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Optoelectronic Telemetry of Electrophysiological Signals

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ABSTRACT

Transmission via diffused radiation is a technique which implements a mobile wireless link exploiting the ambient diffusion of light or infrared radiation; it operates over short range distances and medium range bandwidth and is therefore attractive for a variety of *in-vivo* laboratory experiences involving stimulation and/or monitoring of different physiological parameters on freely-moving animals.

In this paper, the main features of the optoelectronic transmission are presented making a comparison with other approaches, namely electric and fiberoptic cabling and RF links. The diffused channel is characterized in terms of attenuation, bandwidth and S/N ratio showing that it is suitable for transmission of biological signals in a typical laboratory environment.

A two-way transmission system is described that has been specifically designed for telemetry on small animals. The system consists of a pair of LED/photodiode transmitters and receivers. The mobile unit has been implemented in surface mount technology (SMT) to achieve adequate compactness. The link offers an accuracy of 0.5% in amplitude and a signal bandwidth from d.c. to 1KHz and operates for over 15 hours with two standard lithium batteries. This system is being routinary used for *in-vivo* polarographic determinations of brain neurotransmitters and their metabolites (DOPAC and 5-HIAA) on freely-moving rats.

Moreover, it is pointed out that the optoelectronic approach can eliminate the severe crosstalk interference which has so far prevented the concurrent pickup of low-level electrophysiological signals during polarographic determinations.

Experimental data are reported on polarographic measurements on freely-moving rats and on simultaneous recordings of polarographic and different neurological signals, such as EEG (ECG, EMG, EOG) and single neuron firing activity.

2. INTRODUCTION

As it is well-known, biomedical telemetry consists in the transmission of physiological information from humans and animals to a remote apparatus[1]. The goals of telemetry include long-haul applications such as studying of wildlife in its native habitat as well as transmission of medical signals and images for monitoring and diagnosis on patients living in isolated areas. It also includes a broad range of laboratory and clinical studies where freedom from wires allows minimum restraint and disturbance of the normal activity of the subject.

Moreover, a wireless interconnection is often desirable in a noisy environment to reject electromagnetic interference that could be collected by wires. Another special case, that will be considered below in some detail, is the simultaneous recording of multiple physiological signals to investigate their mutual correlation, where wire suppression can reduce crosstalk between the two measuring settings.

Virtually every physiological parameter can be monitored by telemetry, including elettrocardiograms, pH, temperature, pressure, blood flow, muscle contractile forces, metabolite concentration and neurological signals. In the following we will consider specifically telemetry for brain investigation, and first we will briefly recall the characteristics of the signals that are to be managed in polarographic and EEG experiences.

3. TELEMETRY OF NEUROLOGICAL SIGNALS

Brain polarography is a powerfull tool for monitoring *in vivo* the concentration of neurotransmitters and methabolites such as Dopamine, Serotonin, DOPAC, 5-HIAA and their variations down to a sensitivity of 10^{-10} M. In a conventional setup, a slowly-varying ramp is applied to a couple of electrodes and the oxidation component of the current through the preparation gives the concentration of a chemical species that is identified by its oxidation potential. The basic approach has a number of drawbacks, and in the following we will consider an improved version, i.e., three-electrode pulse polarography, which proved suitable for determination of brain neurotransmitters [2,3]. The voltage waveform is a ramp, typically ranging from -200 to + 400 mV, that carries a series of pulses (20-40 ms in duration, 20-60 mV in amplitude). The oxidation takes place at the surface of a specially-treated carbon fiber working electrode. The recorded current include a

background component of about 50-100 nA and a signal component as low as 1nA. This technique features good selectivity and extended electrode lifetime. Coaxial cables are usually employed to connect the laboratory animal to the polarograph.

