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Correlation Between Behavioural and Electrophysiological Effects of Pyrithoxine in Unrestrained Cats and Rabbits *

G. Sierra, C. Acuña** and J. Otero

Department of Physiology and Biochemistry. Medical School.
Santiago de Compostela (Spain)

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The mechanisms of action of the Pyrithoxine (Bis-3-hydroxymethyl-2 methylpyridyl-(5)-methyl-disulphide-dihdrochloride monohydrate) were study in chronic cats and rabbits. The experimental variables were: modifications of visual input as measured by evoked potentials techniques; electrical stimulation of the brain; aggressive behaviour; sexual behaviour; and the modifications of food intake.

It is concluded that Pyrithoxine induce an impairment of sexual behaviour in male rabbits, an increase in the threshold to electrical stimulation of amygdala and caudate nucleus and variations in the amplitude in the late response of the visual evoked potentials.

HOTOVY *et al.* (4) reported that pyrithoxine (bis-3-hydroxy-methyl-2-methylpyridyl-(5)-methyl-disulphide-dihdrochloride monohydrate) induce a sedative effect, improvement in rats' endurance in running tests, improvement in the psychomotor functional response in voluntary test subjects and an increase in the blood flow through the carotid arteries in dogs. SIERRA and REINOSO-SUÁREZ (10) have showed modifications in the EEG of the cat with chronically implanted electrodes. The most consistent modifications were elicited in the amygdaloid nucleous.

The aim of the work described here and carried out in chronic cats and rabbits is to undertake a further study of the effects of pyrithoxine with several neurophysiological and behavioural techniques. Modifications on visual input, electrical stimulation of the brain, aggressive and sexual behaviour and food intake were the

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parameters used to examine the mechanisms of action of the drug.

Materials and Methods

VISUAL EVOKED POTENTIALS. — Visual evoked potentials, were recorded in chronic cats and rabbits with atropinized eyes by means or two silver ball electrodes aproximatelly 2.5 mm apart, held in a nylon plug. The electrodes were placed in contact with the dura over the occipital area. The electrode wires were soldered to a Winchester plug which was in turn fastened to the craniun with acrylic plastic. For an experiment the animals were put inside a sound-proof room, placed in a hammock and the head held by a non-painful procedure to prevent both lateral and vertical movements. The strobe lamp of a GRASS Model PS2 photo stimulator were facing the animals at a distance of 1 m. The lead from the animal was led to a Tektronix 122 preamplifier with a frequency range of 8 to 250 c/seg. The ELATRON 1,600 computer was used for averaging the responses. A summation of 400 stimuli were computed, recorded in the oscilloscope's computer and photographed by a GRASS camera.

The means of the evoked potentials of control experiments were cimpared with those obtained after the intravenous (rabbit) or intraperitoneal (cats) injections of 10, 20, and 40 mg/kg of pyrithoxine or normal saline of identical volume and pH equal to that of the pyrithoxine.

ELECTRICAL STIMULATION OF THE BRAIN. The animal used in this series of experiments was the cat. Bipolar nichrome electrodes were placed stereotaxically in the septal areas, hippocampus, amygdala and caudate nucleus. Stimulation consisted of trains of 1 msec square wave pulses at 100 pulses/sec. They were generated by a type 161 Tektronix pulse generator connected into an Argonaut isolation transformer, model LIT 069.

The intensity of the current was measured using a GRASS model CCU-1 constant current unit. Behavioural and motor responses elicited by electrical stimulation before and after the drug injection, were filmed by a Leicine S-8 camera.

Histological verifications of the position of all implanted electrodes was made.

AGGRESSIVE BEHAVIOUR. — A pilot study of aggressiveness in cats had shown the difficulties in inducing aggressive behaviour in satiated animals towards anesthetized rats. For this reason we used unanesthetized rats and mice in order to test cat's aggressiveness before and after intraperitoneal injection of the drug at doses of 10, 20, and 40 mg/kg.

