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# Dishabituating Effects of an ACTH 4–9 Analog in a Vigilance Task

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BORN, J., G. FEHM-WOLFSDORF, M. SCHIEBE, B. ROCKSTROH, H.-L. FEHM AND K. H. VOIGT. *Dishabituating effects of an ACTH 4–9 analog in a vigilance task.* PHARMACOL BIOCHEM BEHAV **21**(4) 513–519, 1984.—Ten male adults were tested in a vigilance task after oral administration of either 40 mg ACTH 4–9 analog, ORG 2766, or placebo in a single three hour session. EEG spectra, averaged auditory evoked responses, heart rate and blood pressure, and behavioral performance were measured during a vigilance task. ACTH 4–9 analog treatment led to a decreased inhibition of the central nervous system across the experiment: to less mean power density and faster center frequencies within the alpha band, and to less attenuated amplitudes of the components of the auditory vertex potential (P50, N100, P200). Treatment effects increased towards the end of the session and might indicate a dishabituating effect, probably due to suppression of inhibitory influences of limbic structures on mesencephalic reticular activity.

Neuropeptides ACTH ORG 2766 Event-related potentials EEG Heart rate Blood pressure Vigilance Dishabituation

THERE has been accumulating evidence that neuropeptides influence behavior in humans after peripheral administration. These effects are thought to be mediated by a modulatory influence of neuropeptides on neural transmission. One of the most extensively studied neuropeptides in humans is a small fragment of corticotropin: ACTH 4–10 and its highly potent analog, ORG 2766 (for a review see [22]). In rats radioactive labeled ORG 2766 accumulated in limbic structures, especially in septal and hippocampal regions [29]. There is, however, still no direct evidence that ORG 2766 (as intact peptide) does reach limbic and hypothalamic brain regions.

In humans ORG 2766 treatment was found to alter EEG power spectra [7, 9, 24, 25, 28] and in addition to modulate the amplitudes and/or latencies of N100 and P300 components of the auditory evoked potential (AEP), and of the contingent negative variation (CNV) [8, 23, 24, 25]. On the level of overt behavior, changes after treatment with the ACTH 4–9 analog were interpreted in terms of enhanced vigilance and motivation [10, 11, 12] or improved focussed attention [8, 25, 27]. However, results from studies taking into account physiological parameters do not unequivocally support one of these interpretations. Increased heart rate and/or systolic blood pressure during task performance found in some studies [4, 8, 12] but not in others (e.g., [24]), may speak for an arousing effect of the ACTH 4–9 analog, as well. Similarly contradicting results concerning spontaneous EEG activity were reported: on one hand, a reduced increase in alpha power during a vigilance task was found after oral intake of 40 mg ORG 2766 [18]. Opposite results were reported, using the same dosage in a warned reaction time paradigm [24,25], and still other studies failed to show any effect [2,17]. In view of these contradictory findings, it seems necessary to assume that task requirements are an important factor for ORG 2766 treatment effects to occur.

Furthermore, reported ACTH 4–9 influences on amplitudes and latencies of evoked potentials do not help to clarify the picture [8, 16, 24]. Although averaged evoked potentials may indicate changes in focussed attention, they are also related to fluctuations of arousal [6,21]. Without experimental control of central nervous arousal level it seems premature to describe ACTH 4–9 induced changes in EEG activity and evoked potentials solely in terms of more focussed attention. A more basic dishabituating effect of ORG 2766, mediated through inhibitory structures of the limbic system [26], could also explain secondary attentional effects. Long term habituation, here, refers to increased inhibition of mesencephalic reticular activity. Task dependence of effects after intake of ORG 2766 may be well related to the indirect influence of the substance—i.e., mediated through limbic inhibitory structures—on mesencephalic reticular activity. During rest conditions, for example, effects of the peptide on physiological parameters often fail to appear [10, 17, 28].

