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MSH/ACTH$_{4-10}$ and Task-Induced Increase in Tendon Reflexes and Heart Rate

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BRUNIA, C. H. M. AND A. VAN BOXTEL. *MSH/ACTH$_{4-10}$ and task-induced increase in tendon reflexes and heart rate.* PHARMAC. BIOCHEM. BEHAV. 9(5) 615–618, 1978.—Earlier studies revealed that during a binary choice reaction task an increase of tendon reflex amplitudes and heart rate can be found, together with a suppression of heart rate variability. The results were interpreted as a task-induced increase in generalized arousal. In this study two experiments, consisting of a rest period and a binary choice reaction task, were done. In Experiment 1, twenty subjects, in a cross-over design, received 15 mg MSH/ACTH$_{4-10}$ or a placebo. Only reflexes were recorded. In Experiment 2, three groups of 9 subjects received either 30 or 15 mg MSH/ACTH$_{4-10}$ or a placebo. Reflexes, heart rate and heart rate variability were recorded. Rest-task differences of reflexes and heart rate were enhanced by the drug. We hypothesized that MSH/ACTH$_{4-10}$ intensified the arousal effect of the task.

MSH/ACTH$_{4-10}$ Task Tendon reflex Heart rate Heart rate variability

PITUITARY hormones have been reported to influence different kinds of learning behavior [4]. Recently there has been an increasing amount of data, indicating that ACTH fragments produce behavioral changes without influencing adrenal cortex activity [9]. In addition to the many animal studies, there is growing evidence of MSH/ACTH$_{4-10}$ effects on the behavior of human subjects [5, 6, 8, 13, 14, 15, 17, 18, 19, 20, 23]. Among the hypotheses of the effects of MSH/ACTH$_{4-10}$ are that motivation [8], activation [5, 6, 8] or even selective attention [14, 15, 18, 19] may be positively influenced by the peptide. This has been reported on the basis of physiological changes, behavioral performance and rating scales.

Endröczi *et al.* [6], using subjects with "minor neurological symptoms," have reported a decrease of the number of synchronized EEG responses to regularly repeated stimuli after treatment with ACTH$_{4-10}$. According to the authors these responses are characteristic of a stage of habituation, so that their results might be interpreted as disinhibition. In normal subjects MSH/ACTH$_{4-10}$ caused a shift to higher frequencies in the occipital EEG [15]. In the same study no effects were found on CNV, basal heart rate, digital and cephalic pulse volumes, electrodermal activity and respiration. Sannita *et al.* [20] found no significant effects of MSH/ACTH$_{4-10}$ on the EEG of normal human subjects. Changes in electrically induced hippocampal rhythmic slow wave activity in rats have been reported, which were interpreted as compatible with positive effects of MSH/ACTH$_{4-10}$ on the general arousal level [22].

In a disjunctive reaction time task, a persistence of the arousal reaction in the EEG to significant warning stimuli has been found after 30 mg MSH/ACTH$_{4-10}$ whereas habituation took place to nonsignificant warning stimuli [15]. The subjects had to react to the former, but not to the latter. In a predrug session habituation took place to both kinds of warning signals. The authors interpreted their results as an enhancement of selective attention. With a self-paced reaction time task, it was shown that the decrease in performance, which generally occurs if time on task is relatively long, could be prevented by MSH/ACTH$_{4-10}$ [8]. This effect was interpreted as an increase in activation or motivation. An improvement in visual memory, using the Benton Visual Retention Test, was found in several studies [14, 15, 18]. Because this task requires attention to detail, it has been suggested that MSH/ACTH$_{4-10}$ may have significance for attentional-perceptual functioning [18]. An increased performance on other tasks under the influence of MSH/ACTH$_{4-10}$ also points to an enhancement of attention, both in normal [14,18] and mentally retarded subjects [19]. In men, MSH/ACTH$_{4-10}$ induced a reduction of state anxiety test scores [15,19]. However, other studies in men [14] and women [23] showed no effect on anxiety.

Although it is still premature to interpret the data, some findings suggest an action of ACTH-like peptides on the nonspecific reticulo-limbic system [17,22]. As far as behavioral changes are concerned, some authors [14, 15, 18] claim to have found effects on attention, whereas others [5,8] interpret their data in terms of a general arousal effect.

In earlier experiments, one of us [1] studied the effect of a binary choice reaction task on the monosynaptic Achilles tendon (T) and Hoffmann (H) reflexes. T reflex amplitudes give an impression of changes in the excitability of alpha and gamma motoneurones, whereas H reflexes are supposed to reflect only changes in alpha motoneurone excitability. It was shown that T reflex amplitudes were larger during the task, whereas H reflex amplitudes did not show significant changes. The results were interpreted as a facilitatory effect of generalized arousal on the fusimotor system, causing a

higher sensitivity of the muscle spindles in the soleus muscle during the task. The increase of T reflex amplitudes during the task was consistently found in other studies [2,3]. Moreover an increase in heart rate [3] and a suppression of heart rate variability [16] was found during the same task. Hence in this study the influence of $MSH/ACTH_{4-10}$ on Achilles tendon reflexes, evoked at rest and during task, was tested. In one of the experiments also heart rate was recorded.

