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Responses of the hypothalamic–pituitary–adrenal axis and pain threshold changes in the orofacial region upon cold pressor stimulation in normal volunteers

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ABSTRACT

Aim: This study focused on the relationship between the HPA axis function and the heat pain threshold in the orofacial region upon cold pressor (CP) stimulation.

Methods: Ten healthy male individuals participated in this study. CP stimulation was applied to each participant, and their peripheral blood was collected 5 min before, during and 5, 15, 30, 45, 60 min after receiving CP. In addition, 5 of those 10 participants were selected at random and they experienced a mock CP trial on different days. The heat pain thresholds on the facial skin about 10 mm anterior to the right external auditory canal (trigeminal V2 region) in each subject were simultaneously recorded 5 min before and 5, 30, 60 min after CP stimulation. The blood pressure and heart rate were continuously monitored throughout the course of the CP and mock trials using an electric blood pressure meter.

Results: Significant increases in the plasma concentration of cortisol, β-endorphin and ACTH were induced by CP stimulation, while no significant increases were observed under the mock trial conditions. The blood pressure and heart rate showed concomitant increases during CP stimulation. In addition, the heat pain threshold in the orofacial region significantly increased after receiving CP stimulation. These results suggest that CP stimulation activated the HPA axis thereby increasing the heat pain threshold in the orofacial region in healthy individuals.

Conclusions: This observed pain threshold increase might be due to the activation of an endogenous opioid system, such as increase in the circulating β-endorphin levels.

1. Introduction

The life-time prevalence of chronic orofacial and cervical pain syndrome has been currently estimated to be over 70% in the general population,[1] and such syndromes are also considered to substantially affect the patients' quality of life.[2] The current, widely accepted view of most chronic orofacial pain disorders is that they have a multifactorial etiology, including both environmental and genetic components. A popular theory regarding the etiology is that patients have a high stress-responsive nature and this provides an important clue regarding the cause of such pain. Concomitant with a high

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stress-responsiveness, which is presumably due to sympathetic nerve activation, is the activation of the hypothalamic–pituitary–adrenal (HPA) axis. The HPA is the main stress hormone system and currently much attention has been devoted to the association between the abnormalities of the HPA axis and chronic pain conditions.[3–5]

Regarding the activation of the HPA axis, it is widely accepted that corticotrophin-releasing factor (CRF) and arginine vasopressin (AVP) are produced in the ventricular nucleus of the hypothalamus. Moreover, the released CRF controls pituitary adrenocorticotropin (ACTH) which is produced by corticotrophs in the anterior pituitary gland. Circulating ACTH accelerates the release of cortisol, the principal circulating glucocorticoid produced by the adrenal gland and this endogenous hormone internally plays an important role in both adjusting homeostasis and improving the ability of individuals to survive under stressful conditions.

Finally, in addition to cortisol, the release of β-endorphin, whose precursor is pro-opiomelanocortin C (POMC), is also known to be released in greater quantities under stressful conditions. Since the β-endorphin acts as an endogenous analgesia substance,[6,7] any abnormalities in these systems could thus be one of the key features in the pathophysiology of chronic orofacial pain. These findings encouraged us to investigate the relationships among the HPA axis function, the circulating endogenous opioid level and chronic orofacial pain. Our purpose in the current study is therefore to evaluate the normal response of the circulating HPA axis hormone, β-endorphin levels and pain threshold changes in the orofacial region under relatively strong physical stress in healthy male individuals. In order to induce physical stress, we utilised cold pressor (CP) stimulation, which is well known to be an activator of both the sympathetic nervous system and the HPA axis.[8–10] Specifically, we evaluated the changes in the plasma ACTH, cortisol, β-endorphin levels as well as the heat pain threshold of the trigeminal (V2) region before during and after CP stimulation. The null hypothesis tested in this study was that there are no associations among the circulating HPA axis hormones, the endogenous opioid levels and the pain threshold changes in the orofacial region upon CP stimulation.

2. Materials and methods

2.1. Participants

Ten healthy non-smoking male volunteers (mean age: 25.3+/−1.3 years) participated in this study. After completing a screening questionnaire, those individuals deemed potentially suitable were questioned verbally about their medical and dental history to ensure that they could safely participate in the experiment and provide unbiased data. They all were in physically good health and were not presently taking any psychotropic, antihypertensive or other medications. All were free from psychiatric, neurological disorders, symptomatic cardiovascular disease, muscle fatigue, acute or chronic pain conditions. This study protocol was reviewed and approved by the Ethics Committee for Human Study at Okayama University Graduate School of Medicine, Dentistry, and Pharmaceutical Sciences (#304), and informed consent was obtained from each participant before starting the experiment.

2.2. Experimental procedures

The participants were seated comfortably in an upright chair in a laboratory (22–24 °C). Two minutes 4 °C CP stimulation, which involved sustained immersion of a limb in ice water, was applied to their right hand and forearm. The experimental procedure was started between 16:00 and 17:00 h, when the circadian rhythm of HPA axis hormones secretion is stable and low. A heparinized catheter was inserted into an antecubital vein of the left arm to allow for repeated blood drawing. In order to prevent fluctuation of the concentration of the hormones in the blood by the pain sensation induced by the placement of the catheter, the patients were all directed to rest in a supine position for 30 min or more before starting the experiment. In addition, 5 of the 10 participants were selected at random and underwent mock trials. This mock trial involved exactly the same experimental procedures except that the sustained immersion of each subject's right hand and forearm was in an empty bowl, not an ice-water containing bowl. The CP and mock trials were performed on different days.

2.3. HPA axis hormones

Whole blood samples were collected 5 min before, during, and 5, 15, 30, 45, 60 min after CP and the mock stimulation for measuring adrenocorticotropic hormone (ACTH), cortisol and β-endorphin. These samples were then drawn from an anterocubital vein of each subject. Whole blood was centrifuged for plasma separation, and then it was frozen (−20 °C) for a later assay. The cortisol concentrations were determined using radioimmunoassay techniques. The detection limit for cortisol was 0.17 μg/dl. The intra- and inter-assay coefficients of variation were 6.1 and 10.0%, respectively. The ACTH and β-endorphin concentrations were determined using immunoradiometric assay techniques. The detection limit for ACTH was 5.0 pg/ml. The intra- and inter-assay coefficients of variation were 3.5 and 3.9%, respectively. The detection limit for β-endorphin was 14 pg/ml. The intra- and inter-assay coefficients of variation were 4.1 and 9.0%, respectively.

2.4. Cardiovascular parameters

The blood pressure and heart rates were continuously monitored throughout the course of the CP and mock trials using an electric blood pressure meter (Finapress BP monitor; Ohmeda, Louisville, USA). These cardiovascular data were continuously stored in a digital data-recorder (PC-108; Sony Magnescale Inc., Tokyo, Japan) for later analysis, and subsequently were transferred to a computer using a software program (MP100 Workstation; BIOPAC Systems Inc., Santa Barbara, CA, USA) at a 1 Hz sampling rate. The obtained data were separated into the following periods; baseline (5 min before experiment), during the CP stimulation and the recovery 4 sections (recovery 1: 0–15 min after CP stimulation; recovery 2: 15–30 min after CP stimulation; recovery 3: 30–45 min after CP stimulation; recovery