Electroencephalographic (EEG) signals can be derived by different districts such as cerebral cortex (ECG), eye (EOG), muscles (EMG) [3]. Silver or stainless steel electrodes are used. Also, single neuron activity (firing) can be recorded by lowering a thin tungsten electrode in a brain area [4]. Such signals consists of a series of peaks the amplitude of which is in the range of 10-100 mV with repetition rate 10-100 ms. Special care must be taken to reject electromagnetic interference. The electrodes are connected with coaxial cables and the animal is put in a Faraday cage and grounded.

The characteristics of *in vivo* polarography, namely the high anatomical specificity and accurate time resolution, make it well-suited for studying correlations between the concentration of brain neurotransmitters and recordings of EEG signals or neuronal firing. Unfortunately, in the standard settings (with wires), this attractive technique is severely limited by crosstalk between the two electrode systems[4]. As shown in Fig. 1, in addition to the oxidation current I_1, a parasitic component I_2 is present because the grounds '1' and '2' shall somewhere be connected together. This current flows through the brain to the EEG ground electrode and causes a voltage umbalance at electrodes A and B that is typically an order of magnitude greater than that of the EEG signal; in addition, it can cause a severe tissue damage near the auxiliary polarographic electrode. Floating one of the two grounds would eliminate the d.c. component of I_2 thus avoiding tissue damage; however, the electromagnetic interference from laboratory instrumentation and power lines would be increased to unacceptable levels.

4. THE OPTOELECTRONIC CHANNEL

Different options [1,5] can be considered to interface an implanted transducer to its measuring circuitry, i.e.:

i) Wires and cables: this standard low-cost solution does not require special instrumentation. However, it does not allow freely-moving experiences and suffers from interference. The second drawback can be fixed without signal attenuation by using fiberoptic cables, which requires, however, a transmitter/receiver couple.

ii) Radio frequency : this is the most popular solution for both long and short haul links. It represents a well-established technique that can rely on a number of standard monolithic integrated circuits to implement specific functions; the circuitry can be therefore miniaturized, reliable and suitable for full implatation. One drawback of this approach is the overcrowding of the RF spectrum and its sensitivity to interference from laboratory instrumentation and machinery (spins, motors). Another approach exploits electromagnetic induction, both as a power supply and as a means to transmit information. This solution is viable only on very short distances and is very sensitive to interference.

iii) Diffuse optoelectronic link: this technique relies on the diffusion of light or infrared radiation by the ambient walls and ceiling (Fig.2a). It allows to work on distances up to 10 m with typical bandwidth of a few MHz. Low power, low voltage design is possible and no antenna is needed. A very high degree of immunity to electromagnetic interference can be achieved. Also, different experiments can be separated simply by optical screening or filtering.

A characterization of the diffuse optoelectronic channel has been performed [6] and is summarized in the following:

a) *Attenuation*: in the case of moderate fied of illumination and neglecting the contributions of multiple path diffusion, the channel attenuation P_r/P_t amounts to:

$$P_r/P_t=(\delta/\pi)A_r/(H^2(1+d^2/H^2)) \qquad (1)$$

where δ is the ceiling diffusivity, A_r the detector area, H is ceiling height and d is the distance between transmitter and receiver; a complete overlap of the field of view (f.o.v.) over the field of illumination (f.o.i) is assumed (see Fig.2a).

b) *Bandwidth*: an intrinsic limitation for the diffused channel bandwidth B arises from the multipath propagation, i.e., the multiplicity of lightpaths connecting the transmitter to the receiver, each with a different delay. This delay spreading depends on the angular widths θ_{FOI}, θ_{FOV} (see Fig.2a) as well as on the room height H and the relative distance d. Here we limit ourselves to report an approximate result, valid for $d/H << 1$, i.e.:

$$B=0.22\ (c/H)(\cos\theta_{FOI}/(1-\cos\theta_{FOI})) \qquad (2)$$

where c is the speed of light. From eq. (2), it follows that the channel can be characterized in terms of a distance-bandwidth product BH, once θ_{FOI} has been fixed. As an example, for $\theta_{FOI} = \pi/6$, we get BH = 427 MHz m. Thus, a bandwidth of

up to a few hundred MHz is in principle available in all practical cases.

c) *Signal to noise ratio*: in most applications, where at least a moderate level of background illumination is present, the shot noise due to the stray light photogenerated current I_L, i.e.:

$$I_N = (2q\, I_L B)^{1/2} = (2q\sigma^* A_r E B)^{1/2} \qquad (3)$$

is the main contribution to noise. In eq.(3), σ^* is the luminous sensitivity (A/lm), E the illumination (lux), B the front-end bandwidth, q is the electron charge.