METHOD

Experiment 1

Twenty healthy subjects (7 women and 13 men), 18–25 years of age, took part in the experiment. In a double blind crossover procedure, with an intersession interval of 10–21 days, they were given intramuscular injections with 15 mg $MSH/ACTH_{4-10}$ or a placebo. The subjects were injected after the technical arrangements for the reflex recording were made. Fifteen min later the experiment was started. Reflexes were evoked during a 15 min rest period which was followed by 30 min task. T reflexes were evoked while the subjects were seated in a specially devised chair. Tendon taps were given by means of a Bruël and Kjaer 4309 vibration exciter with a frequency of 1 per 3 sec. Surface Ag-AgCl electrodes of the usual EEG type were used. Peak-to-peak amplitudes were measured by a digital voltmeter (Hewlett Packard 3440A) and punched in paper tape. The tape was fed off-line into a DEC LAB 8E computer. For each subject means and standard deviations were calculated per period of 3 min. Per subject the mean values were transformed into modified standard z-scores so that the values of different subjects were comparable and could be averaged. A z-score was calculated by dividing the difference between a period mean and the mean of all reflex amplitudes in the session by the square root of the within-period variance estimate (the latter can be considered as the error term in a single factor experimental design with periods as the experimental factor).

The subjects had to perform a paced binary choice reaction task. Tones of high and low pitch were presented in a random order with a frequency of 65 tones per min. The subjects had to press a button with their right hand if the pitch was high and with their left hand if the pitch was low.

Experiment 2

Twenty-seven healthy subjects (7 women and 20 men), of the same age as in Experiment 1, were divided randomly into 3 equal groups. In a double blind procedure the first group received an intramuscular injection with 30 mg $MSH/ACTH_{4-10}$, the second group with 15 mg and the third group with a placebo. Half of the subjects in each group started with 15 min rest, followed by 15 min task, the other half vice versa. As in Experiment 1, recording of the reflexes started 15 min after the injection. The same recording procedure and z-score transformation was employed as mentioned above. The ECG recordings were carried out with Beckman electrodes, fixed to the thorax. The ECG signal was stored on magnetic tape (Philips Analog 7) and analysed by the LAB 8E computer. For each subject the mean R-R interval per period of 3 min was calculated. The standard deviation of the R-R intervals was taken as a measure of heart rate variability.

RESULTS

In Experiments 1 and 2 mean T reflex amplitudes were obtained by averaging the z-scores over subjects (Figs. 1 and 2). The same was done for the heart rate in Experiment 2 by averaging the R-R interval values of individual subjects (Fig. 3).

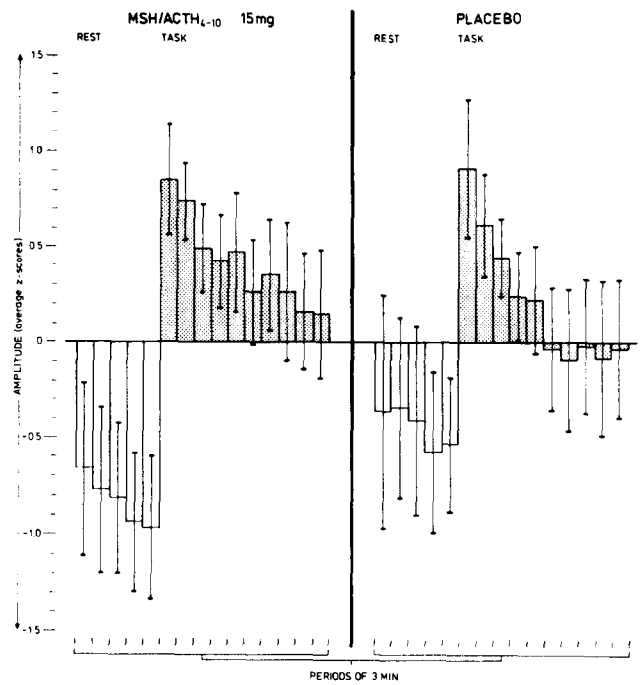

FIG. 1. Mean T reflex amplitude in Experiment 1. The vertical lines show the 95% confidence intervals.

An analysis of variance (multifactor design with repeated measures) was performed on the T reflex z-scores in both experiments. The factors included in the design were: rest-task, peptide condition, periods of 3 min and subjects. We will present the rest-task main effect and the rest-task × peptide condition interaction because they are relevant to the problem studied here.

