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INHIBITORY INFLUENCE OF OXYTOCIN INFUSION ON CONTINGENT NEGATIVE VARIATION AND SOME MEMORY TASKS IN NORMAL MEN

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SUMMARY

A double-blind study combining electrophysiological and psychometrical approaches was carried out to investigate the central effects of an intravenous oxytocin (OT) infusion in normal men. Contingent negative variation (CNV) was selected as the measure of central cognitive evoked potential, and the psychometric tests measured mood, vigilance and memory. OT infusion induced a significant decrease of CNV amplitude and an increase of post-imperative positive potentials in vertex derivations. A similar effect was still evidenced one week after treatment in frontal derivations, suggesting a long time effect of OT on human brain. No significant influence of OT on mood or vigilance tests was apparent; only one item of a memory test revealed a significant impairment of some mnesic performances. These observations provide new electrophysiological arguments supporting a central action of peripheral OT administration in man.

INTRODUCTION

THE NEUROHYPOPHYSEAL PEPTIDES, vasopressin (VP) and oxytocin (OT), seem to modulate in opposite directions memory and learning processes in animals and man (for general review, see de Wied & Versteeg, 1979). Previous studies in rats led to the conclusions that VP facilitates passive avoidance behavior (Ader & de Wied, 1972; Bohus *et al.*, 1972) and increases resistance to extinction of active avoidance behavior and approach responses (de Wied, 1971; Bohus *et al.*, 1972; Hostetter *et al.*, 1977). Opposite effects of OT have been found on the maintenance of avoidance behavior (Schulz *et al.*, 1974; Bohus *et al.*, 1978a; 1978b; Kovacs *et al.*, 1978). Intracerebroventricular (i.c.v.) administration of anti-OT serum was reported to facilitate passive avoidance behavior (Bohus *et al.*, 1978a), whereas i.c.v. administration of anti-VP serum resulted in a marked deficit of passive avoidance behavior (van Wimersma Greidanus *et al.*, 1975; van Wimersma Greidanus & de Wied, 1976).

Studies in humans are more controversial. An improvement of several memory tasks by VP

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analogs was reported especially in amnesic, elderly and psychiatric patients (Legros *et al.*, 1978; Oliveros *et al.*, 1978; Gold *et al.*, 1979; Vranckx *et al.*, 1979; Weingartner *et al.*, 1981a), but some reports have been negative (Blake *et al.*, 1978; Jenkins *et al.*, 1982). A significant improvement of learning abilities following desglycinamide-AVP (DGAVP) (a VP agonist with only central effects) administration to patients with dementia has been reported (Peabody *et al.*, 1985). In unimpaired subjects, a beneficial effect of VP-like peptides also has been found (Weingartner *et al.*, 1981b; Beckwith *et al.*, 1982; 1983; Laczi *et al.*, 1982; 1983; Nebes *et al.*, 1984). In contrast, an impairment of human memory by OT has been suggested by the results of different psychometric tests (Ferrier *et al.*, 1980; Kennett *et al.*, 1982; Fehm-Wolfsdorf *et al.*, 1984).

While psychometric studies have suggested a role for OT in the control of memory in man, electrophysiological correlates have not yet been reported. Therefore, we decided to investigate the effects of OT on human memory through the use of an electrophysiological approach in parallel with psychometric evaluation. Administration of lysine-VP (LVP) has been shown to induce significant modifications of contingent negative variation (CNV) in humans (Timsit-Berthier *et al.*, 1982). This slow potential is recorded during a simple experimental situation where stimuli and responses are serially organized and can be regarded as the reflection of a complex and associative function set at a high level of mental activity (Walter *et al.*, 1964). Previous results indicate that CNV has relatively constant and reliable characteristics when a rigorous protocol is clearly defined (Timsit-Berthier *et al.*, 1984). The fact that CNV amplitude decreases with habituation under repetitive recording conditions (Timsit-Berthier *et al.*, 1981) has been taken into account in our protocol. In addition, because previous work has shown long-term effects of VP in animals and in humans (de Wied, 1971; Timsit-Berthier, 1984), we decided to investigate this possible characteristic of OT as well.

METHODS

Subjects

Twenty-eight healthy male volunteers (age range from 23 to 30 yr) participated in the experiment. They were instructed to have normal food and drink, a normal night's sleep, and to abstain from alcohol and any medication the day prior to the experiment. They were also requested not to smoke or to take stimulating beverages on the day of OT administration. Previous control tests consisting of a standard CNV and psychiatric examination (Present State Examination) were carried out in order to eliminate subjects out of CNV or psychological normal range. Eight of the subjects had to be rejected because of slight psychological disorders or CNVs outside the normal range.

