A Chronic Implant to Record Electroretinogram, Visual Evoked Potentials and Oscillatory Potentials in Awake, Freely Moving Rats for Pharmacological Studies

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SUMMARY

Electroretinogram (ERG), widely used to study the pharmacological effects of drugs in animal models (e.g., diabetic retinopathy), is usually recorded in anesthetized rats. We report here a novel simple method to obtain chronic implantation of electrodes for simultaneous recording at the retinal and cortical levels in freely moving, unanesthetized animals. We recorded cortical (VEPs) and retinal (ERGs) responses evoked by light (flash) stimuli in awake rats and compared the results in the same rats anesthetized with urethane (0.6 mg/kg) before and after the monocular administration of scopolamine methyl bromide (1‰ solution). We also compared the retinal responses with those derived from a classic acute corneal electrode. Anesthesia induced consistent changes of several VEP and ERG parameters like an increase of both latency and amplitude. In particular, the analysis of the variation of latency, amplitude, and spectral content of rapid oscillatory potentials could be important for a functional evaluation of the visual system in unanesthetized versus anesthetized animals.

KEYWORDS

urethane, scopolamine, VEPs, ERGs, OPs

INTRODUCTION

Electroretinograms (ERGs), visual evoked potentials (VEPs), and oscillatory potentials (OPs), neurophysiologic methods that yield reproducible results in routine clinical practice, provide an objective functional measure of the visual pathways and related neural systems. These methods have been studied in large groups of normal subjects and in patients having a wide variety of neurological, endocrine and dysmetabolic diseases. Visual evoked potentials and ERGs are used for diagnostic applications in the presence of dysfunction in retinal layers and/or in the occipital cortex (Parisi, 2001). Such techniques can also provide a further therapeutic approach through the possibility of monitoring neurophysiologic changes related to diseases, to the alteration in the number or concentration of neurotransmitters or drugs, or to other situations that modulate the neuronal response to external/ internal stimulation.

Instead, OPs reflect short-term synchronization of neuronal electrical activity. Oscillations around the gamma range (40 to 100 Hz) reportedly play a role in attention-related mechanisms and synaptic

plasticity in cortical structures because they promote coherence and possible 'binding' of local and neuronal activity (Adjamian, 2004; Babiloni, 2004; Tallon-Baudry, 2003). Animal studies have been performed to confirm these hypotheses, in which the efficacy of various pharmacological agents or the differential impact of different behavioral states can be tested thoroughly (Van der Linden, 1999, Loizzo, 1998).

Although several studies have been published on VEPs, very few experiments have been carried out to study ERG parameters in awake rats (Szabo-Salfay, 2001; Galambos, 1994). In fact, such studies generally refer to restrained (Boyes, 1983) or anesthetized animals, with acute electrode implants (Schaeppi, 1988; Shaw, 1998), but anesthesia is known to affect electrophysiological responses (Dyer, 1994; Rigdon, 1988; Hetzler, 1989; Porciatti, 1999). Therefore, here we describe a new method to analyze the visual system of freely moving, unanesthetized rats that provides a model for simultaneously recording potentials at both retinal and cortical levels. This technique has been used in mice with optimal compliance (Lopez, 2002; Loizzo, 2002). We performed a comparison of retinal responses derived from this new method with those obtained from a 'classic' acute implant of electrodes, which is usually performed in anesthetized animals, using surface corneal electrodes. Furthermore, we verified the effects of a cholinergic antagonist using quaternary scopolamine because the structure of the molecule prevents crossing through blood-brain barrier, thus behaving as typical mydriatic agents used in patients and experimental rats.

2. EXPERIMENTAL

2.1 Animals

Sprague Dawley rats (Charles River Italy, Calco, Italy) (n=8) weighing 250 g each were housed in a transparent plastic cage under standard animal conditions with free access to food and water, a 12 hrs light/dark cycle, and an ambient temperature of 21 °C. The animal care and use followed the directives of the Council of the European Communities. The Bioethical Committee of the Italian National Institute of Health approved the experimental protocol.

