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ORIGINAL ARTICLE

P300 event-related potential and serotonin-1A activity in depression

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Summary – The identification of the brain structures and neurotransmitters responsible for the generation and/or modulation of P300 could lead to important clinical implications. Since serotonin disturbances seem to play a critical role in depression, the aim of the study was to assess the possible relationships between the P300 event-related brain potential and serotonergic activity in depression. The study was conducted among 45 major depressive inpatients, and serotonergic activity was assessed by prolactin (PRL) response to flesinoxan (a 5-HT1A agonist). Results showed a significant negative correlation between P300 amplitude and PRL response to flesinoxan ($r = –0.40$, $P = 0.007$ at Cz; $r = –0.47$, $P = 0.001$ at Pz). In contrast, both P300 latency and reaction time were not related to endocrine response. This study supports a role for serotonin-1A in the neurobiological modulation of P300 amplitude. © 1999 Elsevier, Paris

depression / flesinoxan test / P300 / serotonin-1A

INTRODUCTION

The P300 component of the event-related potential (ERP) is a positive deflection which occurs when a subject detects an informative task-relevant stimulus. It is particularly interesting for the study of cognitive processes both in normal subjects and in psychopathological conditions [1, 2]. P300 reflects memory updating [1], or context closure [3], and perhaps represents the transfer of relevant information to consciousness [2]. P300 amplitude is related to stimulus probability, stimulus significance, task difficulty, motivation, and vigilance [4, 5]. On the other hand, P300 latency is mainly influenced by the task complexity but not response difficulty [6, 7], and reflects the stimulus time evaluation [8].

P300 has been applied in depression with controversial results. Reduced P300 amplitude as compared to a control group has been reported in several studies [9-11], whereas no differences have been described in other studies [12-16]. Concerning P300 latency, depressed patients and controls were found to exhibit similar values in most reports [9, 11, 15, 17-19], but Bruder et al. [16] reported an increased latency using a complex discriminative task. A major source for these controversial results could result from the diversity of depressed patients included in the different studies. Indeed, the heterogeneity of depressed patients may have obscured effects that could be specific to only a subgroup of patients. Supporting this assumption, depressed patients characterized by impulsivity exhibited higher P300 amplitude when compared to others characterized by blunted affect [20, 21]. Moreover, the presence of suicidal behavior [22, 23] and psychotic features [19] could significantly influence P300 amplitude.

The identification of the brain structures and neurotransmitters responsible for the generation and/or the modulation of P300 could contribute to a clearer understanding of its functional significance, and may give rise to interesting clinical implications. In this context, psychopharmacological studies have provided some in-

teresting insights into the underlying neurobiological substrate of P300. Cholinergic effects on P300 amplitude and latency have been described, with a decrease of P300 amplitude and increased latency after the injection of an anticholinergic agent (i.e., scopolamine), and the opposite results with cholinergic drugs (i.e., physostigmine) [24-26]. The influences of the noradrenergic, dopaminergic, and gabaergic systems has been reported in many studies [27-30]. Clonidine (an alpha-2-noradrenergic agonist) decreases P300-like potential in monkey [28], and methylphenidate dopaminergic agonist enhances P300 amplitude in attention-deficit hyperactivity disorder children [27]. Moreover, the benzodiazepine alprazolam reduces P300 amplitude in normal subjects [29].

However, little data is available concerning the serotonergic modulation on P300 amplitude and latency. Pritchard et al. [31] found no significant effect of the fenfluramine serotonergic antagonist on P300 component. Again, Meador et al. [26] have reported no significant influence of the antiserotonergic agent methysergide on P300, and Unrug et al. [32] found no effect of the anxiolytic buspirone on P300 amplitude. However, Ito et al. [33] have demonstrated a significant relationship between P300 amplitude and the cerebrospinal fluid (CSF) concentration of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in demented patients. Moreover, Meador et al. [34] have reported an interactive role of the cholinergic and serotonergic systems on P300 latency. These inconsistencies in the literature could suggest that the influence of serotonin on P300 seems to be indirect rather than direct.

Recently, by using a neuroendocrine challenge with flesinoxan (a 5-HT1A agonist), we found a negative relationship between the serotonergic activity and the P300 amplitude in normal subjects [35]. Since serotonin has been widely implicated in the pathophysiology of depression, the aim of the present study was to investigate whether or not our results could be transferable to depression, and to test their possible clinical relevance to the illness.

