

Serotonergic modulation of the P300 event related brain potential

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ABSTRACT

While dopaminergic, noradrenergic, cholinergic and gabaergic effects on the P300 component of the human event-related brain potential have been largely described, little is known about serotonergic influence. Therefore, we investigated the relationship between P300 and serotonergic activity as reflected by prolactin (PRL) response to flesinoxan, a 5-HT_{1A} full agonist, among 28 normal subjects. Results showed a significant negative correlation between P300 amplitude and PRL response to flesinoxan ($r = -0.47$, $p = 0.01$ at Cz; $r = -0.45$, $p = 0.01$ at Pz). In contrast, both P300 latency and reaction time were not related to endocrine response. This study supports a role for serotonin in the neurobiological modulation of P300 amplitude. Clinical implications of these results are considered.

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, and it is particularly interesting to the study of cognitive processes in normal subjects and in psychopathology (Donchin and Coles, 1988; Picton, 1992). P300 reflects memory updating (Donchin and Coles, 1988), or context closure (Verleger, 1988), and perhaps represents the transfer of relevant information to consciousness (Picton, 1992). P300 amplitude is related to stimulus probability, stimulus significance, task difficulty, motivation, vigilance (Johnson, 1986; Sommer and Matt, 1990), and P300 latency is mainly influenced by task complexity, but not response difficulty (McCarthy and Donchin, 1981; Smulders *et al.*, 1995), and reflects the stimulus time evaluation (Kutas *et al.*, 1977).

The identification of the brain structures and neurotransmitters responsible for the generation and/or modulation of P300 will contribute to a clearer understanding of its functional significance. In this context, psychopharmacological studies have provided some interesting insights into the underlying neurobiological substrate of P300. Cholinergic effects on P300 amplitude and latency have been largely described, with a decrease of P300 amplitude and increased latency after injection of an anticholinergic agent (i.e. scopolamine) and the opposite results with cholinergic drugs (i.e. physostigmine) (Hammond *et al.*, 1987; Meador *et al.*, 1989; Meador, 1995). The influences of noradrenergic, dopaminergic and gabaergic systems have been reported in many studies (Jonkman *et al.*, 1997; Swick *et al.*, 1994; Semlitsch *et al.*, 1995; Hansenne *et al.*, 1995). Clonidine (an alpha-2-noradrenergic agonist) decreases P300-like potential in monkey (Swick *et al.*, 1994), and methylphenidate dopaminergic agonist enhances P300 amplitude in attention-deficit hyperactivity disorder children (Jonkman *et al.*, 1997). Moreover, the benzodiazepine alprazolam reduces P300 amplitude in normal subjects (Semlitsch *et al.*, 1995).

However, few data are available about the serotonergic modulation of P300 amplitude and latency. Pritchard *et al.* (1986) found no significant effect of fenfluramine serotonergic antagonist on P300 component. Meador *et al.* (1989) reported no significant influence of the antiserotonergic agent methysergide on P300. However, Ito *et al.* (1990) 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, recent studies have reported synergistic effects of combined antiserotonergic (i.e. fenfluramine) and anticholinergic (i.e. scopolamine) agents on P300 latency (Meador, 1995).

Neuroendocrine strategy may provide an indirect index of central neurotransmission. Recently, our group have developed a serotonergic challenge test using flesinoxan (Pitchot *et al.*, 1995; Hansenne *F*, 1997). Flesinoxan is a highly potent and selective 5-HT_{1A} agonist inducing a significant and dose-dependent release of prolactin (PRL) in normal subjects.

The aim of the present study was to investigate the relationship between serotonergic activity and P300. More precisely, we assessed the relationship between the P300 component and the 5-HT_{1A} activity reflected by the PRL response to flesinoxan challenge test in normal subjects.

Methods

The study was conducted in 28 normal subjects who were not familiar with psychophysiological methods. The sample comprised 11 men and 17 women with a mean age of 39.2 years (SD = 9.8). The subjects were free of medical illness, as evidenced by clinical examination, past history and electrocardiogram (ECG). The protocol was approved by the Ethical Committee of the University of Liège Medical School and all subjects gave their informed consent.