The present study investigates the effects of ORG 2766 on habituation as indicated by EEG parameters, changes in blood pressure and/or heart rate, and by overt vigilant behavior. Indicators of behavioral long term habituation are a time related decrement in task performance; heart rate and systolic blood pressure decrease [6,14]. With respect to the EEG an increase in power within the alpha band (7–14 Hz), sometimes accompanied by a decrease in power within the beta range (14–26 Hz) is to be expected. Gradually slower frequencies within these bands become prominent. In addition the amplitudes of the components of the AEP decrease

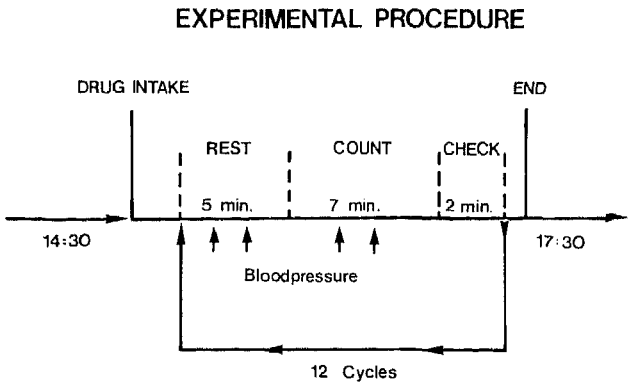


FIG. 1. Schematic representation of the experimental procedure. One experimental session consisted of 12 identical cycles, each containing a rest (REST), a counting (COUNT), and a check (CHECK) period. The latter was used to check counting performance of the subject. Blood pressure and heart rate were measured twice during counting and twice during rest. At the beginning of each session about 5 min were needed for instructing the subject and at the end a short paper and pencil vigilance task was given.

over time [1, 15, 21]. Long term habituation is best visible during lengthy and monotonic tasks, which nonetheless require some amount of permanent mental effort. A related aim of the study was to find out the onset of appearance of effects after drug intake.

Even strong dishabituating effects of ORG 2766 would not exclude the possibility of additional actions of the peptide on specific sensory processing unrelated to arousal. For example, temporal recovery of AEP components—as relative refractoriness—may be well related to short term habituation, which seems, however, less dependent on generalized levels of arousal [19,20]. Effects of ORG 2766 on the differential temporal recovery of components of the AEP were investigated.

## METHOD

### *Subjects*

Twelve male adults (age between 25 and 40 years) voluntarily participated in the experiment. Two subjects had to be discarded from further analysis because of equipment failures. All subjects did not smoke cigarettes and were free of medication at the time of the experiment. At least 12 hours prior to the experimental session the subject had to abstain from coffee and alcoholic beverages.

### *Design and Procedure*

All sessions were scheduled for 2:30 p.m. and lasted for three hours. During the experiment subjects sat in a reclining chair in an electrically shielded sound-attenuated booth. Testing started right after oral intake of either 40 mg of ORG 2766 or placebo and was held double blind. The subjects were informed that the effect of a peptide on EEG, heart rate, and blood pressure was investigated. The physiological nature of the experiment was emphasized and nothing about possible effects on vigilance or fatigue was mentioned in order to diminish placebo effects thereby avoiding an additional no-treatment control group. Indeed, only one subject assumed to have got an active agent after the experiment (see Results).

Figure 1 shows a flow chart of the experimental procedure. Twelve cycles of about 200 tone pips (1000 c/sec, 60 dB SPL, 40 msec) each, were presented through earphones to the right ear. Intervals between stimuli (ISIs) were either 1, 2, or 3 sec and varied randomly with the constraint that within a sequence of 39 tone pips equal numbers of each interval were presented. The subject's task was to covertly count the number of stimuli within each block as accurately as possible. The subjects were instructed to fixate on a dot, to suppress eye blinks as far as possible, and to avoid gross body movements throughout the counting period. This task is very boring and it takes permanently mental effort to keep on counting. Just 40% of all counts were totally correct. Each cycle began with a five minute rest period.

Afterwards subjects were given two different versions of a paper and pencil vigilance test [3]. Within five minutes they had to cross specially marked letters within fourteen lines of letters, as fast and as accurately as possible. At the end of the session subjects rated their perceived physiological changes and feelings of boredom during the experiment on seven point rating scales. They also reported whether they assumed to have received the peptide or placebo.