Experiment 1

The main effects and interactions of the fixed factors were tested against the corresponding subject × fixed factor interaction terms. The rest-task main effect was highly significant, $F(2,38)=14.43$, $p<0.0001$. The rest-task × peptide condition interaction was not significant, $F(2,38)=2.10$, $0.10<p<0.25$. Hereafter all subject × fixed factor interaction terms were pooled [24] because at least some of them were not significant in previous experiments. Preliminary tests on these terms could not be done because there was only one observation per cell so that the within-cell error term could not be computed. When using the pooled error term in testing the main effects and interactions of the fixed factors, not only the rest-task main effect but also the rest-task × peptide condition interaction was significant, $F(2,551)=8.91$, $p<0.0005$. An a posteriori analysis of this interaction by comparison between means revealed that the difference between the rest level on the one side and the two task levels

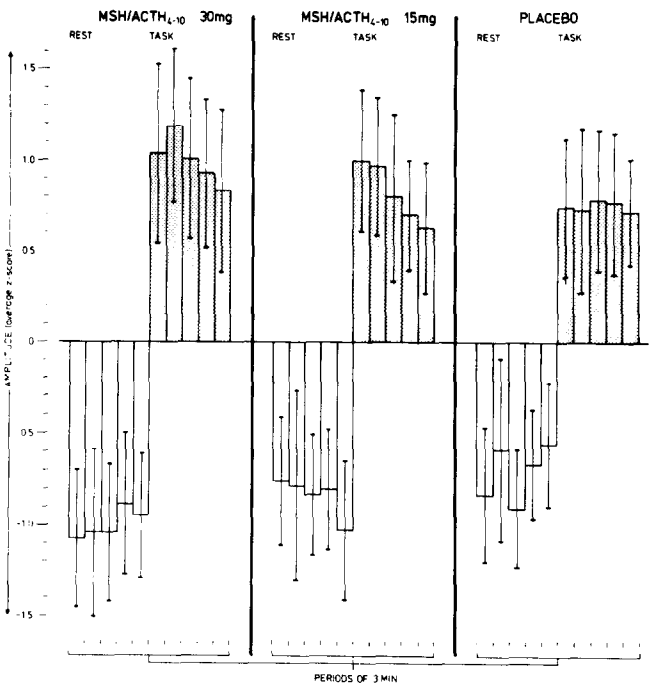

FIG. 2. Mean T reflex amplitude in Experiment 2. The vertical lines show the 95% confidence intervals.

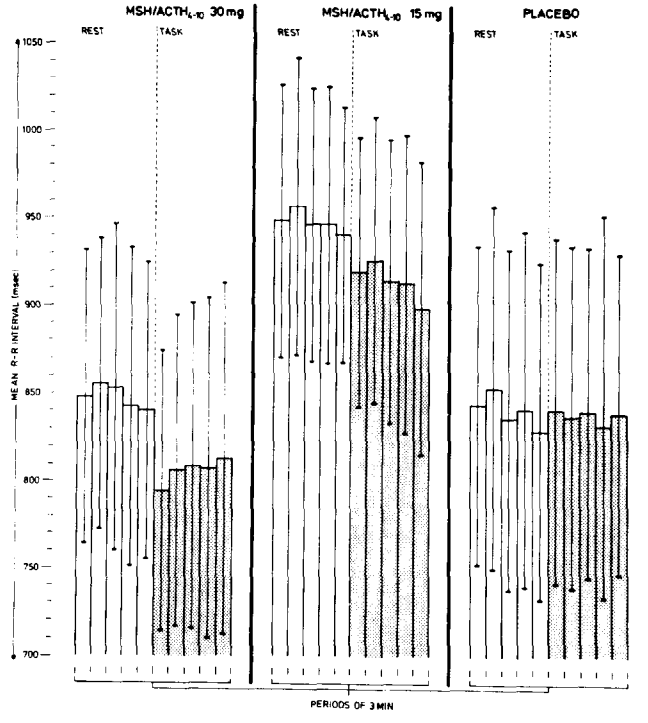

FIG. 3. Mean R-R interval in Experiment 2. The vertical lines show the 95% confidence intervals.

on the other hand formed the only significant contribution to the interaction, $F(2,551)=8.36$, $p<0.001$. The difference was larger in the MSH/ACTH$_{4-10}$ condition than in the placebo condition.

Experiment 2

As in Experiment 1 the rest-task main effect was highly significant, $F(1,24)=65.33$, $p<0.0001$, and the rest-task × peptide condition interaction was not significant, $F(2,24)=0.78$, $p>0.50$. The interaction was significant when the pooled error term was used, $F(2,216)=5.08$, $p<0.01$. The interaction was entirely the effect of the variation of the rest-task difference between the peptide conditions. The difference was largest in the MSH/ACTH$_{4-10}$ 30 mg condition and smallest in the placebo condition.