SEXUAL BEHAVIOUR. — A quantitative analysis was made in the basis of gross observations of overt-sexual responses. The study was limited to the recording of copulatory behaviour in sex deprived male rabbits.

The male was kept in isolation during 1 week. After this period the male received an intravenous inyection of saline or the drug carroding to a latin square design. The male was then given access to a box inside of which was placed a female on heat. The number of mountings performed during one half hour were counted and the experiments was repeated weekely.

The mean of the mounting performed under each conditions (saline o drug) was calculated and the differences between means was studied.

FOOD INTAKE. — The drug was administered during one week to several animals at doses of 10, 20, and 40 mg/kg and the effect on food and water intake was compared with a control period.

Results

VISUAL EVOKED POTENTIALS. — Neither the configuration nor the amplitude of the primary response in the visual areas of the rabbits were modified by the drug. In the late responses a significant increase in the amplitude of the events ocurring between 130-250 msec after flash were observed (Fig. 1).

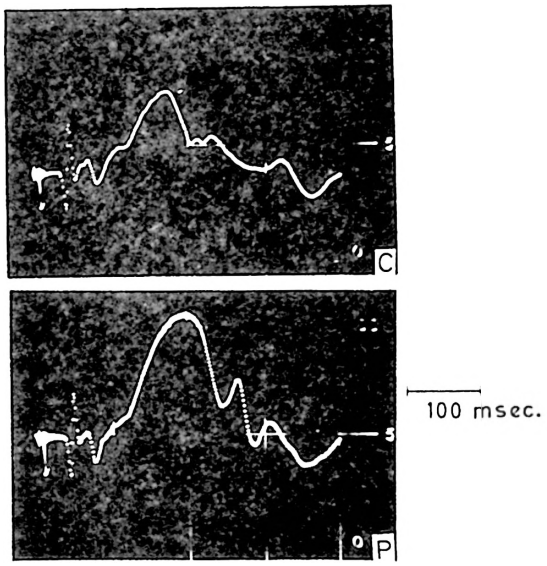

Fig. 1. *Rabbit: visual evoked potentials.* C = Control; P = After Pyrithoxine (40 mg/kg, i. v.).

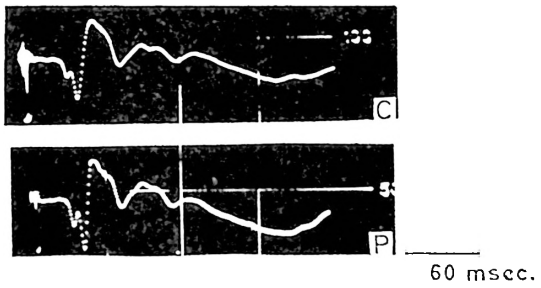

Fig. 2. *Cat: visual evoked potentials.* C = Control; P = After Pyrithoxine (40 mg/kg, i. p.).

In cats no modifications of the primary responses were found but the amplitude of the late responses specially those ranged between 70-120 msec were increased (Fig. 2).

ELECTRICAL STIMULATION OF THE BRAIN. Pyrithoxine at doses of 40 mg/kg increased the threshold in the amygdala. specially in the cortico-medial complex and in the caudate nucleus (Fig. 3). No modifications have been found in the threshold of septum and hippocampus. At doses of 10, and 20 mg/kg the modifications of the threshold for the amygdala and caudate nucleus, however, was less noticeable.

Inhibition of motor responses induced by electrical stimulation of amygdala's cortico medial complex during simultaneous stimulation of septum were partially reduced by the drug.

AGGRESSIVE BEHAVIOUR. — In some animals pyrithyroxine at dosis of 40 mg/kg abolished aggressive behaviour towards rats, but the effect was inconstant and the results showed significant variations from day to day.