On the other hand, the photogenerated signal current on the photodiode can be expressed as:

$$I_S = \sigma P_r = \sigma A_r (\delta/\pi)\, H^{-2}(1 + d^2/H^2)^{-2}\, P_t \qquad (4)$$

where σ is the radiant sensitivity (A/W).

5. THE OPTOELECTRONIC TRANSCEIVER

Starting from the analysis of the previous section, a miniaturized transmission system [7,8] has been designed for telemetry on small laboratory animals. In Fig. 2b we report the block scheme of each channel of the two-way transceiver. The main unit transmits the slow voltage ramp generated by the polarograph to the mobile unit on the rat. On the receiver, after demodulation, the ramp is applied to the electrodes implanted in the rat brain.The response current is amplified and the signal is sent back, via the return channel, to the polarograph, where the information about the metabolite concentration is extracted. Square wave voltage to frequency conversion has been used as the modulation scheme and electrical multiplexing allows to separate channels, whose subcarries are located at 8KHz (first channel) and 80 KHz (return channel). The optical carrier is at λ= 950 nm for both channels. This choice allows to maximize the LED efficiency (≈10%) and LED/photodiode matching.

An electronic feedback loop has been implemented around the front-end amplifiers, where the well-known cold resistance scheme is employed. A current generator sinks the photogenerated current in a frequency range from d.c. to about 500 Hz, so as the effect of sun and lamps is cancelled, at the expense of a 3 dB deterioration of the S/N ratio. This scheme prevents the front-end from saturation allowing to operate in presence of relatively high levels of ambient illumination.

To achieve a higher level of EMI immunity, dummy wiring has been made in close proximity to each photodiode using high value resistors connected to the non-inverting input of the operational amplifier. Since the dummy wires collect nearly exactly the same electrical interference as the photodiode, the two contribution cancel each other at the output. In typical operating conditions, the S/N ratio can be improved of about 30 dB.

The main tranceiver includes an array of 6 LEDs and 6 photodiodes while single components are used on the satellite, which has been designed for low voltage, low drain supply (it requires two thin Li-batteries for a few hour operation). The circuit has been made compact (40 x 30x 5 mm) by SMT technology implementation and using miniaturized components, and is shown in Fig. 3.

The transmission system allows to implement a link in the range of a few meters with a good S/N ratio. As an illustration of the performances in typical operating conditions, the S/N ratio has been calculated from eqs.(3),(4) for E = 300 lux, L= 5 m, thus obtaining S/N=60 dB for the first channel and S/N= 30dB for the return channel.

The tranceiver offers a maximum bandwidth of about 1KHz, a dynamic range of ± 1 V and a linearity error less than 1%. The baseline drift is less than 20 mV over the whole battery life.

These characteristics allows to use the system in a number of application other than polarography, e.g., for stimulation only or for monitoring of EEG and other electrophysiological signals; the specific application requires to modify only the circuit settings and possibly some minor changes on the interface vs. the laboratory animal.

