o.r. (1-(amplitude in light/amplitude in dark)) during sinusoidal rotation in a subject-stationary surround before (▲) and after baclofen (△). The data in *D* and *E* are from the monkey whose data are shown in *A–C*. Note that the animal had no difficulty in suppressing the v.o.r. after baclofen.

a lighted, subject-stationary surround. In the normal animal the initial jump in eye velocity during a step of angular velocity in darkness (Fig. 9*A*, Post) is reduced in a subject-stationary surround (Fig. 9*A*, Per), and eye velocity falls more rapidly to zero. The maximum eye velocities achieved during steps of angular velocity of 60, 90 and 120 deg/s in a subject-stationary surround before baclofen are shown by the filled triangles in Fig. 9*D*. At a dose that caused considerable shortening of the v.o.r. time constant (3·5 mg/kg), the animal was still able to reduce the size of the initial jump in eye velocity at the onset and end of rotation (Fig. 9*D*, △). Animals were also

TABLE 1. Amplitude–duration relationship of saccades

Control				Baclofen (4 mg/kg)			
Amplitude (deg)	Duration (ms)	S.D.	*N*	Amplitude (deg)	Duration (ms)	S.D.	*N*
0–5	17	16	54	0–5	17	13	62
5–10	34	9	40	5–10	41	22	42
10–15	44	14	57	10–15	52	19	45
15–20	57	21	91	15–20	71	31	47
25–30	71	26	54	25–30	65	22	38
30–35	78	23	44	30–35	83	26	29
35–40	87	26	19	35–40	72	14	10
40–45	90	20	11				

TABLE 2. Amplitude–maximum velocity relationship of saccades

Control				Baclofen (4 mg/kg)			
Amplitude (deg)	V_{max} (deg/s)	S.D.	*N*	Amplitude (deg)	V_{max} (deg/s)	S.D.	*N*
0–5	171	52	52	0–5	216	131	62
5–10	288	54	40	5–10	290	85	42
10–15	410	83	57	10–15	378	95	45
15–20	495	113	91	15–20	420	130	60
20–25	584	127	85	20–25	522	156	48
15–30	643	148	55	25–30	653	177	40
30–35	658	163	44	30–35	608	167	26
35–40	698	159	19	35–40	690	212	10
40–45	771	114	11				

able to reduce eye velocity during sinusoidal angular rotation at 0·1 Hz at various velocities from 30 to 150 deg/s before and after receiving the drug (Fig. 9*B* and *C*; Fig. 9*E*, ▲ and △).

In addition to being able to suppress rapid changes in eye velocity, a mechanism exists in the vestibular system that rapidly reduces the time constant of o.k.a.n. or per- or post-rotatory nystagmus. This effectively discharges or 'dumps' activity from the velocity-storage integrator during o.k.a.n. or vestibular nystagmus, causing the responses to be of short duration. This mechanism is activated by brief periods of visual fixation (Cohen *et al.* 1977; Raphan *et al.* 1979) or by tilting the head (Raphan *et al.* 1981; Waespe *et al.* 1985*b*). After baclofen animals had no difficulty in reducing stored activity during post-rotatory nystagmus or o.k.a.n. in response to brief periods of visual fixation or when they were tilted. Thus, baclofen did not inactivate the dump mechanism.

Saccades and quick phases of nystagmus

Baclofen did not alter the animal's ability to generate normal saccades and quick phases of nystagmus. The relationship between amplitude and duration (Table 1) and between amplitude and maximum velocity of saccades (Table 2) were unchanged after 4 mg/kg of the drug, although the standard deviations were somewhat higher. As shown in Figs 1, 4 and 5 the ability of the animals to produce linear slow phases

of velocity and to hold lateral eye positions in darkness was unaffected by baclofen. Therefore, baclofen did not affect the saccadic system or the final common neural integrator (Skavenski & Robinson, 1973; Robinson 1975).