On the basis of the individual CNV profiles, two homogeneous groups of 10 subjects each were constituted following paired CNV parameters.

Experimental protocol

The study was conducted in a double-blind fashion on two groups of 10 subjects, one group receiving OT infusion (group I) and one control group receiving a placebo (group II). To avoid an erroneous interpretation of the data due to individual variability as well as to the habituation process of CNV and learning effects in psychometric tasks, each subject was compared to himself in a three-session experimental scheme. In session A, both groups received an intravenous infusion of 0.9% saline for 45 min starting at 0930 h. Psychometric evaluation began after 10 min (PRM and 30 Figures). At the end of the infusion, a full CNV recording was carried out (CNV-A).

Session B began just after this first CNV recording; group I was infused with OT (84 mIU/min), and group II received a placebo (0.9% saline), for 45 min. Psychological testing started 10 min later, and a second full CNV recording took place at the end of the infusion (CNV-B). Infusions were delivered by a peristaltic pump. OT (Syntocinon, Sandoz, 10 IU/ml) was diluted in 150 ml 0.9% saline, leading to a final solution of 60 mIU OT/ml. Each subject received a total dose of 3,780 mIU OT. Arterial pressure and cardiac frequency were measured at the beginning and at the end of each infusion period.

Session C was performed one week later at 1100 h, and included only one CNV recording (CNV-C).

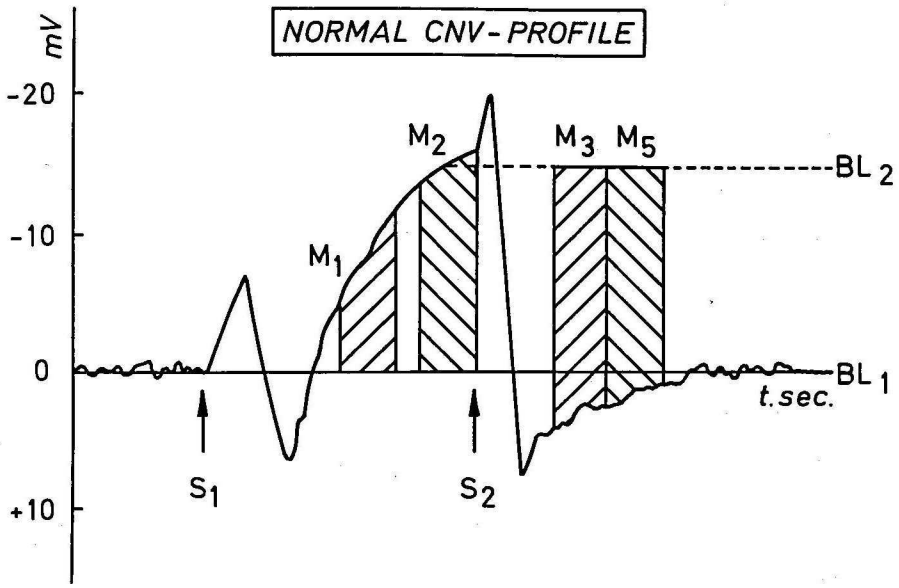

FIG. 1: Normal Contingent Negative Variation (CNV) profile and selected voltage and area parameters. (see explanations in Methods section)

CNV recording procedure

After placement of electrodes, the subjects were lying down on a bed in a dark, sound-proofed and faradised room, and had to keep their eyes closed during the recording. They were submitted to a series of 80 to 100 uninterrupted couples of stimulations. Each stimulative couple consisted of a brief tone (S_1: 1000 Hz, 50 ms) followed by an imperative stimulus S_2, a series of flashes (18 flashes/sec) with a time interval S_1-S_2 of 1 sec. The subject had to interrupt the series of flashes by pressing on a button. The time interval between stimulation trials varied randomly between 7 and 27 sec. Each recording session lasted about 40 min.

Derivations were obtained from frontal (F_z) and vertex (C_z) electrodes, with an electrode on left ear lobule (A_1) as reference. The electroencephalogram (EEG) was recorded by a Grass electroencephalograph with active filtering and a cut-off frequency of 33 Hz (attenuation: 30 dB/octave), and was amplified with a time constant of 5 sec.