6. EXPERIMENTAL RESULTS

The optoelectronic system has been accurately tested by comparing the polarograms obtained both *in vitro* and *in vivo* (on rats) with those made by the standard wire connection in the same operating conditions.The shape and reproducibility of the oxidation current peaks of chemical species such as ascorbic acid, DOPAC, dopamine, 5-HIAA, have been found satisfactory. As an example, we show in Fig.4 a determination of DOPAC in nucleus accumbens. The peak shape and height are virtually equal to those of a wire determination. Also, the expected relative increase in concentration after

injection of a drug (Haloperidol 0.5 mg/Kg) is correctly measured. In Fig.5 the concentration of 5-HIAA detected in hippocampus using optoelectronic telemetry is reported. The observed behavioural modifications (see Fig. 5c) induced by the injection of a drug (5 HTP, 10 mg/Kg) are those typical of a free animal, cofirming that the rat does not suffer from carrying the satellite circuitry. For comparison, a determination with wires is also reported.

The optoelectronic telemetric system is currently being used for routinary determinations on freely moving rats in behavioural experiences aimed at studying the dopaminergic and serotoninergic systems by measuring the concentration of brain metabolites, namely, DOPAC and 5-HIAA in different operating conditions. These include the administration of drugs, the exposure to different stressful stimulations, olfactory stimuli (see Fig.6) or social interactions (Fig.7).

Another class of experiments is aimed at investigating the brain neurotransmitter concentration changes in correlation to the sleep/ waking cycle. This requires simultaneous recording of EEG and polarographic signals. As explained in Sect.3, when one attempts to make such experiments by a standard wire connection, the EEG signal is corrupted by huge artifacts during each polarographic sweeping, as shown in Fig.8a. As a consequence, a great amount of information is lost and the sleep/ waking diagram (which is obtained by processing of the EEG signals) is incomplete (see Fig.9). Evidence of tissue damage has also been demonstrated. The implementation of the optoelectronic link between the polarograph and its electrode system has proven a very effective solution as it allows to break the path between grounds '1' and '2' (see Fig.1) so that current I_2 vanishes. Moreover, since the satellite transceiver is put directly onto the rat and no wire passes through the Faraday cage, electromagnetic interference is also greatly reduced[8,9]. Thus, the EEG determination is of the same quality as if separately detected, as shown in Fig.8b. This approach has proved viable also in monitoring of neuronal single unit activity during voltammetric recordings. Fig. 10 shows such concurrent measurement in hippocampus: note once more the absence of artifacts.

Future work will be devoted to simultaneous transmission of both polarographic and EEG signals on freely moving rats to completely exploit the advantages of the optoelectronic telemetry.We also plan to furtherly reduce the dimensions of the satellite circuitry by custom monolithic integration.

7. ACKNOLEDGMENTS

The authors wish to thank Dr. S. Algeri, Dr. M.G. De Simoni of 'Istituto di Ricerche Farmacologiche Mario Negri', Milan, Italy and Dr. L. Imeri, Dr.M. Mancia of 'Istituto di Fisiologia Umana II', University of Milan, Milan, Italy, for the experiments on live animals and the discussion of results.

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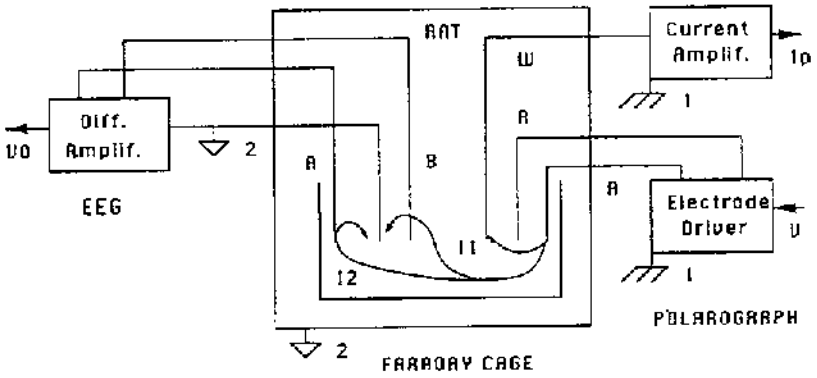

Fig.1 Simultaneous polarographic determination and monitoring of EEG signal.