Modelling of vestibular and optokinetic responses after baclofen: results of simulation

The data were simulated by the model, analysed in Waespe *et al.* (1983), and the effects of baclofen were related analytically to the changes in its parameters. Time constants taken from the data were used in the model, and the envelopes of slow-phase velocity were compared to those obtained experimentally. In the model (Fig. 10*A*) vestibular nystagmus is generated by head velocity signal r_h, which through the cupula dynamics generates the signal r_v that appears in semicircular canal afferents in the vestibular nerve. This information activates the integrator as well as projecting around it, to form a component of the eye velocity command signal in the vestibular nuclei, denoted by V_n. O.k.n. is initiated by relative movement of the visual surround, the optokinetic stimulus r_o. From this signal is subtracted head velocity and eye velocity whose sum is gaze velocity. This generates the retinal slip signal E. The slip signal can be extinguished by light switch L or transmitted centrally to two elements. One element labelled flocculus produces the signal V_f that is responsible for rapid changes in eye velocity. The second is a non-linear function whose output activates the velocity-storage integrator (visual coupling to the integrator). Its characteristics are shown in Fig. 10*L*. For retinal-slip velocities less than E_s, estimated in this study to be 20 deg/s, the system is in the positive-gain region. In this region proportional increments in retinal slip give rise to proportional increases in the input to the integrator. Above E_s further increases in retinal slip produce proportional decrements in the input to the integrator, the negative-gain region. The summation of V_n and V_f is the eye velocity command signal. The suppression switch S in the model is utilized to discharge or 'dump' the integrator rapidly during visual or tilt suppression (Waespe *et al.* 1983).

Model predictions of vestibular nystagmus are shown in Fig. 10*B* and *C*. The three traces represent simulated activity in semicircular canal afferents (cupula, Cup.), in the velocity-storage integrator (Int.) and the resultant slow-phase velocity (s.p. vel.) Integrator time constants T_0 of 20 s (Fig. 10*B*) and 5 s (Fig. 10*C*) correspond to overall v.o.r. time constants of 24 and 6 s, respectively, since the cupula time constant T_c and the integrator time constant T_0 combine to produce the overall response (Raphan *et al.* 1979). In the simulations the gain of the response was unaffected by decreasing the integrator time constant, although this produced a faster decline in eye velocity (Fig. 10*C*). The decrease in the integrator time constant was associated with a decrease in the duration of the plateau (Fig. 10*B* and *C*, arrows). The envelope of slow-phase velocity with an integrator time constant of 20 s (Fig. 10*B*) is similar to the velocity envelopes of the per- and post-rotatory nystagmus, shown in Fig. 1, T_0 and T_{24} h, while the response with a 5 s integrator time constant (Fig. 10*C*) simulates the data obtained after baclofen (Fig. 1, T_2 h). These results are consistent with the postulate that baclofen has little effect on peripheral processing in the labyrinth and acts mainly to reduce the falling time constant of the velocity-storage integrator.

O.k.n. and o.k.a.n. were simulated at 30 and 60 deg/s (Fig. 10*F–K*). Each of the