2.2 Surgery

Under xylazine (Rompun, Bayer AG, Leverkusen-Germania, 20 mg/kg i.p.) and ketamine (Ketavet 100, Gellini Farmaceutici Spa, Peschira Borromea-MI, 32 mg/kg i.p.) and locally injected lidocaine (Lidocaina 2%, Azienda Terapeutica Italiana A.T.I. srl, Ozzano Emilia-BO, 0.1 ml s.c.) anesthesia, the animals were chronically implanted, the position of electrodes being determined with reference to the sagittal suture and bregma. For each animal, four L-shaped monopolar epidural stainless-steel electrodes (0.8 mm diam./15 mm length) were implanted on sensorimotor cortex for VEPs recording: left and right posterior (5 mm from the bregma and 4 mm lateral to the sagittal suture bilaterally), right anterior (4 mm from the bregma and 2 mm from the sagittal suture). To assure stability to the dental cement implant on the skull, we positioned a fourth electrode symmetrical to the active one (left posterior, 1.5 mm caudal to bregma). This electrode was not connected. For flash ERGs recording two teflon coated tungsten electrodes (0.2 mm diameter), covered with an anallergic and insulating varnish, except for the tip (0.5 mm), were applied: one was used as reference and was inserted subcutaneously over the nasal bone (1.5 cm long), and one behind the ocular globe (7 mm long).

The position of ERG electrodes leaves the retina just in the middle. The "active" electrode was applied as to obtain a physical contact between the electrode tip and the eye's posterior tunica, and is placed after drilling the left anterior
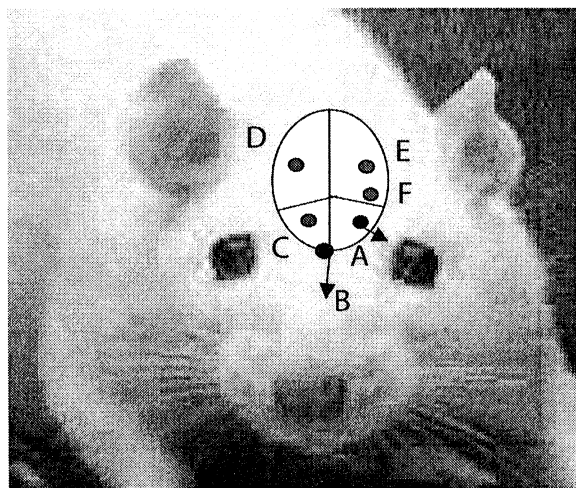
Fig. 1 A. ERG active electrode; B. ERG reference electrode; C. (D+) cortical electrode; D. (D–) cortical electrode; E. Ground cortical electrode. F. Support electrode, used only to enforce the electrode structure embedded in dental cement to the skull.

part of the skull (3 mm from the bregma and 2 mm from the sagittal suture). The drill (always held in the same hole) was inclined to leave of 35 degrees on the frontal plane and of 35 degrees on the sagittal plane to perforate the orbital bone behind the left eye. The recording electrode was inserted for ~7 mm, so that the bare tip was in contact with the posterior part of the eye. We could control the position by gently pushing the electrode to induce a reversible extroflession of the eye. The implant was fixed with dental cement. During the surgery, a heated table maintained the body temperature at 37 °C. A recovery period of 1 week was allowed before the ERG and EEG recordings.