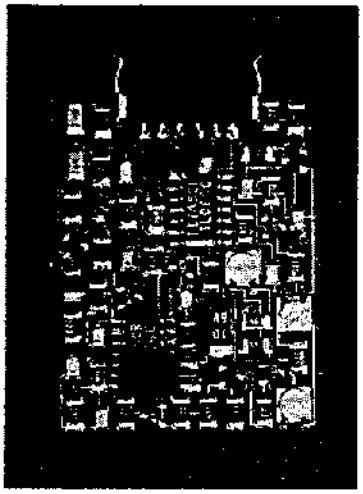

Fig.3 Miniaturized satellite transceiver.

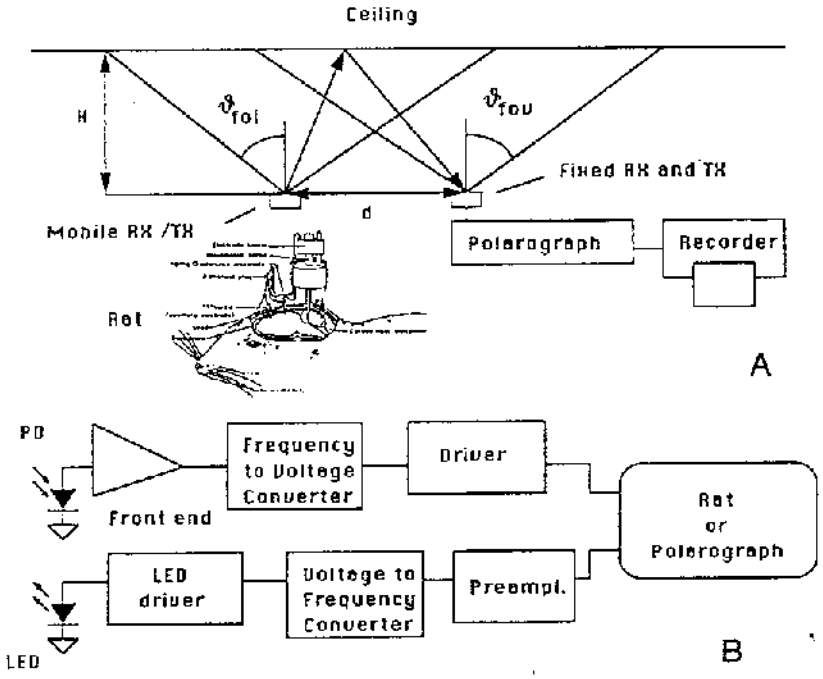

Fig. 2 a) Schematic of the telemetric system: for sake of clarity, only the f.o.i. and f.o.v. of one channel, i.e., the one from the rat to the polarograph are shown; b) Block scheme of one channel.

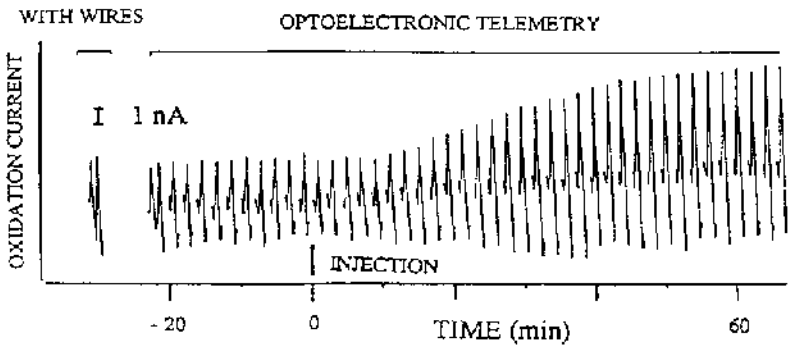

Fig.4 *In vivo* determination of DOPAC in a rat using optoelectronic telemetry; the response to injection of a drug (Haloperidol 0.5 mg/Kg) is also shown.

