Pergamon

Psychoneuroendocrinology, Vol. 20, No. 8, pp. 865–877, 1995

0306-4530/95 $9.50 + .00

0306-4530(95)00015-1

# LONG-TERM HABITUATION OF BRAIN EVOKED POTENTIAL RESPONSES AND PITUITARY–ADRENAL SECRETION WITH REPEATED (PLACEBO) TESTING

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*(Received 16 September 1994; in final form 25 March 1995)*

## SUMMARY

To study whether changes in late auditory evoked potentials (AEPs) and/or in stress-sensitive hormones of the hypothalamic–pituitary-adrenal (HPA) system take place between a first and a second placebo experiment and if so, whether these changes are possibly related to each other, we conducted two identical placebo sessions (2 ml 0.9% saline) and one cortisol session (50 mg) with 10 subjects on three different days. Plasma cortisol concentrations were significantly higher at the beginning of the first placebo experiment than the second, with a concordant decrease of plasma adrenocorticotropin hormone (ACTH) concentrations. In the AEP domain, a consistently lower P2 amplitude was observed in the first session. Since the change in late auditory processing could not be demonstrated after exogenous administration of cortisol, a direct mediation through an elevation of plasma cortisol concentrations or indirect mediation through a decrease of plasma ACTH concentrations seems unlikely. We rather propose that other stress-sensitive mechanisms, such as CCK, might account for the novelty-induced P2 amplitude lowering.

**Keywords**—Auditory evoked potentials; Repeated testing; Cortisol; ACTH; Arousal; Habituation; Anticipatory stress.

## INTRODUCTION

Monitoring of late auditory evoked potentials (AEPs) combined with intravenous administration of hormones provides an adequate approach to explore perceptual changes in humans caused by centrally nervous active substances (Born et al., 1991; Fehm & Born, 1987; Rockstroh et al., 1981). Since AEPs show higher inter-individual than intra-individual variability, studies on experimentally-induced changes in auditory evoked potentials should be based on within-subject comparisons (Segalowitz & Barnes, 1993).

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Concerning the effects of repeated measurements under placebo conditions on late AEPs in within-subject designs, Shelley et al. (1991) reported a lower P2 amplitude in the first than in the second placebo experiment, and postulated possible habituational effects on the first experimental day. Habituational processes have also been described affecting other electrophysiological parameters, e.g. the contingent negative variation (CNV) (Timsit-Berthier et al., 1980). The presence of changes in the electroencephalogram (EEG) caused by habituational processes in repeated testing situations is also well known in sleep research, where sleep observations are always started with at least one "habituation night" under laboratory conditions (Agnew et al., 1966; Mendels & Hawkins, 1967; Rechtschaffen & Verdone, 1964).

The unfamiliar experimental situation could serve as a causative factor for this phenomenon. It is well known that human subjects placed in novel situations display increased HPA secretory activity (Davis et al., 1981). When confronted repeatedly with the same experimental situation, adrenocortical activation dimishes gradually (Al'Absi & Lovallo, 1993; Voigt et al., 1990). These differences between the electrophysiological and the endocrinological domains in the first and consecutive placebo experiments led to the hypothesis that alterations in hypothalamic–pituitary–adrenocortical (HPA) system activity in the first experimental session are related to the changes observed in late AEPs. In this context, previous studies investigating the effects of exogenously administered cortisol on late AEPS have yielded conflicting results (Born et al., 1987, 1988).

Therefore, two identical placebo sessions with IV administration of 2 ml 0.9% NaCl were conducted with 10 subjects on different days, the second placebo measurement (placebo 2) being used as a baseline measurement. To investigate whether possible changes in late AEPs are possibly caused by raised plasma cortisol concentrations (or the resulting decreased plasma ACTH concentrations), we administered cortisol (50 mg) in an additional session, ranked randomly on the second or third experimental day. Our hypothesis was that if the AEP effects observed were related to cortisol effects, these would be even more pronounced following higher circulating plasma cortisol concentrations (and increased concordant suppression of ACTH). To obtain these elevated circulating plasma cortisol concentrations, we administered pharmacological doses in the morning hours when endogenous plasma cortisol concentrations are at their highest. Moreover, this approach allows us to separate possible exogenous effects of cortisol from fluctuations in physiological circulating hormone levels.

Late AEPs were computed for each experimental day. In all three sessions, plasma ACTH and cortisol concentrations were determined for evaluation of hormonal stress responses. Furthermore, heart rate and blood pressure were monitored as indicators of cardiovascular stress responses.

Thus, the goal of the present study was to investigate whether habituational processes in repeated testing situations in the electrophysiological (evoked potentials), cardiovascular and neuroendocrinological domain occur, and how they are related to each other.

## METHODS

*Subjects*

Ten healthy young men (range 20–25 years) took part in the study, which was approved by the Ethics Committee of the Max Planck Institute of Psychiatry. They had given informed consent in accordance with the Declaration of Helsinki. None of them had prior experience