2.3 Stimuli

A Grass Instrument PS 22 photic stimulator model supplied the flash stimulation. During the recording, 90 successive light flashes (stimulus rate:

1 flash per second, duration: 10 µs) were presented. Two intensities of stimulation, corresponding to 236.4 mcd/m^2*s and 945.6 mcd/m^2*s respectively, were used. The stimulus intensity range was chosen according to the results obtained in preliminary sessions published elsewhere (Lopez, 2002)

2.4 Experimental protocol

The recording sessions, each lasting 120 min, took place at the same time each morning to avoid interferences due to circadian rhythm. Each rat was recorded alone while housed in a cage with mirrored walls, with the ceiling corresponding to the flash stimulator positioned outside the sound-proof cage to avoid acoustic interferences. First, we recorded VEP and ERG in the awake, freely moving rat. Then the same animal was anesthetized with urethane (Sigma Chemical Co, Germany; 0.6 mg/kg) and VEP and ERG were recorded in both conditions, i.e., through the chronic and the acute implants. The latter consisted of a DTL electrode (Bayer, 2001) positioned in the conjuntival sac and recorded against a reference electrode inserted subcutaneously over the nasal bone. The recording procedure was repeated on the anesthetized animal, after placing 50 µl of scopolamine (scopolamine methyl bromide, 1% solution, Sigma Chemical Co, Germany) on the left eye where the ERG electrodes were positioned.

The EEG and ERG signals were amplified through a DC powered preamplifier, with a gain of 1000X and an analogic filter at 1 Hz highpass (HP) and a 500 Hz lowpass (LP) 6dB/octave. The acquisition was performed at 2 kHz sampling rate. An InstruNet A/D 16 bit conversion board delivered the signals to the acquisition system (Superscope- GW Instruments, Somerville, Massachusetts, USA) on a personal computer (Macintosh 8150 Power PC) customized and adapted by Analysa (Villafalletto CU, Italy). Brain and retinal activity and trigger were continuously acquired and saved as raw data to be analyzed off-line. The

protocol of the experiment was the following: a
stimulation frequency of 1 Hz was used for each
stimulation intensity, with a 10 min interval
between each intensity level. The animals were not
scotopically adapted. Repetitions were performed
when more than 3 movement artifacts were visible
in the raw data. The amplitude and latency of the
VEP and the ERG responses were measured after
baseline normalization. The latency was calculated
as the absolute value between stimulus onset and
the peak of the first negative response, whereas
amplitude was taken both as an absolute value of
negative peak amplitude and as peak-to-peak value
between the first negative peak and the following
most prominent positive peak. Oscillatory potentials
(OPs) were extracted through the application of a
digital 50 Hz HP filter (linear phase FIR, 6 dB/
octave) to the raw data (Lopez, 2002). The latency
of the oscillation was measured in ms from the
trigger to the response peak. The amplitude was
calculated as the peak-to-peak value between the
first negative and the first positive peaks.

2.5 Statistical analysis

The latencies and peak-to-peak amplitudes of
the major peaks of the evoked responses and of the
OPs were measured, and the differences between
pre- and post-treatment were compared in the same
animal. The differences in latency and peak-to-
peak amplitude were evaluated using Student's t
test for paired data. When comparing the retinal
responses coming from chronic and acute implants,
Student's t test for the difference of the average
was used.