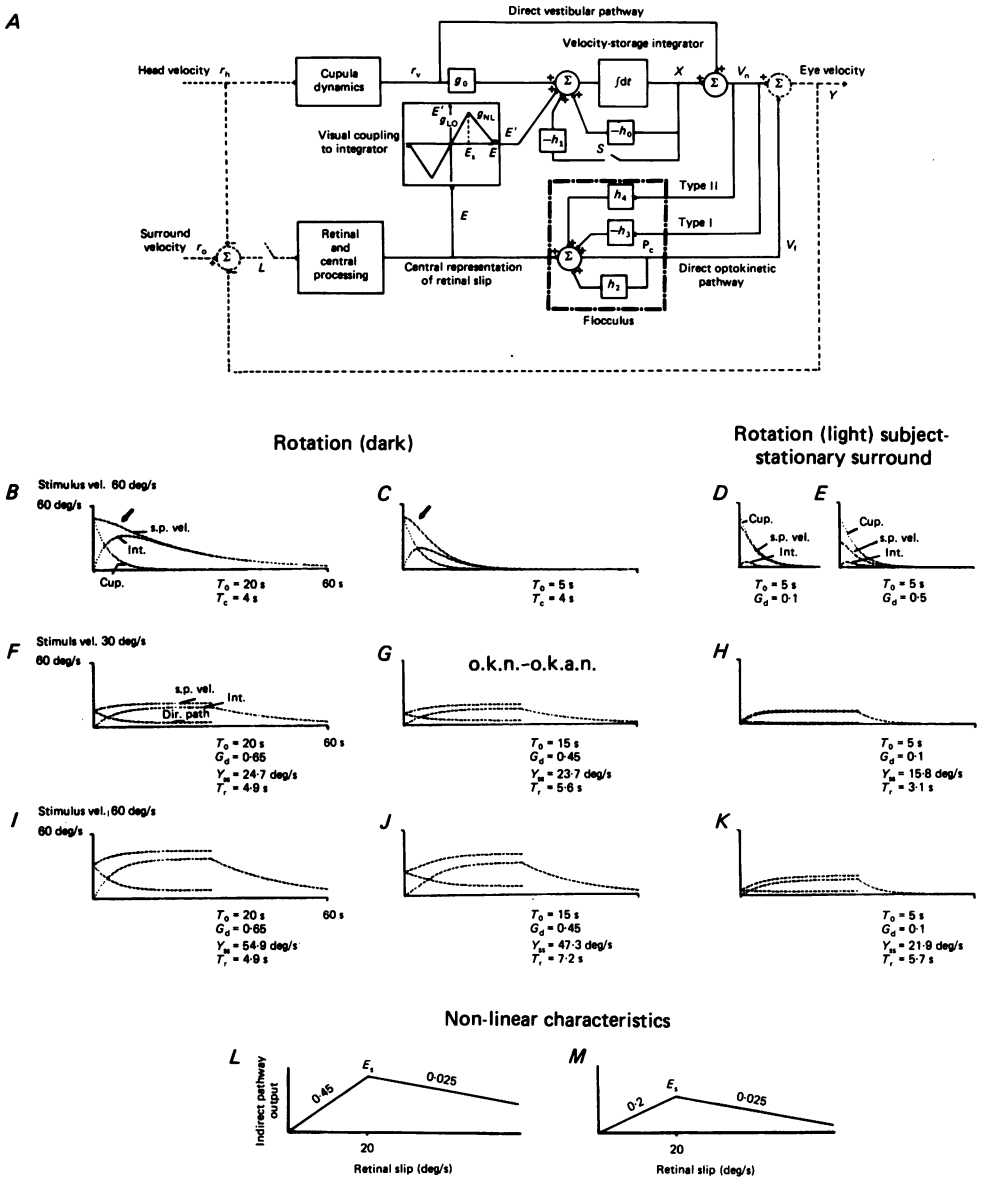

Fig. 10. *A*, model of the v.o.r., o.k.n. and o.k.a.n. and of visual–vestibular interaction from Waespe *et al.* (1983). *B–K*, model simulations under different conditions. The numbers next to each simulation refer to the falling time constant of the integrator (T_0), the time constant of the cupula (T_c), the gain of the direct visual pathway (G_d), peak steady-state velocity (Y_{ss}), and the rising time constant of the integrator (T_r). In the model $G_d = 1/2 - h_2$, and it was assumed that $h_4 = h_3$ (see Waespe *et al.* (1973) for derivation). *B* and *C*, response of the v.o.r. to steps of angular velocity in darkness with integrator time constants (T_0) of 20 s (*B*) and 5 s (*C*). The traces are slow-phase eye velocity (s.p.vel.), the output of the semicircular canals (Cupula, Cup.), and the state of the velocity-storage integrator (Int.). Note the shorter dominant time constant of the v.o.r. and the loss of the plateau (arrows) when the time constant of the velocity-storage integrator beclofen was reduced. *D* and *E*, simulation of the v.o.r. in response to a velocity step in a subject-

simulations is composed of three traces, the response of the direct pathway (Dir. path), the response of the indirect pathway and the velocity-storage integrator (Int.) and the resultant slow-phase velocity (s.p. vel.). Based on the data of Figs 5 and 7 it was assumed that baclofen produced a reduction both in the falling time constant of the integrator and the gain of the direct visual pathway during o.k.n. Parameters used for simulating o.k.n. and o.k.a.n. in the untreated state (Fig. 10*F* and *I*) were an integrator time constant T_0 of 20 s and a direct pathway gain G_d of 0·65. From the data of Figs 2*B* and 7*A* it was assumed that medium and large doses of baclofen would cause T_0 to go to 15 and 5 s and G_d to 0·45 and 0·1 respectively. The structure of the non-linearity was chosen for the normal state such that the positive incremental gain was 0·45 and the negative incremental gain was 0·025 (Fig. 10*L*). Also shown are the values of steady-state o.k.n. slow-phase velocity Y_{ss} and of the rising time constant of the integrator T_r.