Artifactual data were eliminated on line after visual control of each trial. About 70 stimulus couples were delivered to obtain 48 artifact-free trials. Reaction time and heart rate were simultaneously recorded.

Analysis of CNV parameters

CNV amplitudes were measured over the average of six sequences (48 trials in total). Two series of parameters were retained; the negative deflection between S_1 and S_2 (Pre-imperative potentials), and the voltage level occurring after S_2 (post-imperative potentials). Two different baselines were used as references: The first baseline (Bl_1) was the average of the points over 1 sec before S_1, and the second baseline (Bl_2) was the average of the points between 800 and 1000 msec after S_1. The following six values were selected according to international CNV norms and practice (Fig. 1):

M_1: voltage difference between Bl_1 and the average of the points from 500 to 700 msec post-S_1.
M_2: voltage difference between Bl_1 and the average of the points from 800 to 1000 msec post-S_1.
M_3: voltage difference between Bl_2, and the average of the points from 300 to 500 msec post-S_2.
M_5: voltage difference between Bl_2, and the average of the points from 500 to 700 msec post-S_2.
M_1M_2 area:average surface difference from 500 to 1000 msec post-S_1.
M_3M_5 area:average surface difference from 300 to 700 msec post-S_2.

A normal habituation is observed under long-lasting or repetitive recordings; this is marked on the CNV profile by a voltage decrease of M_1, M_2, and M_1M_2 area, whereas M_3, M_5 and M_3M_5 area show voltage increases over successive sequences.

Psychometric Evaluation

Four psychometric tests were selected which serially explored memory, mood, and vigilance states:

— Profil de Rendement Mnésique (PRM) (Rey, 1966)

This test is composed of seven sub-tests or items. The material includes twenty small drawings representing objects, animals, or plants easy to identify. For item 1, the subject has just to name the different objects. He is not informed that he will have to memorize them. For item 2, the drawings are simplified, and the subject has to find out the former object to which they correspond. For item 3, the drawings are very schematic, consisting of one or two lines suggestive of the initial object. The subject is first presented with the three series (complete, simplified, then schematic), so that he can appreciate the progressive transformation. Then the first two series are hidden, and the subject has to recall the initial objects on the basis of the schematic forms. For item 4, the schematic drawings are presented in a mixed order. Item 5 is a repetition of item 2. Then, the subject is asked to recall immediately (item 6) and 20 min (item 7) after the last presentation.

— 30 Figures of Rey (Rey, 1966)

Thirty complex geometric figures, each completed by two details, are presented to the subject during two min. The task is to complete a second sheet showing only the elementary designs in the same order, remembering most of the details shown previously. Scores are given only to correct and well-localised reproductions. PRM and 30 Figures exist in at least two distinct versions; during the second infusion period, the subjects were given a different form for each of both tests in order to avoid learning effects as far as possible.

— Mood Scale

During this trial, the subject must complete a battery of 10 visual analogue scales (Ansseau *et al.*, 1984). The pairs of items are derived from the Hamilton Anxiety Scale to assess both physical and somatic symptoms of anxiety.

— Vigilance Test

Two columns of graphical signs comprise this test, one of which is the erroneous copy of the other. Each has about 20 lines of 17 letters and signs. The subject is asked to correct the wrong column as quickly as possible. Time, correct signs, omissions, and errors are recorded and yield a final score according to established tables. The test evaluates the individual's capacity for attention, rapidity, and precision.

Statistics

Preliminary ANOVAs considering groups, time sequences and electrode locations were performed for the different electrophysiological parameters. Then, for each group, CNV parameters and psychometric scores were compared before and after OT or placebo infusion (A-B), as well as before and one week after treatment (A-C), by a paired t test (CNV parameters) and one-way ANOVA (psychometric scores).

RESULTS

CNV parameters

By ANOVA, the most significant group differences were for M_1M_2 area ($F1,104 = 3.98$; $p < 0.05$), and for M_3M_5 area ($F1,104 = 5.72$; $p < 0.02$). For all CNV parameters, a highly significant effect of electrode location was found (the least significant F value was 13.55). There was no significant effect of space time sequences.

As shown in Fig. 2, mean M_1 was significantly reduced compared to saline in the OT-treated group (group I) at the C_Z and F_Z derivations, and M_1M_2 area was significantly reduced at the C_Z derivation. Mean M_3M_5 area was increased in the OT-treated group at the C_Z derivation. No significant differences in these parameters occurred in the placebo-treated group (group II).