### *Recording and Apparatus*

Recordings were obtained of EEGs (5-sec time constant, 30 Hz/3 dB high-frequency roll off) from Fz, Cz, and Pz leads referenced to linked earlobe electrode locations. In order to monitor the vertical EOG, skin electrodes were attached approximately 1 cm above and below the right eye. A ground electrode was attached at Fpz. EEG and EOG signals were amplified by a Beckman type R 611 dynograph, digitized (sampling rate 385 Hz) and stored on magnetic tape pulse-code-modulated (Johne und Reilhofer, W-Germany). In addition the sequence of tone pips was stored for triggering the offline averaging of AEPs. Heart rate and blood pressure were automatically measured by a BC 40 (Bosch und Sohn, W-Germany) four times within each block, twice during counting and twice during the rest phase (see Fig. 1).

### *Data Reduction and Analysis*

For analysis of the spontaneous EEG activity the EEG data were reduced by resampling at a rate of 96 Hz. Subsequent epochs of the EEG record, each of 10 sec length, were transformed into power spectra. Averages were then formed from sweeps of the first versus the second half of a counting period. Statistical analysis was performed on mean power density and center frequencies of the theta (4–7 Hz), alpha (7–14 Hz) and beta (14–26 Hz) bands.

Averaging of the AEPs was done according to different classes of experimental conditions: TREATMENT (ORG 2766 vs. placebo), ISI (1, 2, and 3 sec), ELECTRODE location (Fz, Cz, Pz, and EOG), CYCLE (1–12), SECTION of block (tone pip 1–30, 31–80, 81–end). The latter subclassification was introduced in order to get a measure for changes *within* each cycle. The averaging epoch covered a 20 msec baseline and 960 msec after tone onset. Epochs were excluded from analysis if they contained eyeblinks, gross eye movements, or skin potentials.

A principal component analysis (PCA) applied to the covariance matrix was used to define components of the AEP. The number of components was arbitrarily limited to six or less. A varimax rotation was performed. Latencies of components were defined through maxima and minima of amplitudes within latency bins; i.e., the minimum between

43 msec and 147 msec after tone onset for the N100, and the maximum between 105 msec and 250 msec for the P200. Statistical analysis performed on amplitude values based on this second method, did confirm results based on PCA. Only PCA based results will be reported here.

For subsequent repeated measures ANOVAs of AEP and EEG data average values of four consecutive cycles were used. Since there were apparently no treatment effects during the first four cycles of the experiment the average value for this period could be used as a baseline. ANOVA factors were as for AEP averaging, except that, now, a factor BLOCK referred to four consecutive cycles of the experiment. For statistical evaluation of the spontaneous EEG activity only two SECTIONs of a cycle (first vs. second half of the counting period) were analysed.

Data of systolic and diastolic blood pressure and heart rate were collapsed for each counting and rest period, separately, and in addition—as EEG and AEP data—averaged across four consecutive cycles, and then submitted to ANOVA including a factor TASK (counting vs. rest). Treatment effects on behavioral parameters were evaluated by *t*- and F-tests.

## RESULTS

### *Behavioral Data*

There were no significant differences between treatment groups in any of the scores that resulted from the two versions of the paper and pencil vigilance test (errors of omission and comission, and total number of letters checked). Also the distribution of correct, almost correct (±5), and wrong counts was similar in both treatment groups. As for the rating scales, the ORG 2766 group reported that they were less tired during the experiment ($t=2.6$, $p<0.05$). Strong placebo effects appeared to be unlikely since only one of the placebo subjects and no ORG 2766 subject believed to have got an active drug. No side effects were reported.

### *Blood Pressure and Heart Rate*

ANOVAs of the heart rate and blood pressure data did not give evidence for strong autonomic actions of the peptide. There was a significantly higher systolic, $F(1,16)=13.63$, $p<0.01$, and diastolic, $F(1,16)=9.3$, $p<0.02$, blood pressure during counting as compared to the relaxation period. Also, across blocks of the experiment heart rate, $F(2,16)=30.16$, $p<0.001$, and systolic blood pressure, $F(2,16)=3.05$, $p<0.07$, decreased, whereas the diastolic blood pressure did not.