3. RESULTS

Figures 2.1, 2.2, and 2.3 contain illustrations
of different types of visual responses recorded in
the rat. We analyzed only P2 and OP_2 for VEPs
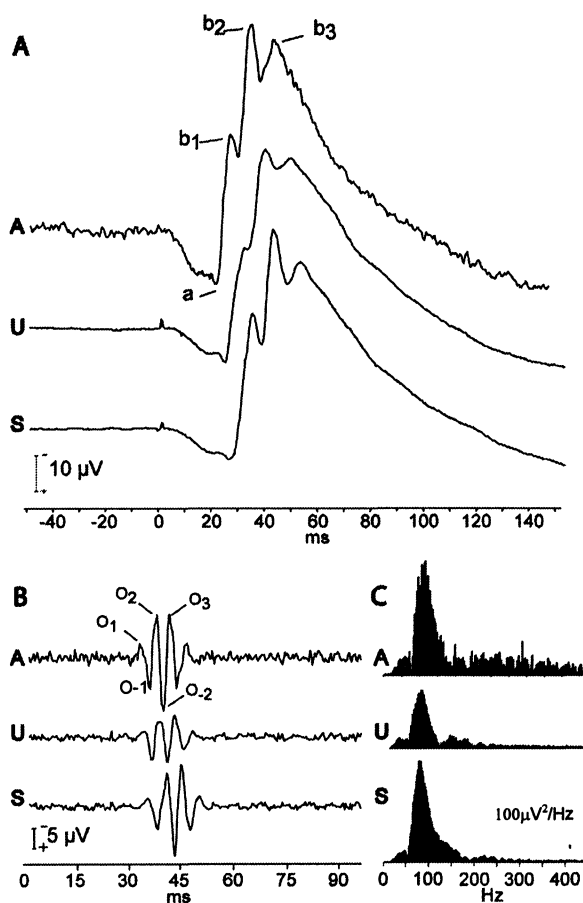and b2 and O_2 peaks for ERGs because it has been
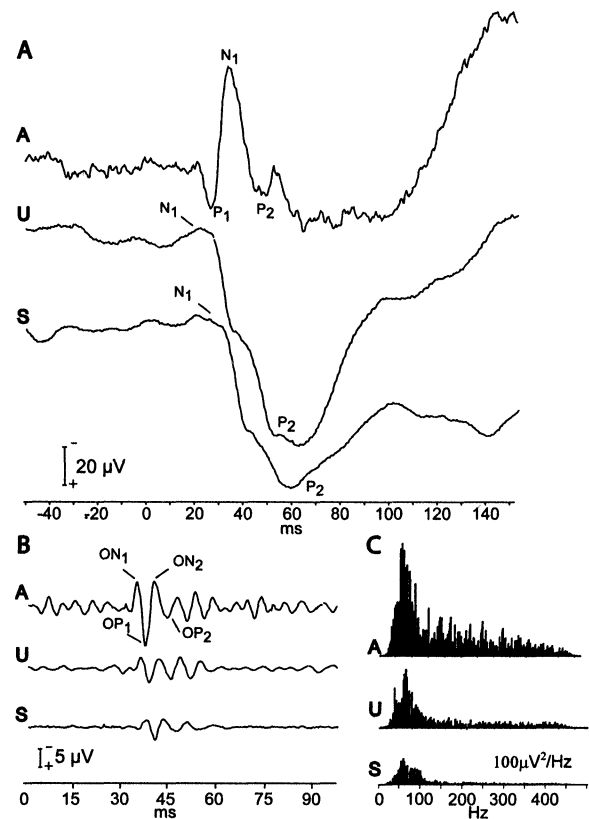
Fig. 2.1 A. Example of VEP in three different conditions: in
awake (A), anaesthetized (U), and treated with scopol-
amine (S). Positive and negative peaks labeled as N1,
P2, and N2 characterized baseline awake VEPs. B.
Superimposed on peaks, a train of higher frequency
positive and negative oscillatory potentials is labeled
as ON_1, ON_2, and OP_1, OP_2, respectively C. Power
spectrum of cortical oscillatory potentials shown in B.

already shown that after anesthesia with urethane,
the cortical VEPs show a change in morphology
because of the disappearance of some negative
peaks (Dyer, 1994).

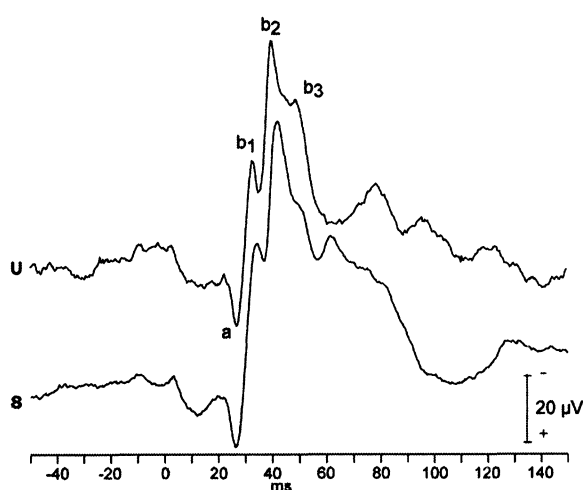## 3.1 VEP parameters before and after urethane and scopolamine