An analysis of variance of the mean R-R intervals in Experiment 2 showed a significant rest-task main effect, $F(1,24)=20.28$, $p<0.0005$, and a significant rest-task × peptide interaction, $F(2,24)=4.35$, $p<0.05$. The difference was largest in the MSH/ACTH$_{4-10}$ 30 mg condition and absent in the placebo condition. For the heart rate variability only the rest-task main effect was significant, $F(1,24)=47.16$, $p<0.0001$.

DISCUSSION

The peptide main effect on the T reflex could not be tested in our experiments because the different conditions of the factor were tested in different sessions. The reflex amplitude within a session is for a substantial degree dependent on stimulation and recording variables such as the force of the tendon tap, tension of the Achilles tendon, posture of the subject and position of the recording electrodes. Also the state of arousal of the subject is important. Thus basal reflex amplitude cannot be compared between different sessions of the same subjects (Experiment 1), or between different subjects (Experiment 2). Consequently, a possible effect of peptide on basal reflex amplitude cannot be evaluated. For assessment of such an effect, an experimental design with a pre- and post-drug condition within sessions would be needed.

Nevertheless, in our experiments we are able to test the effect of the peptide condition on the change in reflex amplitudes which appears at the introduction of the task, because we used normalized amplitude measures. This change may be caused by a generalized arousal due to the task because the motoneurone pool of the soleus muscle is not involved in the performance of the task. For the performance of the task it is only necessary to discriminate between tones and to react with both hands. The reflex data show significant rest-task differences which are greater under the influence of MSH/ACTH$_{4-10}$. In Experiment 2 the size of the difference was dependent on the dose of the peptide. Presumably MSH/ACTH$_{4-10}$ intensifies the arousal effect of the task. Consequently, it probably brings about an enhancement of the supra-spinal facilitation or disinhibition of the fusimotor system, and perhaps also of the alpha motoneurones. An increase of muscle action potentials in the rat after treatment with MSH/ACTH$_{4-10}$ was found [21]. Stimulation of the sectioned motor nerve did abolish the increase, thus it was concluded that MSH/ACTH$_{4-10}$ had a central effect rather than a peripheral influence on the motor unit. Monosynaptic reflex amplitudes were reported to increase after administration of β-MSH in the spinal cat [11].

This implies an effect of the peptide on the spinal level. Although a spinal effect cannot be ruled out in our experiments, the increase of the rest-task difference after treatment with MSH/ACTH$_{4-10}$ makes an influence of the peptide on supraspinal pathways more likely.

In this study the heart rate variability decreased during the binary choice reaction task, as was found by others [16]. The heart rate showed an increase during the task in the MSH/ACTH$_{4-10}$ conditions, but not in the placebo condition (Fig. 3). This is not in conformity with an earlier study [3], in which the same task caused an increase of heart rate in the placebo condition too. This discrepancy might be explained by data which suggest that a heart rate increase is only seen at higher levels of task load [16]. Although the task demand was equal in both studies, the cognitive effort of the subjects in the earlier study might have been greater than in this study.

The binary choice reaction task requires cognitive effort from the subject. Tasks which have this property (e.g., mental arithmetic) produce an increase in heart rate [12,25], while tasks which require attention to external stimuli lead to heart rate deceleration [10,12]. It has been shown that an increase in heart rate may not only reflect cognitive effort but also the stressful and novel aspects of the task [25]. Such kinds of tasks may lead to a variety of reactions within the sympathetic nervous system [7]. The heart rate reaction to the binary choice reaction task may be an aspect of the response because administration of the β-blocking agent propranolol reverses this increase [3]. Therefore we are inclined to interpret the increase in heart rate in Experiment 2 in terms of a general arousal effect rather than in terms of selective attention.

In this study MSH/ACTH$_{4-10}$ increased the heart rate reaction to the task. Others [13, 14, 15, 18, 23] found no effect of MSH/ACTH$_{4-10}$ on heart rate. In one study MSH/ACTH$_{4-10}$ caused a significant heart rate deceleration to the test stimulus of an orienting sequence [19]. This discrepancy between our results and the negative findings of many other studies might be due to the fact that the latter concerned the influence of MSH/ACTH$_{4-10}$ on the absolute heart rate level while we studied the difference between the heart rate in two experimental conditions (rest and task).

In conclusion, we found that MSH/ACTH$_{4-10}$ resulted in an increase of sympathetic activity and a facilitation or disinhibition of the fusimotor neurones, and perhaps of the alpha motoneurones.

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