Concerning treatment effects, there was a slight trend towards a less pronounced decrease in heart rate across blocks for the ORG 2766 group (for the third hour after drug intake: ORG 2766: −3.5 b/min; placebo: −6.8 b/min; TREATMENT × BLOCK: $F(2,16)=2.55$, $p<0.1$). With respect to the blood pressure the treatment groups differed in the expected direction, but without any statistical significance.

### *EEG Activity*

Topographically theta activity was highest at frontal leads, $F(2,16)=11.24$, $p<0.01$, whereas alpha and beta activity was most pronounced at parietal leads, $F(2,16)=6.96$ and 5.96, $p<0.05$. The distribution of the alpha mean power density was correlated with the distribution of its center frequency, i.e., at Pz mean power density *and* center frequency, $F(2,16)=17.73$, $p<0.01$, were highest, and at Fz both parameters were lowest. Changes towards less arousal within the alpha band were more significant across (mean power density: $F(2,16)=14.05$, $p<0.01$; center frequency: $F(2,16)=7.46$, $p<0.05$) than within blocks (mean power density: $F(1,8)=4.93$, $p<0.1$; center frequency: $F(1,8)=4.79$, $p<0.1$). For theta center frequency it was just the opposite (within blocks: $F(1,8)=7.3$, $p<0.05$; across blocks: $F(2,16)=3.54$, $p<0.1$). Also, habituation is clearer at locations of highest amplitudes and frequencies for alpha mean power density (Pz; $F(4,32)=4.67$, $p<0.05$) and theta center frequency (Fz; $F(2,16)=4.50$, $p<0.05$), respectively.

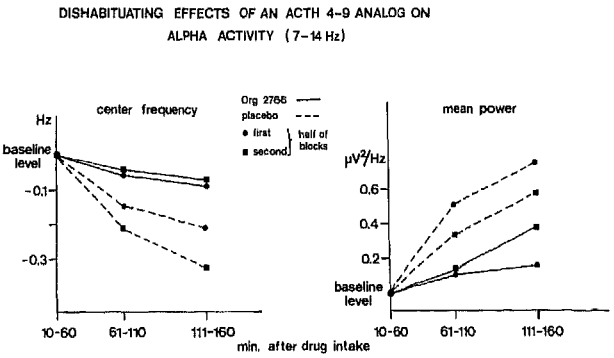


FIG. 2. The ORG 2766 group showed almost no decrease of the center frequencies (left panel) and less enhanced mean power density (right panel) across sessions, as compared with the placebo group. Treatment differences increased with time after drug intake.

Figure 2 summarizes treatment effects on EEG alpha activity. For both treatment groups a significant habituation is visible as a slow and gradual increase of alpha amplitudes and a decrease of alpha center frequencies. These habituational changes were less marked in the ORG 2766 group. The differences between treatment groups were most pronounced during the third hour after drug intake; i.e., at the very end of the experiment (TREATMENT × BLOCK × HALF: center frequency, $F(2,16)=4.02$, $p<0.05$; mean power density, $F(2,16)=2.20$, $p<0.15$). For the center frequency, but not for the mean power density, they were more pronounced during the second half of the experimental blocks (TREATMENT × HALF: $F(1,8)=8.43$, $p<0.05$).

Treatment effects on EEG theta activity are shown in Fig. 3. For the placebo group the center frequency drastically increases if compared with the baseline of the first four blocks after drug intake. This increase is stronger for the second half of the experimental blocks. The ORG 2766 group, however, showed slower center frequencies during the latter phases of the experiment for the first half of the blocks and only a small increase for the second half (TREATMENT × ELECTRODE × HALF: $F(2,16)=6.54$, $p<0.05$).