In awake rats, P2 appeared at a mean latency of 46.5 ± 1.8 (SEM) ms and an amplitude of 24.2 ± 6.3 μV at the lower intensity of stimulation and at a latency of 46.2 ± 2.1 ms and an amplitude of 30.7 ± 5.9 μV at the higher intensity of stimulation.

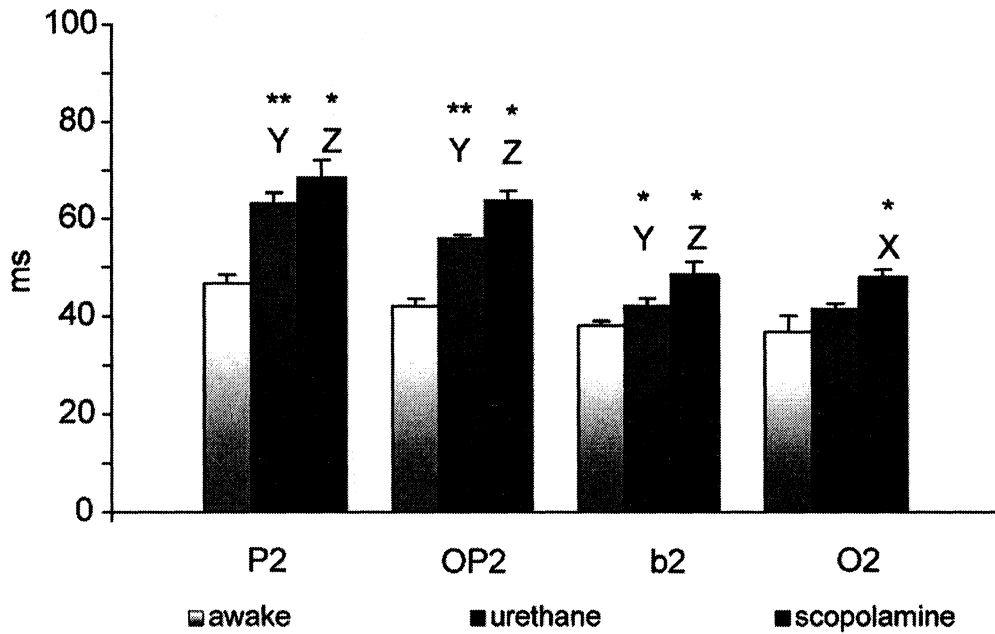After anesthesia it showed a consistent increase of latency (62.9 ± 2.3 ms and 58.8± 1.7 ms at the lower and higher intensities of stimulation, in both cases P < 0.01) (Fig. 3) and amplitude (66.2 ± 11.2 μV and 88.7 ± 11.9 μV respectively, P<0.01) (Fig. 4). The same trend of latency was observed after treatment with scopolamine methyl bromide (68.3 ± 3.6 ms P<0.05 at lower and 61.3 ± 2.7 ms P<0.05 at higher intensity of stimulation) (Fig. 3). The amplitude was lower then after anesthesia; this decrement was significant only at the higher intensity (88.7 ± 11.9μV vs 44.4 ± 13.2 μV, P<0.01) (Fig. 4).

The peak OP2 showed a latency range between 38 and 43 ms at stronger intensity of stimulation in awake animals. Latency to intensity relationship curves displayed a very similar trend to VEPs, but amplitude decreased after anesthesia with urethane, especially at the lower intensity (8.1 ± 0.9 μV vs 2.1 ± 0.2 μV, P<0.01). The latency of OP2 increased after scopolamine (55.7 ± 0.7 ms vs 63.6 ± 2.0 ms and 53.1± 1.9 ms vs 59.3 ± 2.9 ms at both intensities considered, P<0.05) (Fig. 3), while amplitude decreased (2.1 ± 0.2 μV vs 1.3 ± 0.2 μV and 2.6± 0.5μV vs 1.3 ± 0.2μV; P<0.05) (Fig. 4).