In order to simulate the increased time constant of rise after moderate doses of baclofen (Figs 5*B*, 8*B* and 8*D*), it was necessary to reduce the slope of the positive incremental gain of the visual coupling to the integrator. Based on the data of Fig. 8 the slope chosen for the simulations after baclofen (Fig. 10*G*, *H*, *J* and *K*) was 0·2 (Fig. 10*M*). It was assumed that baclofen did not affect the crossover velocity (E_s) from the positive- to the negative-gain region, and it was left at 20 deg/s of retinal-slip velocity. The basis for this is that the rising time constant of o.k.n. and o.k.a.n. increased after baclofen for velocities as low as 15 deg/s. If the increase in time constant at 30 and 60 deg/s had been due to a modest reduction in the crossover point, such an increase would not have been present at 15 deg/s, a velocity that was low enough to keep the system entirely in the positive-gain region. On the other hand, more drastic reductions in E_s would have caused prolongation in the rising time constant at 15 deg/s, but this would also cause the time constant of rise to be much longer at 30 and 60 deg/s than was observed experimentally. Therefore, E_s was assumed not to have been affected by baclofen.

Under these conditions for a moderate dose of baclofen that reduced T_0 to 15 s, steady-state o.k.n. velocity fell, o.k.a.n. had a lower maximum velocity and was of shorter duration, and the charging time constant of o.k.a.n. T_r increased from 4·9 to 5·6 s at 30 deg/s (Fig. 10*F* and *G*) and from 4·9 to 7·2 s at 60 deg/s (Fig. 10*I* and *J*). The greater increase in the charging time constant at 60 (Fig. 10*J*) than at 30 deg/s (Fig. 10*G*) was due to the system's spending more time in the negative-gain region at the higher velocity. With a further reduction in integrator time constant to 5 s and a direct pathway gain of 0·1, steady-state responses to stimulation at both 30 and 60 deg/s were reduced further, but the rising time constants were now shorter (3·1 and 5·7 s, Fig. 10*H* and *K*, respectively). The rising time constant T_r at 60 deg/s (Fig. 10*K*) was longer than at 30 deg/s (Fig. 10*H*) because at 60 deg/s the system

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stationary lighted surround with a T_0 of 5 s and a direct visual–oculomotor pathway gain (G_d) of 0·1 (*D*) and 0·5 (*E*). Slow-phase velocity was of short duration in both conditions but was less only when G_d was high in *E*. *F–K*, o.k.n. and o.k.a.n. with various parameter values. Surround velocity was 30 deg/s for *F–H* and 60 deg/s for *I–K*. The integrator time constant was 20 s in *F* and *I*, 15 s in *G* and *J* and 5 s in *H* and *K*. The structure of the non-linearity for the stimulations in *F* and *I* is shown in *L* and for *G*, *H*, *J* and *K* is shown in *M*. See text for further explanation.

never left the negative-gain region. The envelope of slow-phase velocity in Fig. 10*I* at a stimulus velocity of 60 deg/s without balcofen was similar to that of the normal animal in Fig. 5*A*, while slow-phase velocities in Fig. 10*J* and *K* approximated the experimental results in Figs 5*B,C* and 6, predicting the increase in the rising time constant at small or moderate dosages and the fall at higher dosages.