### *Evoked Potentials*

AEPs were submitted to PCA. Six principal components explaining 70.7% of the total variance resulted. Components 1 to 4 could be easily identified as "slow wave," P300, P200, and N100, respectively. The topographic distributions for these components were statistically significant (slow wave: $F(2,16)=10.13$, $p<0.01$; P300: $F(2,16)=23.26$, $p<0.01$; P200: $F(2,16)=5.23$, $p<0.05$; N100: $F(2,16)=48.98$, $p<0.01$), with a

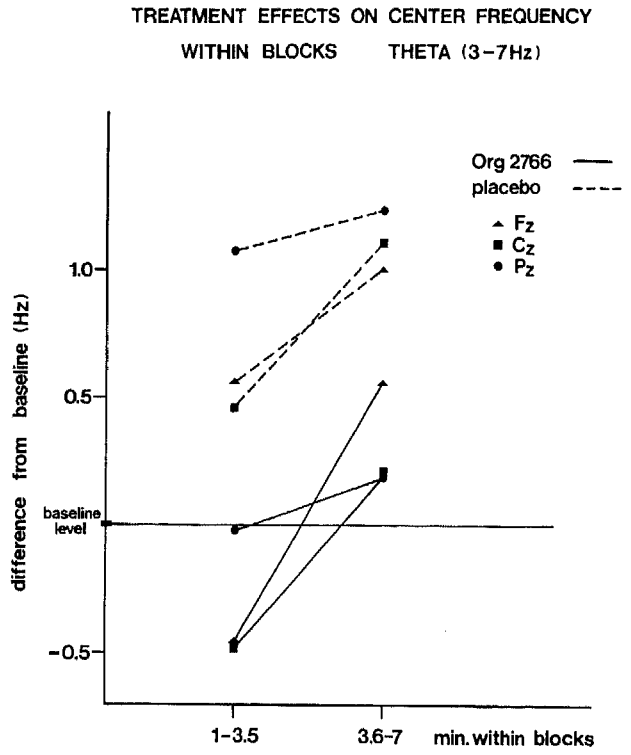


FIG. 3. Theta center frequency increased with reference to the baseline level in the placebo group over the course of the experiment. This increase was more pronounced for the second halves of the counting periods. On the other side, ORG 2766 subjects showed decreased theta center frequencies—especially at Fz and Cz leads—during the first halves of the counting periods (with reference to baseline level).