MATERIALS AND METHODS

The study was conducted with 45 depressive inpatients admitted to the Psychiatric Unit of the University Hospital of Liège (Belgium). The sample comprised of 18 women and 27 men with a mean age of 42.3 years (SD = 13.9). All patients met DSM-IV criteria for major depressive disorder [36] with a score of at least 18 on the 17-item Hamilton depression scale [37] on the day when the P300 recording was carried out. The patients were free of medical illness, evidenced by history, clinical examination, electrocardiogram (ECG), electroencephalogram (EEG), chest X-Ray, and routine laboratory tests. Moreover, the P300 recording and the challenge test were carried out after a drug-free period of at least three weeks. Since suicidal behavior was previously shown to influence P300 amplitude [22, 23], all of the selected patients were free from a history of suicide attempts. The protocol was approved by the ethical committee of the University of Liège Medical School, and all patients gave their informed consent.

The P300 recording was performed in a sound-attenuated room. The subjects were tested until a total of 150 trials were obtained after rejecting trials contaminated by eye movement or other artifacts. The auditory stimuli were presented binaurally in a random series at the rate of one trial every second. The frequent stimuli were tones of 1470 Hz, 70 dB, and 40 ms duration, and the other 20% (target) were tones of 1000 Hz, 70 dB, and 40 ms duration. The subjects were asked to press a button for the rare stimuli. P300 was measured as the largest positive voltage over a 280–450 ms time window following stimulus onset. P300 trials contaminated by blinks or large amplitude eye movements were automatically excluded by using a 50 μV rejection criterion. Analysis of the N100, P200 and N200 components will be reported elsewhere.

The EEG was recorded using silver-silver chloride electrodes attached at Cz and Pz, using linked earlobes for reference and the right forehead for ground. All sites were cleaned with acetone and abraded to maintain a resistance below 5 kOhms. EOG was recorded from above the left eye. Amplifier gains were set at 10,000, with a band pass of 0.05–35 Hz, and digitized at 250 sample/s for 900 ms epochs (of which the first 200 ms were pre-stimulus activity).

The flesinoxan challenge test was performed on the day after the P300 recording. An indwelling catheter was inserted into a forearm vein of the subjects at 8.30 am. Blood samples of 10 mL were collected 30 min before, and immediately before the injection of flesinoxan at 9.30 am. Successive blood samples were collected 15, 30, 60, 90 and 120 min after the slow (10 min) intravenous injection of flesinoxan (1 mg/70 kg body weight), diluted in saline to obtain

20 mL. Blood samples were centrifuged within 2 h, and serum immediately frozen and kept at –18 °C until analysis.

Prolactin (PRL) was measured by radioimmunoassay (RIA) with intra- and inter-assay coefficients of variation of 10.0 ± 10.0% and a detection limit of 10 mIU/mL. Hormonal response following flesinoxan was assessed by peak values following the injection, as well as by the area under the curve situated between injection and the last blood sample. Analyses were performed using relative (delta) PRL values. Since the correlation between peaks and area under the curve relative values were very high (r = 0.91), only the area under the curve (AUC) relative (delta) values will be reported here.

The relationship between PRL values and the psychophysiological data were assessed by Pearson product-moment correlation coefficients (two-tailed), and performed using Statistica (4.5) for Windows (Statsoft Inc 1993, Statsoft, Tulsa, USA).

RESULTS

The mean P300 amplitude was 9.5 μV at Cz and 10.1 μV at Pz, with values between 0.6 and 23.5 at Cz, and between 2 and 21.9 at Pz. Mean P300 latency was 340 ms at Cz (SD = 31.7), and 342 ms at Pz (SD = 31.8). The reaction time (RT) ranged from 219 to 663 ms, with a mean of 366 (SD = 110). PRL AUC response to flesinoxan ranged from 8655 to 150300 with a mean of 45259.6 mIU min/mL (SD = 32523.7).

Significant negative relationships were found between the P300 amplitude and the PRL values (r = –40, P = 0.007 at Cz; r = –0.49, P = 0.001 at Pz; *figure 1*). In contrast, no relationships existed between PRL values and both P300 latency (r = –0.16 at Cz and r = –0.17 at Pz), and reaction time (r = 0.08).