The model also reproduced the experimental results during suppression of the v.o.r. The data during rotation in a subject-stationary surround were simulated with an integrator time constant of 5 s and direct-pathway gains of 0·1 (Fig. 10*D*) and 0·5 (Fig. 10*E*). The integrator was only weakly excited during this stimulus because the dump mechanism was activated, shortening the integrator's time constant and reducing its capacity to store charge. If the direct-pathway gain was reduced to 0·1 (Fig. 10*D*), the initial jump in slow-phase velocity would have been 0·9 of the velocity of the response in darkness (Fig. 10*C*). However, as shown in Fig. 8*D*, the initial step of eye velocity was reduced to about 0·5 after baclofen in a subject-stationary surround. When the direct-pathway gain was set at 0·5 (Fig. 10*E*), the initial jump in eye velocity in light was smaller than the response in darkness (Fig. 10*C*), approximating the experimental data. This indicates that the direct visual–oculomotor pathway gain was not reduced during v.o.r. suppression after baclofen.

DISCUSSION

The data indicate that the major action of baclofen on the oculomotor system was to reduce the dominant time constant of the v.o.r. Each component of nystagmus that depends on the velocity-storage mechanism in the v.o.r. was similarly altered. In contrast, the ability to produce rapid changes in eye velocity from either the vestibular or saccadic systems was unaffected by the drug, and visual suppression of the v.o.r. was intact, as was the final common integrator for generating eye position (Skavenski & Robinson, 1973; Robinson, 1975). As yet, ocular pursuit has not been studied, but there is some indication (e.g. Figs 6 and 9) that it may be at least partially preserved. Thus, effects of the drug, while not solely limited to a single oculomotor component or subsystem, were nevertheless surprisingly discrete.

The detailed analysis of o.k.n. and vestibular nystagmus during modelling gives insight into which parameters of the system were affected by the drug. Effects on vestibular nystagmus could be predicted simply by altering the characteristics of the velocity-storage integrator. Simulations of o.k.n. and o.k.a.n. also emphasize the role of the storage integrator in producing these responses, but demonstrate that it is also necessary to consider the non-linear coupling of the visual system to the indirect pathway and the integrator to explain the characteristics of the nystagmus before and after drug administration. Variations of each of the parameters of the non-linearity would affect the shape and time course of o.k.n., but only by modifying the positive-gain region could we adequately simulate the data. According to the results of modelling, baclofen reduced the ability of the velocity-storage integrator to respond to large retinal slips during o.k.n. by two methods. It altered the positive gain of the non-linearity, thereby reducing the input to the integrator. It also reduced the falling time constant of the integrator, increasing its leak and its ability to store activity related to high velocities of movement of the visual surround.

The effects of baclofen on the ability of the visual system to produce rapid changes

in eye velocity were paradoxical. There was a reduced gain of the initial jump in slow-phase velocity during o.k.n., but animals were still able to suppress the v.o.r. visually and could generate slow-phase velocities of 30–40 deg/s on occasion (Fig. 6). This could best be explained if the rapid component of o.k.n. and ocular pursuit were to be differently affected by baclofen. While both processes appear to utilize the same pathways through the flocculus (Miles & Fuller, 1975; Lisberger & Fuchs, 1978; Zee, Yamazaki, Butler & Gucer, 1981; Waespe & Henn, 1981; Waespe *et al.* 1983; Waespe, Rudinger & Wolfensberger, 1985*a*), they are not identical. The rapid rise in o.k.n. is a reflex mechanism, while pursuit is a voluntary act. In addition, the rapid component of o.k.n. is lost after cortical lesions while ocular pursuit can recover (Zee, Butler, Optican, Trisa & Gucer, 1982). If the implication of separate processing of these two components is correct, then baclofen could be used to separate them.

The data also gave insight into transmitters utilized in controlling the v.o.r. In view of the normal gain of the step response of the v.o.r. at the highest doses of baclofen (Fig. 2*A*), it is unlikely that $GABA_B$ receptors control excitation in the 'three neurone arc' (Szentágothai, 1950). The failure of second-order vestibular neurones that project to the abducens nucleus to take up tritiated GABA while reabsorbing tritiated glycine suggests that glycine, not GABA, is the inhibitory transmitter in this part of the horizontal v.o.r. (Spencer & Baker, 1985). On the other hand, GABA, acting through $GABA_B$ receptors, seems likely to be the inhibitory transmitter used in controlling velocity storage. The strong relationship between the dose of baclofen and the time constant of the storage integrator in all its functions supports this view. As noted, baclofen also appeared to affect the positive gain of the visual coupling to the integrator. It is likely that this parameter is also under GABAergic control.