A long-term effect of OT was supported by CNV results recorded one week after OT infusion (Fig. 3). A significant decrease of M_1M_2 area and a significant increase of M_3M_5 area persisted. However, these differences were mainly evident at the anterior derivation F_Z; at the C_Z derivation, only the M_3M_5 area was still significantly increased.

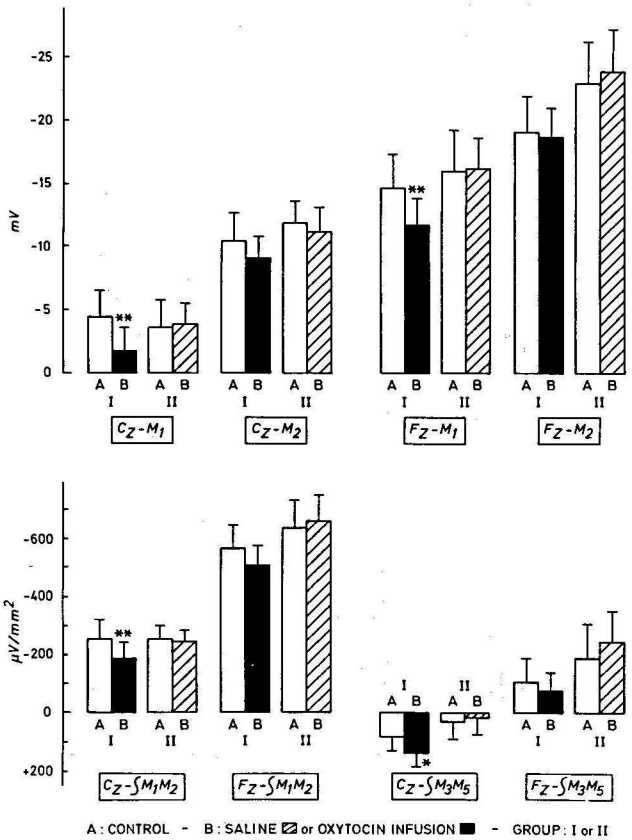

FIG. 2: Comparison between CNV parameters recorded in human male volunteers before (A) and after (B) oxytocin (group I) or placebo (group II) infusion. Significant differences indicated by * ($p<0.05$) or ** ($p<0.025$). F_Z:frontal derivation; C_Z:vertex derivation.

TABLE I. COMPARISON OF MEAN CHANGES IN PRM SCORES FROM BASELINE BETWEEN OT (I) AND PLACEBO (II) GROUPS.

ITEM	GROUP I	GROUP II	F (1,18)	P
PRM 2	+0.4	+1.2	1.15	0.30
PRM 3	+0.5	+0.8	0.18	0.67
PRM 4	+0.1	+1.7	4.70	0.04*
PRM 5	-0.2	+0.3	1.64	0.22
PRM 6	-0.5	-1.4	0.80	0.38
PRM 7	-2.9	-3.0	0.03	0.95

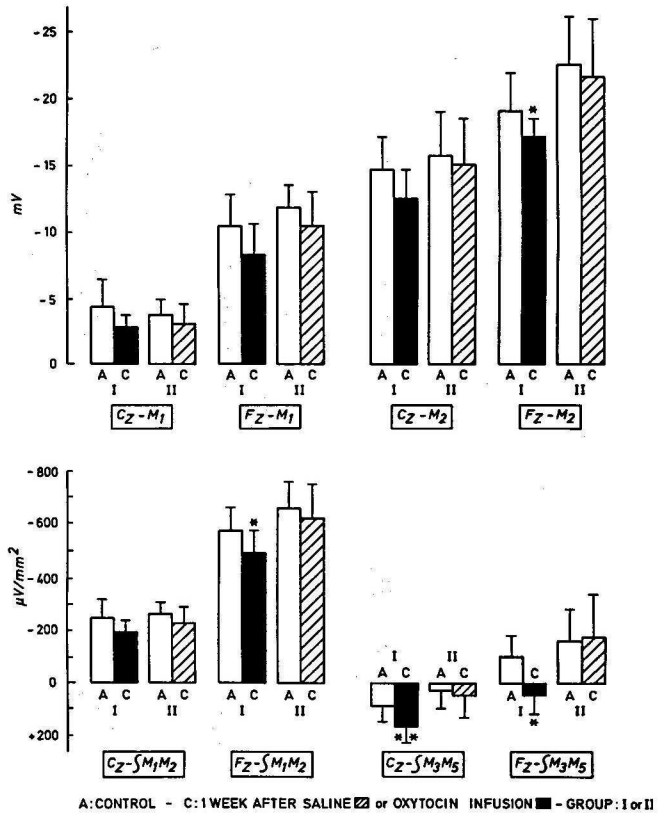

FIG. 3: Comparison between CNV parameters recorded before (A) and one week after (C) oxytocin (group I) or placebo (group II) infusion. Significant differences indicated by * ($p<0.05$) or ** ($p<0.025$).