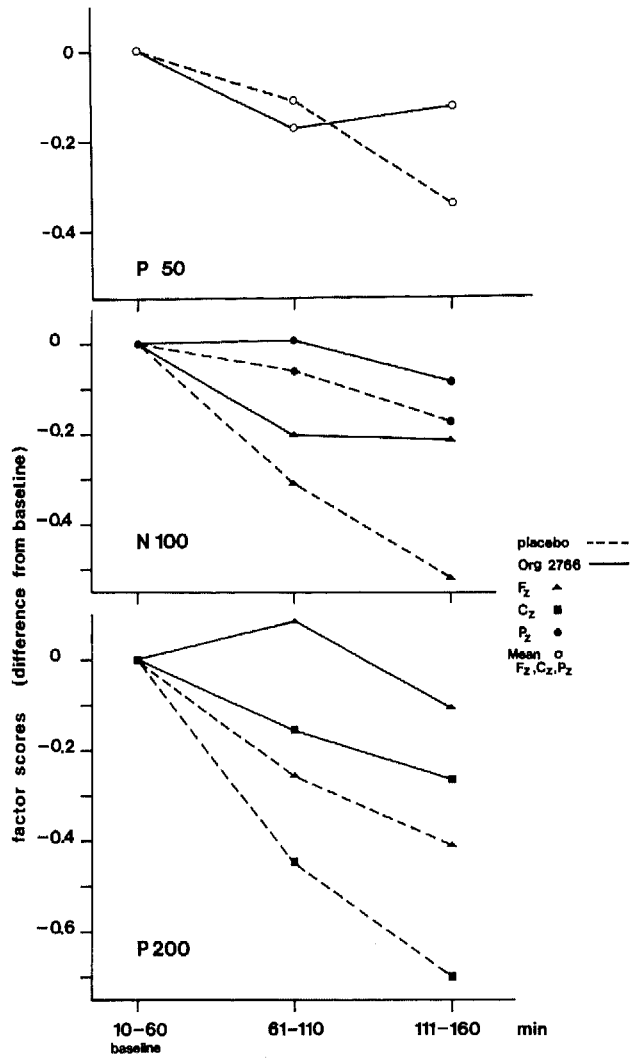


FIG. 4. Treatment effects on P50 (upper panel), N100 (middle panel), and P200 (lower panel) amplitudes. The ACTH 4–9 analog group showed less amplitude reduction across blocks. The dishabituation was strongest during the last third of the experimental session. For the N100 component treatment effects were most obvious at Fz and weakest at Pz, whereas treatment differences concerning P200 amplitude were most evident at Cz and least at Fz electrode locations. For the P50 component mean amplitude reductions across Fz, Cz, and Pz electrode locations are shown.

fronto-central negative peak for the N100, a more central positive maximum for the P200, a parietal positive peak for the P300 and a negative to positive voltage gradient for the "slow wave" component with its maximum at parietal electrode sites. Component 5 had maximum loadings about 140 msec after stimulus onset and no specific scalp topography. Since this component strongly overlapped with component 4, the N100, it could be an additonal N100 component copying changes in latency of the N100 across the experimental blocks. Interpretation of this component is, however, not unambiguous, and since there were no treatment effects related to this component it will be omitted in further discussions of data. Component 6—with maximal loadings about 50 msec after tone pip onset—characterized a P50.

*Habituation*

All of these components showed at least some degree of habituation, i.e., their amplitude significantly decreased over time: P50 across blocks (BLOCK: $F(2,16)=6.35$, $p<0.05$), within blocks only at Fz (ELECTRODE × SECTION: $F(4,32)=3.58$, $p<0.05$); the N100 and P200 components within and across blocks (BLOCK: N100, $F(2,16)=8.45$, $p<0.05$; P200, $F(2,16)=33.30$, $p<0.01$; SECTION: N100, $F(2,16)=13.80$, $p<0.01$; P200, $F(2,16)=20.13$, $p<0.01$) with a more pronounced decrease for the P200; the P300 across blocks, only (BLOCK: $F(2,16)=4.01$, $p<0.05$). Amplitude changes were most pronounced at the dominant location of the respective component (N100, P200, P300: ELECTRODE × BLOCK: $F(4,32)=13.50$, 4.04, 5.39, respectively, $p<0.05$), and for the slow wave at Fz towards more positivity within blocks (ELECTRODE × SECTION: $F(4,32)=3.41$, $p<0.05$).

Significant treatment differences on amplitude reduction were obtained for the P50, N100, and P200 components. The ORG 2766 group was characterized by a less attenuated P50 amplitude at the end of the experimental session than the placebo group (TREATMENT × BLOCK: $F(1,8)=5.26$, $p<0.05$). Also, N100 and P200 components showed more amplitude reduction over time in the placebo group (Fig. 4). The difference of the N100 amplitude between treatment

groups was strongest at Fz location and weakest at the Pz location; the difference of P200 amplitudes between treatment groups was strongest at Cz. Treatment effects were also enhanced for the third hour after drug intake if compared with the second hour (TREATMENT × ELECTRODE × BLOCK: N100, $F(2,16)=3.81$, $p<0.05$; P200, $F(2,16)=7.77$, $p<0.01$).

Latencies of N100 and P200 were shortest at Pz and Fz, respectively (ELECTRODE: N100, $F(2,16)=14.26$, $p<0.01$; P200, $F(2,16)=3.60$, $p<0.1$), and decreased across blocks (BLOCK: P200, $F(2,16)=9.39$, $p<0.05$), for the N100 most obvious at the location of fastest latencies (ELECTRODE × BLOCK: $F(4,32)=2.74$, $p<0.05$). Within blocks, only P200 latencies decreased over time at the location of fastest latencies (ELECTRODE × SECTION: $F(4,32)=2.89$, $p<0.05$).