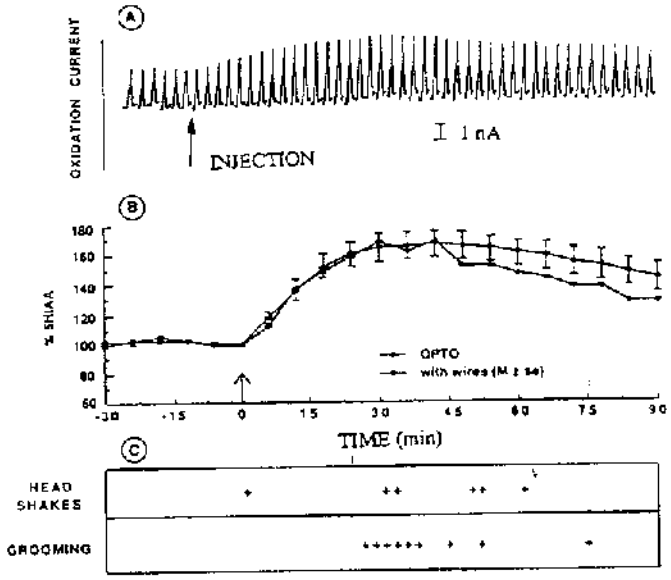

Fig.5 Effect of 5HTP (10 mg/Kg,ip) on 5HIAA concentration in hippocampus of freely moving rats: A) peaks recorded by the optoelectronic system; B) comparison between concentration as detected by the optoelectronic system and by wires, and C) behavioural observations relative to A).

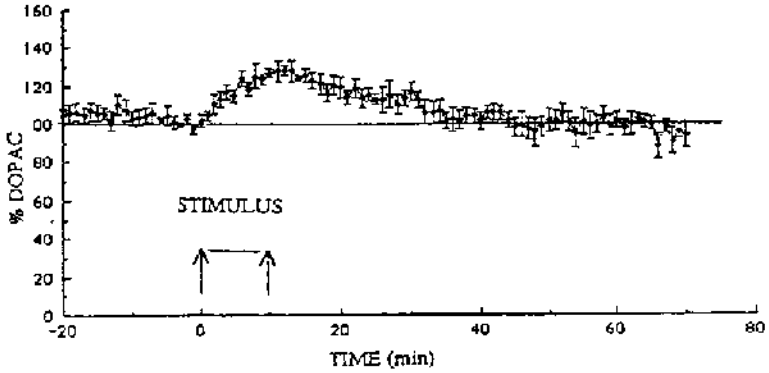

Fig.6 DOPAC concentration changes following an olfactive stimulus (wafer) in freely moving rats.

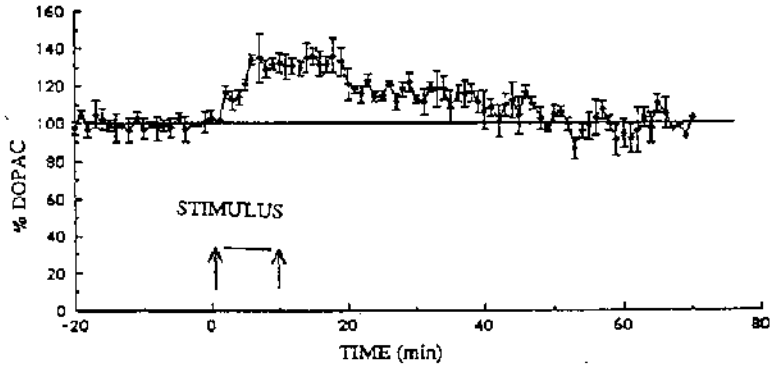

Fig.7 DOPAC concentration changes in a case of social interaction (female rat in the cage) in freely moving rats.