The P300 event-related potential recording was performed in a sound-attenuated room. The subjects were tested until a total of 150 trials were obtained, after rejecting trials for eye movement or other artifact. 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 per cent (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 amplitude and latency were measured as the difference in voltage between baseline and the higher point between 280 and 450 ms after the stimulus. P300 trials contaminated by blinks or large amplitude eye movements were automatically excluded by using a 50 μ V rejection criterion. Analysis of 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 right forehead for ground. All sites were cleaned with acetone and abraded to maintain a resistance below 5 k Ω . 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 presentation activity).

The flesinoxan challenge test was performed in the same week as the P300 recording. An indwelling catheter was inserted into a subject's forearm vein at 08:30. Blood samples of 10 ml were collected 30 min before and immediately before the injection of flesinoxan at 09:30. Successive blood samples were collected 15, 30, 60, 90 and 120 min after the injection. Flesinoxan (1 mg/70 kg body weight), diluted in saline solution to obtain 20 ml, was injected intravenously over 10 min. Blood samples were centrifuged within 2 h and serum immediately frozen and kept at -18°C until analysis.

PRL was measured by radioimmunoassay (RIA) with intra- and inter-assay coefficients of variation of 10.0 ± 10.0 per cent 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 the injection and the last blood sample. Analyses were performed using relative (Δ) PRL values. Since the correlations between peaks and area under the curve relative values were very high ($r = 0.91$), only the peak relative (Δ) values will be reported here.

The relationship between PRL values and the psychophysiological data were assessed by Pearson Product-Moment correlation coefficients, and performed using Statistica (4.5) for Windows (Statsoft Inc, 1993).

Results

The mean P300 amplitude was 10.2 μV at Cz and 10.1 μV at Pz with values between 2.1 and 18.4 at Cz and between 2.5 and 15.4 at Pz. Mean P300 latency was 324 ms at Cz (SD = 18.4), and 323 ms at Pz (SD = 18.7). The reaction time (RT) ranged from 203 to 367 ms with a mean of 284. PRL response to flesinoxan ranged from 20 to 2396 with a mean of 550 mIU/ml (SD = 579.5).

Significant negative relationships were found between P300 amplitude and PRL values ($r = -0.47$, $p = 0.01$ at Cz; $r = -0.45$, $p = 0.01$ at Pz) (Figure 1). In contrast, the relationships between PRL values and both P300 latency ($r = 0.14$ at Cz and $r = 0.21$ at Pz) and RT ($r = 0.26$) were not statistically significant.