Fig. 2.2 A. Example of ERG recorded in rat in three different conditions: awake, anesthetized, and treated with scopolamine rat. The ERG waveform consists of an initial negative a- wave followed by the slow- high amplitude b-waves (identified as b1, b2, and b3). B. Superimposed on this potential there is a train of high positive and negative frequencies (O1, O2, O3, and O-1and O-2 respectively). C. Power spectrum of retinal oscillatory potentials shown in B.

Fig. 2.3 Example of ERG recorded using the DTL acute electrode after both urethane and scopolamine

Fig. 3 Latency mean of the different peaks (P2, OP2, b2 and O2) evaluated in awake rat and after treatment with urethane and scopolamine. Data are elicited by the lower intensities of luminous stimulation (236.4 mcd/m^2*s). Symbols indicate: * = P<0.05; ** = P< 0.01; Y=awake *vs* urethane; Z= urethane *vs* scopolamine; X= awake *vs* scopolamine.
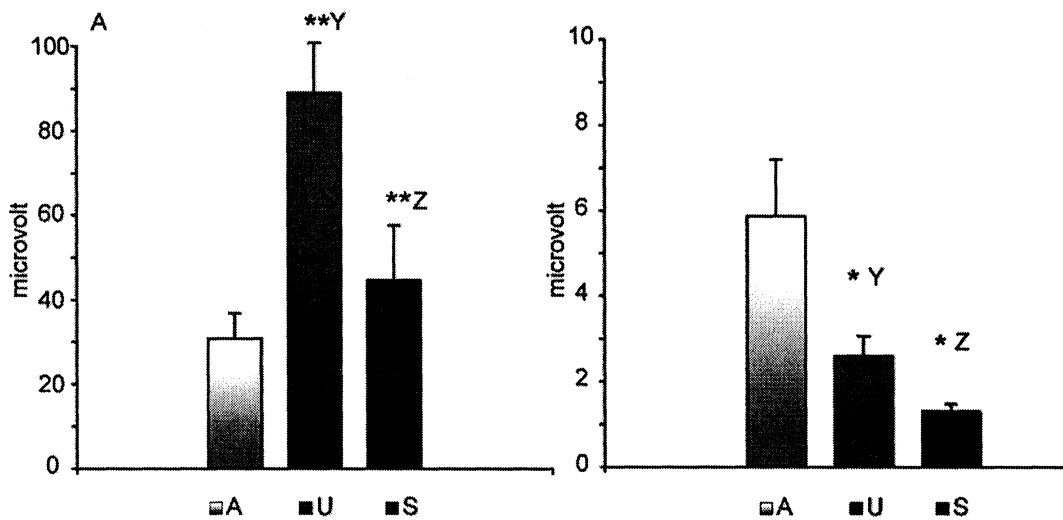

Fig. 4 Amplitude mean of P2 (A) and OP$_2$ (B) peaks evaluated in awake (A) and after treatment with urethane (U) and scopolamine (S) rats. Data are elicited by the higher intensities of luminous stimulation (945.6 cd/m^2*s). Symbols indicate: * = P<0.05; ** = P< 0.01; Y=awake *vs* urethane; Z= urethane *vs* scopolamine; X= awake *vs* scopolamine.