Psychometric parameters

The general evolution of both PRM versions (Table I) was similar in the two groups. As expected, nearly all subjects showed an improvement of their performances, probably through acquisition of a strategy. However, the mean score of item 4 was significantly less improved in the OT-treated group than in the control group subjects. No significant influence of OT was apparent on the other psychometric tests.

Clinical parameters

No side effects were reported after either placebo or OT infusion. No significant variation of the cardiovascular parameters or of reaction-time in relation to the CNV paradigms was observed.

DISCUSSION

The present study combined neurophysiological and psychometric technologies to

investigate the central effects of exogenous OT administration to normal men. Our results demonstrate that OT induced a significant decrease of CNV amplitude and an increase of post-imperative positive potentials in vertex derivations on the day of its administration; similar changes, but only in frontal derivations, were observed one week after OT treatment. The CNV amplitude, mainly represented by M_1 and M_2 components, seems to reflect preparative processes before the response (McCallum, 1979). It may be considered as an indirect measure of motivation and attention of a subject faced with a nonspecific task, while post-imperative M_3 and M_5 components are supposed to be related to the subjective evaluation of the response. In consequence, our results could be interpreted as a dual action of OT upon these central processes.

Studies have been conducted to elucidate the neurophysiological and neurochemical factors underlying CNV genesis. The frontal granular cortex orchestrates the occurrence of the event-related potentials like CNV (Skinner & Yingling, 1977), and the surface positive component (P300) is the direct reflection (volume-conducted) of limbic activity, particularly the hippocampus (Squires *et al.*, 1983). The slow potentials seem to reflect activatory phenomena, while positive potentials are the expression of inhibitory processes (Rebert, 1980; Skinner & King, 1980). CNV amplitude seems to be directly related to attention processes (Timsit-Berthier, 1984). The amplitude of the negative phenomena might be mediated by the cholinergic system and modulated by the catecholaminergic, with a probable influence of GABAergic pathways (reviewed in Marczynski, 1978).

According to these theories, the CNV profile modification observed during OT infusion could be the result of a direct action of OT at the level of its hippocampal receptors (Muhlethaler *et al.*, 1983), OT also could act by inhibition of the catecholaminergic system since CNV amplitude seems to be closely to the degree of activation of this system. However, previous observations failed to draw clear conclusion about OT modulation of catecholaminergic pathways. Studies in rats (Gabor *et al.*, 1979; Telegdy & Kovacs, 1979; Kovacs & Telegdy, 1983; Van Heuven-Nolsen *et al.*, 1984) provide evidence for a specific interaction between OT and populations of noradrenergic neurons but also suggest that the sense of this influence changes with the investigated central area. Finally, the role of cholinergic and GABAergic systems in the genesis of CNV gives rise to a possible relationship between these pathways and the central action of OT. Such an hypothesis, however, currently has no data available to support it.

The changes in CNV profile observed in frontal derivations one week after OT infusion support a long-term central action of OT. Whether these changes are related to complex mechanisms of memory storing is a daring but tempting hypothesis which relates to theories involving the frontal lobe in memory processes (reviewed in Stuss & Benson, 1986).

Our study also provides additional arguments in favor of opposite central actions of OT and VP in humans. In previous work on CNV neuromodulation, we have shown that VP prevents the spontaneous decrease of CNV amplitude that occurs with repetitive sessions and delays the occurrence of inhibitory processes (Timsit-Berthier *et al.*, 1981).

It was not our aim to determine on which of the several complex circuits of memory (input, storing, or retrieval) OT exerts its main action. During the experiment, a significant decrease in the PRM fourth item was detected in the OT-treated group. Even if this isolated observation does not support a major role for OT in human memory, it is in accord with previous studies showing an impairment of other mnesic tests by exogenous OT (Ferrier *et al.*, 1980; Kennett *e t al.*, 1982; Fehm-Wolfsdorf *et al.*, 1984). These amnestic-like properties have been applied in the treatment by intranasal OT of a patient with severe obsessive-compulsive disorder (Ansseau *et al.*, 1987).

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