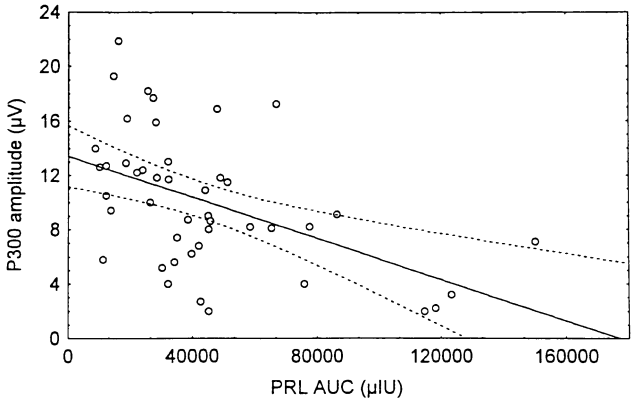

Figure 1. Relationship between P300 amplitude recorded at Pz and PRL area under the curve (AUC) values among 45 depressed patients (r = –0.49, P = 0.001).

DISCUSSION

The main finding of the present study is a negative association between P300 amplitude and serotonergic activity in depressed patients. Since flesinoxan stimulates very selectively post-synaptic 5-HT1A receptors, our results indicate that P300 amplitude could be modulated by the sensitivity of 5-HT1A receptors at the post-synaptic level. The lack of relationship between PRL response to flesinoxan and both P300 latency and reaction time could suggest that the serotonergic system (5-HT1A) does not play a major role in stimulus time evaluation nor in motor response selection in depressed patients. Since the same findings have been observed in healthy subjects, the present results could not be attributed to the depressive status of the patients.

The implication of the serotonergic system in the generation and/or modulation of P300 amplitude has not been well documented and inconsistent results have been reported. In contrast to our results, a positive relationship has been reported between P300 amplitude and the CSF concentration of the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in demented patients [33]. The opposite results of these two studies could be explained by different factors. First of all, the flesinoxan challenge test assesses exclusively the sensitivity of 5-HT1A receptors, and not whole serotonergic activity as reflected by the CSF concentration of 5-HIAA. Moreover, the subjects and the experimental paradigms differed between the two studies. Nevertheless, since several reports have reported inconsistent results in the literature [26, 31-35], the present findings could be attributed to the selectivity of the flesinoxan of 5-HT1A receptors. Thus, the implication of the results of the present study are limited.

In the present study, a decrease of serotonergic function is associated with a high P300 amplitude. In fact from a clinical point of view, high P300 amplitude has been described in antisocial impulsive behavior [38], and in depressed patients characterized by impulsivity [20, 21]. On the other hand, several lines of evidence have suggested an association between low sero-

tonergic activity (and possibly 5-HT1A function) and impulsivity [39-41] or low harm avoidance [42]. Thus, a possible clinical implication of the present results could be to orient patients exhibiting a high P300 amplitude to serotonergic agents. In contrast, depressed patients with low P300 amplitude could be treated by other antidepressant agents. In fact, low P300 amplitude had been demonstrated in association with a decrease of dopaminergic activity [30].

The lack of a relationship between P300 latency and serotonergic activity is surprising since the influences of serotonin on cognition have been reported in many studies [43-45], and that P300 latency is delayed in high cognitive demand tasks as well as in aging and dementia [2, 46]. Again, the lack of an association between reaction time and serotonergic activity is surprising since recent evidence has suggested that serotonin re-uptake inhibitor drugs shorten reaction time in healthy volunteers [47]. However, the selectivity of flesinoxan on 5-HT1A receptors, as well as the simplicity of the protocol used in the present study, could be responsible for the negative results.

In conclusion, this study supports a role for serotonin, and more particularly for 5-HT1A activity, in the neurobiological modulation of P300 amplitude. From a clinical point of view, these findings suggest the interest of P300 amplitude as a possible indicator towards specific antidepressant treatment in depression. However, since the assessment of the serotonergic function in the present study was indirect, and that several reports have provided inconsistent results in the literature, this study could not be considered to provide definitive proof for the serotonergic modulation of P300 amplitude.

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