Latencies of the components of the vertex potential were not unequivocally influenced by ACTH 4–9 analog treatment. There was a tendency towards decelerated latencies during the latest third of a block in the ACTH 4–9 analog group for N100 and P200 (especially at Pz) components (TREATMENT × (ELECTRODE) × SECTION: N100, $F(2,16)=3.68$, $p<0.05$; P200, $F(4,32)=5.06$, $p<0.01$).

*Temporal Recovery*

N100, P200, and slow wave increased in amplitude with increased length of the ISI (ISI: N100, $F(2,16)=14.34$, $p<0.01$; P200, $F(2,16)=25.57$, $p<0.01$; slow wave, $F(2,16)=4.99$, $p<0.05$); for N100 and P200 increase of amplitudes was more pronounced at their dominant location, for the slow wave at Fz (ISI × ELECTRODE: N100, $F(4,32)=4.88$, $p<0.01$; P200, $F(4,32)=4.16$, $p<0.01$; slow wave, $F(4,32)=6.02$, $p<0.01$) and at the beginning of the experiment (ISI × BLOCK: $F(4,32)=3.58$, $p<0.05$). There was a slight, nonsignificant trend for the P200 component to increase in latency with longer ISI, especially at Pz (ELECTRODE × ISI: $F(4,32)=2.69$, $p<0.1$).

There were less treatment effects on temporal recovery of the AEP components. Only temporal recovery of the P200 amplitude was affected by ACTH 4–9 analog treatment (TREATMENT × ISI: $F(2,16)=3.96$, $p<0.05$, Fig. 5). Since temporal recovery was more developed after the 3 sec ISI for the placebo group, habituation of the P200 amplitude was—as expected—increased with increased ISI. Therefore, dishabituation in the ORG 2766 group was expected to come out clearest with the 3 sec ISI. The difference between treatment groups, however, was most pronounced for the 1 sec ISI. For this length of ISI the ORG 2766 group even showed an enhancement of the P200 amplitude during the latter epoch of the experiment. This result might be related to treatment differences in latencies of the same component, which were also most prominent after the 1 sec ISI (TREATMENT × ISI: $F(2,16)=4.72$, $p<0.05$, see Fig. 5).

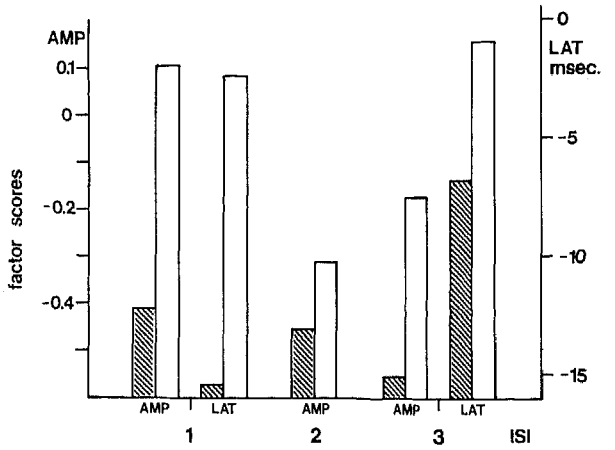


FIG. 5. Treatment effects on temporal recovery of the P200 component. Columns showing the differences of the P200 amplitude (AMP) between baseline and the latter epoch of the experiment, i.e., 60–160 minutes after drug intake, refer to the left ordinate. Columns showing the differences of P200 latencies (LAT) between baseline and the latter experimental epoch refer to the right ordinate. For the placebo group (hatched columns) the decrease of P200 amplitude over time is increasing with increased ISI. This is expected since temporal recovery is more developed after longer ISIs. Amplitude and latency differences between treatment groups are most pronounced for the 1 sec ISI.

## DISCUSSION

Our experiment proved to be useful to create typical long term habituation of several physiological parameters. In the placebo group spontaneous EEG activity changed towards increased mean power density and decreased center frequency of the alpha band across the experiment. Amplitudes of the vertex potential (P50, N100, P200) were attenuated across and/or within experimental blocks. Also latencies of the N100 and P200 components became gradually shorter in the placebo group. These results are in line with previous work on long term habituation as indicated by EEG parameters [1, 5, 15, 21]. A decrease of the tonic heart rate also supports the view of a gradual and general dearousal within the subjects of the placebo group across the experimental session.