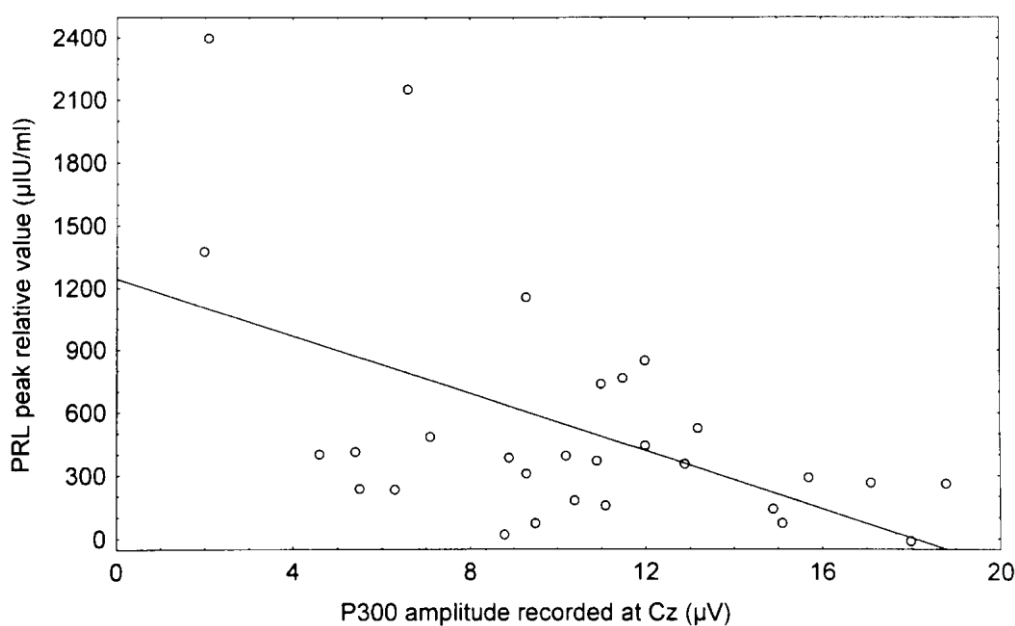


Figure 1. Relationship between P300 amplitude recorded at Cz and PRL response to flesinoxan among 28 normal subjects ($r = -0.47$, $p = 0.01$)

Discussion

By using a neuroendocrine challenge test with flesinoxan, we found a negative association between the serotonergic activity and P300 amplitude in normal subjects. Since flesinoxan stimulates very selectively post-synaptic 5HT1A 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 does not play a major role in stimulus time evaluation nor in motor response selection.

The implication of the serotonergic system in the generation and/or modulation of P300 amplitude has not been well documented. 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 (Ito *et al.*, 1990). The opposite

results of these two studies could be explained by different reasons. First, our flesinoxan challenge test assesses exclusively the sensitivity of 5-HT_{1A} receptors, and not whole serotonergic activity as reflected by the CSF concentration of 5-HIAA. Second, the subjects differed between the two studies (normal versus demented patients), and many studies have reported an altered P300 amplitude and latency in dementia (Polich, 1991). Finally, the experimental paradigms were different: reaction time in the present study versus count in (Ito *et al.*, 1990).

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 (Raine and Venables, 1988), and several lines of evidence have suggested an association between low serotonergic activity (and possibly 5-HT_{1A} function) and impulsivity (New *et al.*, 1997; Coccaro *et al.*, 1989, 1990). Thus, a clinical interest of the present results is a possible link between P300 amplitude and impulsivity. Concerning depressive disorder, another indirect implication of the results is in identifying a subgroup of patients characterized by a high P300 amplitude and to treating them preferentially with drugs which act on 5-HT system. Finally, since P300 amplitude reflects memory updating (Donchin and Coles, 1988), these results support an implication of serotonin in cognitive processes like memory.

The lack of relationship between P300 latency and serotonergic activity is surprising, since the influences of serotonin on cognition have been reported in many studies (Cassel and Jeltsch, 1995; Harder *et al.*, 1996; Buhot, 1997), and that P300 latency is delayed in high cognitive demand tasks and in aging and dementia (Picton, 1992; Polich, 1991). Again, the lack of an association between reaction time and serotonergic activity is surprising since recent results have suggested that serotonin reuptake inhibitor drugs shortens reaction time in healthy volunteers (Hasbroucq *et al.*, 1997). However, the simplicity of the protocol used in the present study could be responsible for the negative results.

An important limitation of the present study is the selective effect of flesinoxan on the 5-HT_{1A} receptors. Indeed, the pharmacologically-induced PRL response to flesinoxan is an indirect index of serotonergic neurotransmission and could involve areas of the brain having nothing to do with the generation of P300. However, the neuroendocrine effects induced by flesinoxan challenge are centrally mediated via 5-HT_{1A} receptors that are found on cell bodies and dendrites of serotonergic neurons in the raphe nuclei (somatodendritic autoreceptors) and also in many brain areas where they occur as postsynaptic receptors (Groenink and Olivier, 1998). On the other hand, anatomical studies have provided some evidence about the existence of multiple P300 generators, including medial temporal lobe, frontal lobes, locus coeruleus, thalamus and parieto-temporal junction (Johnson, 1993).

In conclusion, this study supports a role for serotonin in the neurobiological modulation of P300 amplitude. However, for a more definitive answer on the precise role of serotonergic neurotransmission on P300, future studies should be conducted using agonist and antagonist serotonergic agents.

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