3.2 ERG parameters before and after urethane and scopolamine

In awake animals, b2 showed a latency of 37.8 ± 1 ms at the lower intensity and a latency of 35.5 ± 1.0 ms at the higher intensity of stimulation. After anesthesia we observed a significant (P<0.05) increase of latency at lower intensity of stimulation (41.9 ± 1.6 ms) and no significant variation of amplitude. The same trend was observed for the O_2 wave (Fig. 3) especially after use of scopolamine methyl bromide (41.1 ± 1.3 ms vs 47.8 ± 1.6 ms at lower intensity; P<0.05), these differences, however were not consistent after urethane. The b2 latency variations between electrical responses coming from chronic and acute electrodes were not observed, as expected. On the contrary, the amplitude of the same peak was different, especially at the higher intensity (14.6 ± 6.2 μV vs 47.4 ± 7.4 μV respectively, P<0.01).

Comparing electrical responses coming from chronic and acute retinal electrodes a significant increase of response amplitude recorded from acute electrodes was also observed after using
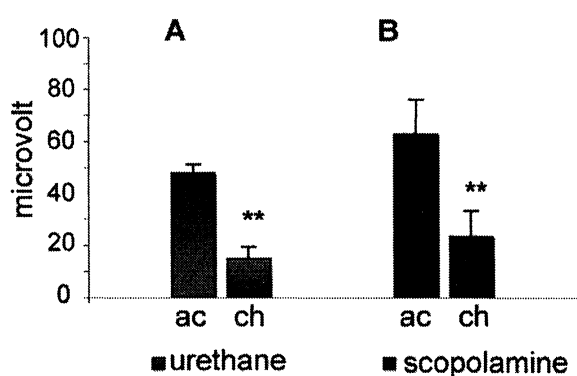
scopolamine, especially at the higher intensity (28 ± 10 μV vs 62.6 ± 16 μV; P<0.01) (Fig 5).

Our experiment was based on the analysis of VEP, ERG, and OP (cortical and retinal) recorded under three different conditions: awake rats, anesthetized rats, and anesthetized rats topically treated with scopolamine methyl bromide. To obtain this experimental model on awake rats, it was first necessary to develop a method for a chronic retinal electrode implant similar to the one previously applied on mice (Lopez, 2002; Loizzo, 2002), on conscious dogs (Sato, 1982), and on monkeys or micropigs (Heynen, 1985; Rosolen, 1999). In particular, ERGs coming from the chronic implant were compared with those recorded from a classic acute one. In fact, the evoked responses from retina are usually recorded in anesthetized animals, but different anesthetics are known to affect the electrophysiological responses of the animal differently (Brown, 1984; Raitta, 1979; Vaegan, 1990). In our experimental conditions, urethane produced qualitative and quantitative alterations in the rat's VEPs. Qualitatively, the dominant effect was the abolition of the N1 peak, already observed by Dyer (1994); quantitatively, we observed a latency increase of the P2, OP_2, b2, and O_2 peaks, a consistent amplitude increase of the P2 peak, and an amplitude decrease of the OP_2 peak. The latency increase, a characteristic of many anesthetics, is due to a depression of conduction in the visual pathways. This effect is not unique to urethane. In general, substances that appear to increase GABAergic inhibition tend to increase the amplitude of the second positive peak evoked in cats by step increments in luminance, whereas substances that tend to decrease GABAergic inhibition tend to decrease the amplitude of this peak (Zemon, 1986).

The use of a digital 50 Hz HP filter was followed by a strong abatement of high frequencies in the spectrum of PEV and therefore of OPs (Fig. 4B). We cannot explain why urethane

Fig. 5:   Difference of b2 peak amplitude between chronic (ch) and acute (ac) implants after treatment with (A) urethane and (B) urethane + scopolamine.
** indicates P<0.01.

treatment is followed by an increase in P2 peak amplitude. One hypothesis is that the drug, which induces a diminution of high frequencies, induces as well a certain shift of frequency power toward lower frequencies.

When we compared the ERG coming from chronic and acute implants, we observed that b2 of the acute implant showed a significant amplitude increase versus the responses coming from the chronic implant. The same trend was observed after local treatment with scopolamine methyl bromide. In the chronic implant, the electrode is positioned behind the ocular globe, and the insulating electric properties of sclera can interfere with the electric transmission of the signal, thus inducing a lower amplitude signal.