Main results of this study suggest a dishabituating effect of the ACTH 4–9 analog: with respect to spontaneous EEG activity the ORG 2766 group was marked by an inhibited deceleration of the center frequency and less amplitude increase over time within the alpha band. These results are in accord with previous findings of diminished alpha enhancement during a similar vigilance task [18]. Results of increased alpha power density after ORG 2766 [24,25] may be due to differences in the applied experimental paradigm. It seems that dishabituation after treatment with an ACTH 4–9 analog is bound to a vigilance task, which permanently demands mental effort. Small breaks may alter the operating mode of the brain, i.e., alpha distribution over time.

AEP results also point to a dishabituating effect of the ACTH 4–9 analog. The most important finding was the small but not completely blocked attenuation of the components of the vertex potential (P50, N100, P200) across the session in the peptide treated group. Components of the vertex potential are directly related to level of arousal [6]; i.e., less inhibited mesencephalic reticular activity enhances amplitudes of the vertex potential. The less pronounced reduction of amplitudes of N100 and P200 in the ORG 2766 group partly fit those of other authors [23, 24, 25], who found an increased P200 amplitude after the second imperative stimulus, but not after the first, warning, stimulus of a warned reaction time paradigm for the ORG 2766 group. P200 amplitudes after the warning stimulus may be contaminated by a developing CNV. We did not find shorter latencies of the N100 component [24], but—in accord with a general dishabituation after intake of the peptide—increased latencies.

Although in the predicted direction, ORG 2766 treatment effects on blood pressure and heart rate are less evident. This could be attributed to the very small habituational changes over time within blood pressure parameters, which do not enable significant dishabituational effects to appear. On the other hand, increased heart rate during performance of a mental task in an ORG 2766 treated group [4,10] suggest a central mediation of effects on heart rate.

EEG and AEP changes as a function of time do not always correlate [20], but both can be altered by mesencephalic reticular activity representing central nervous arousal. The finding of ACTH 4–9 analog to accumulate in limbic structures of rats [29] led us to the assumption that in humans the peptide may reduce limbic inhibitory influences on mesencephalic activity, which are reestablished during habituation. A strong rhythmic theta activity over septum and hippocampal areas would be an indicator of such an inhibited inhibition. The observed significantly decreased center frequency of the frontal theta rhythm in the ACTH 4–9 analog group may be consistent with this interpretation [13].

In line with activating influences of ORG 2766 is the reported feeling of less fatigue during the experiment in the peptide treated group, although none of them believed to have taken the active agent. The paper and pencil vigilance task appears to be too short to be an accurate measure of vigilance decrement over time.

There is evidence from our data that effects of ORG 2766 on central nervous activation—as measured by EEG parameters—arise about one hour after oral intake of 40 mg of the substance, but increase until the third hour after drug intake. For almost all physiological parameters, which indicated clear treatment effects (e.g., P50, N100, and P200 amplitudes, alpha mean power density and center frequency), these effects were most obvious at the end of the experimental session. This is remarkable since the in-vitro half-life of ORG 2766 in human plasma was found to be approximately 60 min. In accord with previous reports the peptide action lasts after most of the parent peptide has cleared the system [22].

Besides the generalized dishabituation caused by ACTH 4–9 analog, we would suggest an additional effect on temporal recovery of the P200 component. The facilitation of temporal recovery of this component cannot be due to a mere increase in mesencephalic reticular activity, since in our experiment the most pronounced treatment effect occurred after the shortest ISI of 1 sec length. A generalized dishabituation would have caused the strongest effect to occur after the longest 3 sec ISI. Since the subject sample was small, these results require replication before further theorizing. Altered temporal recovery after intake of ACTH 4–9 analog, however, would point to additional influence of the substance on sensory processing.

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