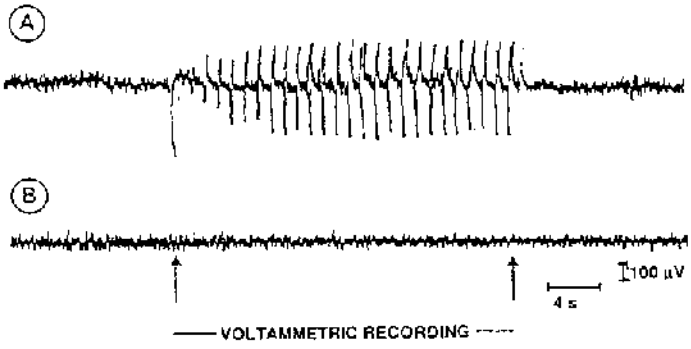

Fig.8 Simultaneous EEG and polarographic recordings: A) with wires and B) using the optoelectronic system; note in this case the absence of artifacts.

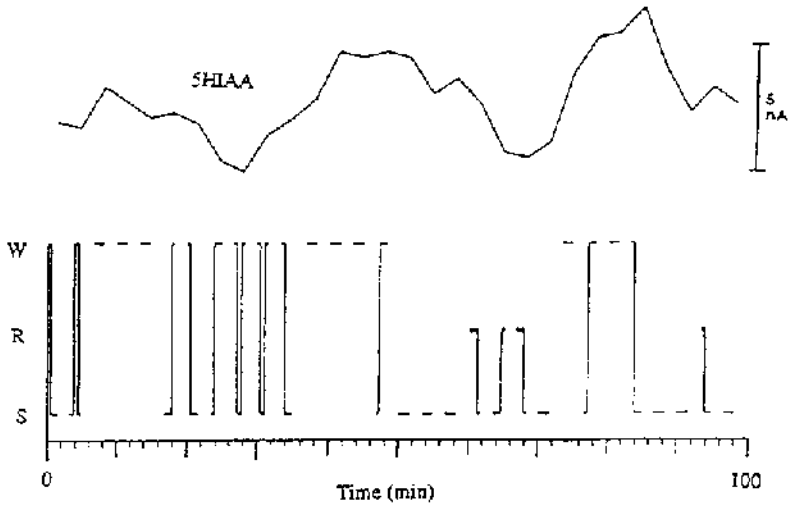

Fig.9 Correlation between 5-HIAA concentration (upper trace) and sleep states (lower trace: W= wake, R= rem sleep, S= slow wave sleep), obtained by standard wire connection. The hypnogram is interrupted during polarographic recordings.

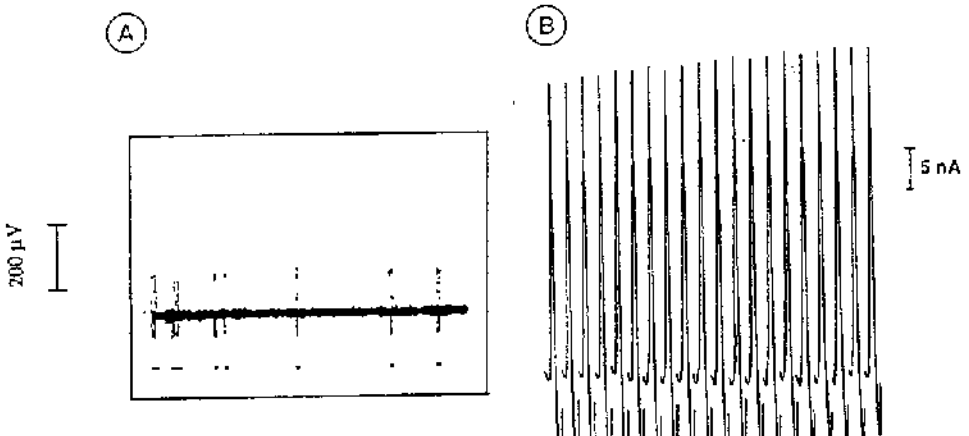

Fig.10 Simultaneous recording of hippocampal single neuron firing activity (A) and polarographic determination of 5HIAA in controlateral hippocampus (B) in a rat by optoelectronic telemetry.