After using scopolamine methyl bromide, we also observed a further increase in the latency of the P2, OP_2, b2, and O_2 peaks and a decrease in the amplitude of the P2 and OP_2 peaks. In the literature, few and controversial data about scopolamine action on eye have been reported. Arakawa et al. (1997) found that in the anesthetized cat, scopolamine (0.7 mg/kg i.v.) increases the amplitude of the responses to ketamine and 1% halothane recorded from the primary visual cortex. Sannita et al. (1993, 1988), by contrast, showed that in conscious humans, scopolamine (0.25, 0.50, and 0.75 mg/kg i.m.) reduces the amplitude of the late components of the flash-evoked potential without affecting latency. In addition, Harding (1994) investigated the action of a topical administration of 0.125 % scopolamine applied monocularly and found no change in latency between the control and experimental and after administering scopolamine.

Our results suggest that this drug could alter not only the amplitude but also and especially the latency of electrical responses, so we suggest that antimuscarinic drugs applied as mydriatics during neurophysiologic experiments can induce variation in the retinal response, even if the drug hardly passes the blood brain barrier, as in the case of methyl bromide scopolamine. As our target was to compare retinal responses coming from chronic and acute implants in the same animals during the same experimental session, we did not perform a comparison between anesthetized and awake animals treated with scopolamine.

From the results of this study, we conclude that the use of the retinal chronic implant allows the recording of visual-evoked responses in awake animals, unrestrained, avoiding physiological changes coming from anesthesia, and possible interactions between the anesthetic and other drugs, which becomes essential when studying drugs acting on retinal pathophysiology. In conclusion, anesthesia in general induced a consistent increase of latency in both VEP and ERG, and an increase in the latency of the oscillatory potentials of VEP and ERG. Anesthesia also induced an increase in VEP amplitude, whereas no consistent differences were recorded for ERG. The oscillatory potentials of VEP were consistently reduced, whereas we could not gather enough data for ERG. An increase in the amplitude of potentials, however, accompanied by a reduction in the decrease of OPs amplitude induced by anesthesia, would indicate a shift of spectral content toward lower bands.

Oscillatory potentials latency and amplitude might be of particular importance in the evaluation of retinal damage and/or changes in neural plasticity induced by experimental (e.g. diabetes) conditions. Oscillatory potentials features can be also modulated during different behavioral states. Therefore, the use of chronic implants that allow recording the high-frequency spectral content of electric responses in awake, freely moving animals can be of help in the evaluation of retinal damage and of the protective effect of drugs (Yu, 1998). This kind of implant persists on site 30 to 45 days and can allow studies on neural/retinal conditions, evolution, and possible pharmacological treatment.
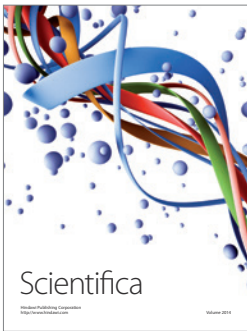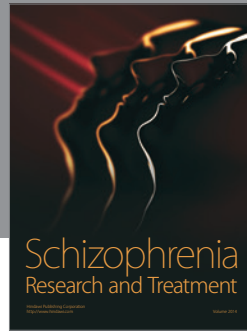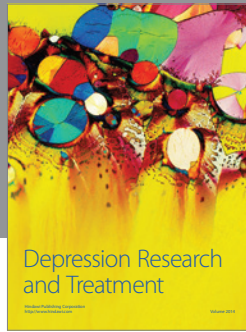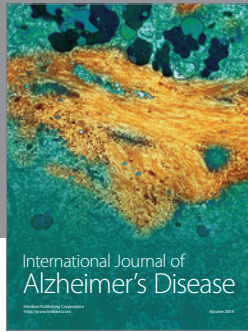
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