The functional significance of the inhibition elicited by baclofen is that it would reduce the compensatory response of the animal to angular head movements at low frequencies or to high retinal-slip velocities. There are two ways in which such inhibitory control of velocity storage might be manifest in the normal operation of the v.o.r. During habituation produced by repeated testing, the time constant of the v.o.r. is reduced without affecting its step gain. This preserves the high-frequency characteristics of the v.o.r. but reduces its response to low-frequency stimulation. Effects are similar during the rapid discharge or 'dumping' of velocity storage that occurs when viewing a subject-stationary surround (Cohen *et al.* 1977; Raphan *et al.* 1979) or when the head is tilted (Raphan *et al.* 1981). The dump mechanism shortens the dominant time constant of the storage integrator to discharge it rapidly, without affecting the step response. Both habituation and the rapid discharge of activity from the velocity-storage integrator are lost after ablation of the nodulus and uvula (Waespe *et al.* 1985*b*), a lesion that would cause a reduction in the GABAergic input from cerebellar Purkinje cells to the vestibular nuclei and brain stem. Taken together, it seems likely that habituation of the v.o.r. time constant and dumping of activity in the velocity-storage integrator are mediated by a system that includes the nodulus and uvula, that utilizes GABA as a transmitter and that acts on $GABA_B$ receptors. In contrast, diazepam, which activates $GABA_A$ receptors (see Tallman & Gallagher, 1985, for review), has little effect on the dominant time constant of the v.o.r. or even lengthens it (Blair & Gavin, 1981; B. Cohen & D. Helwig, unpublished data). This

suggests that $GABA_A$ receptors are not involved in inhibition of velocity storage or in controlling the processes that depend on it.

The exact mode of production of velocity storage is not known, although it is closely linked to the vestibular system (Waespe & Henn, 1977; Precht, 1982; Cohen *et al.* 1983). Lorente de Nó (1933) first suggested that the process of integration requires multiple feed-back loops, and Galiana, Flohr & Melvill Jones (1984) have suggested that these loops are located in the vestibular commissural system. If the commissural fibres are involved in the realization of the velocity-storage integrator, it would explain why velocity storage disappears when the vestibular commissural fibres are cut (deJong, Cohen, Matsuo & Uemura, 1980; Blair & Gavin, 1981). If so, then the time constant of the velocity-storage integrator could be controlled by inhibiting the activity of cells responsible for velocity storage that contribute axons to the commissural system. Since the initial step in eye velocity during impulses of angular acceleration was unaffected by baclofen, cells that receive input from the semicircular canals and project to the oculomotor system to produce the most rapid components of the v.o.r. must be separate from those that are responsible for producing velocity storage. One implication of the present results is that differential uptake of baclofen could provide a technique for identifying 'velocity-storage' neurones and for separating them from canal-related cells that perform other functions.

The data also provide an explanation for why baclofen is effective in treating the periodic alternating nystagmus that occurs after cerebellar or posterior fossa lesions (Halmagyi *et al.* 1980) or after nodulus and uvula ablation (Waespe *et al.* 1985*b*). Periodic alternating nystagmus is believed to be due to an inability to stabilize elements of velocity storage in the vestibular nuclei (Leigh *et al.* 1981). By reducing the time constant of the storage integrator, baclofen would shorten the v.o.r. time constant, stabilizing the system. If correct, then a loss of GABAergic inhibitory control of velocity storage may be a key element in the production of periodic alternating nystagmus. Whether baclofen will be of clinical importance in treatment of other vestibular system disease or motion sickness because of its selective effect on velocity storage remains to be explored.

In summary, baclofen has a discrete but powerful effect on the v.o.r. that can be modelled as an alteration in the time constant of the velocity-storage integrator and as a reduction in gain in visual–oculomotor pathways that couple to it. Systems utilizing GABA and acting through $GABA_B$ receptors appear to provide inhibitory control of velocity storage.

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