SEXUAL BEHAVIOUR. — A significant decrease in the percentage of mountings per-

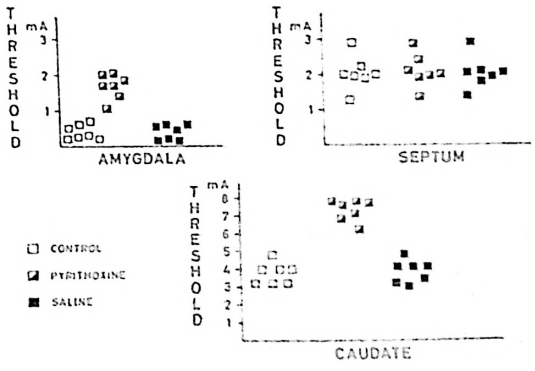

Figure 3

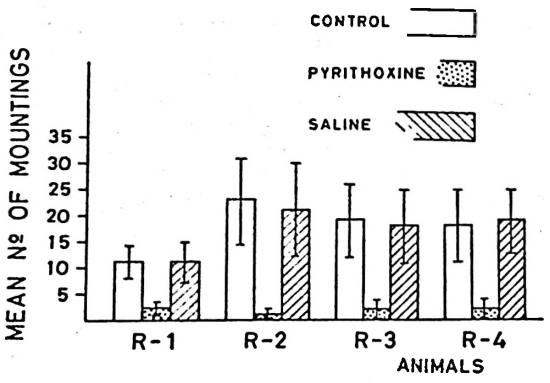

Figure 4

formed under pyrithioxine were found (Fig. 4).

FOOD INTAKE. — No modifications were induce on food consuption in cats by the drug.

Discussion

The present studies demonstrate that pyrithioxine produced an impairment of the sexual behaviour in male rabbits and an increase in the threshold to electrical stimulation of the amygdala and caudate nucleus in cats. These modifications are concurrent with variations in the late response of the visual evoked potentials.

The effect on amygdala agree with those previously observed recording the EEG of several cortical and subcortical structures (10). Pyrithioxine increase not only the amygdala's threshold but reduces the influence of related structures. Electrical stimulation of cortico medial complex of amygdala were inhibited by simultaneous stimulation in the septum (8). This inhibition were diminished by the drug.

The impairment of the sexual behaviour of the male rabbit is difficult to explain because a variety of factors and neural mechanisms may be involved in sex drive. It is different from other primary drives such as hunger or thrist because it is not essential to the survival of the individual or even important to the homeostatic balance of the organism. Sexual motivation is clearly the result of the close interaction between environmental and organismic variables

The modifications in amygdala may account partially for the effects on sexual behaviour. Isolated components of the male matting patterns, such as penile erection and ejaculation have been elicited by electrical stimulation of various rhinencephalic structures (6). On the other hand the olfactory system plays an important role in the sexual behaviour of the male rabbit (5, 11). In spite of this threshold variations, amygdala alone can not explain the modifications of sexual behaviour (9).

Several studies suggest the existence of a zone for neural regulation of sexual drive in the anterior hypothalamus. Lesions in the area of the preoptic and paraventricular nuclei completely abolish sexual motivation without affecting the hormonal balance of the organism an this effect is not reversed by hormone treatment (1, 7). Modifications in hypothalamus, as measured by EEG recordings, were observed under pyrithoxine (10). It was presumed that these changes may also account for our results.

The threshold variation in amygdala may explain at certain extent the sedative effect and the improvement in the psychomotor functional response reported by HOTOVY *et al.* (4).

Visual information as measured by the amplitude of primary visual evoked potentials, did not showed any impairment. Variations in the late response are difficult to evaluate because there is no conclusive evidence for the meaning of the visual late responses. In unrestrained preparations FUSTER and DOCTER (3) have described a secondary response ranged between 100-300 msec after the flash. On the other hand, EVARTS (2) reported a

long latency (80-100 msec) response in the patterns of discharge of single units in the visual areas of the waking cats. The more conspicuous effects observed in the late responses of visual areas of rabbits and cats under pyrithioxine showed a time-course comparable to those described by FUSTER and DOCTER (3) and by EVARTS (2). Under these grounds and as a speculative hypothesis the variations observed in the late responses may be related to changes in the level of the arousal system.

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