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Short communication

Catecholaminergic function and P300 amplitude in major depressive disorder (P300 and catecholamines)

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Abstract

The neurobiology of P300 is still a subject of controversy. P300 amplitude appears to be modulated by multiple neurotransmitter systems, especially dopaminergic, noradrenergic as well as cholinergic and GABAergic. In this study, we investigated the relationship between P300 amplitude and catecholaminergic neurotransmission as assessed by the growth hormone (GH) response to clonidine and apomorphine challenges in 20 major depressive patients. Results showed a correlation of P300 amplitude with the apomorphine test ($r = 0.54$; $P = 0.01$), but not with the clonidine test ($r = 0.22$; NS). This study supports a role for dopamine in the neurobiological modulation of P300 amplitude.

Keywords: P300; Neurobiology; Catecholamine; Clonidine test; Apomorphine test; Major depressive disorder

1. Introduction

The neurobiology of the event-related brain potential P300 is still a subject of controversy. Psychopharmacological studies, in conjunction with invasive anatomical approaches, have provided preliminary insights into the underlying neurobiological substrate of P300 (Callaway, 1991; Halgren et al., 1986). The locus coeruleus and the noradrenergic, cholinergic and dopaminergic systems seem to play an important role in the generation and the modulation of P300 (Duncan and Kaye, 1987; Meador et al., 1989; Pineda et al., 1991).

The relation between brain monoamine metabolites and brain potentials constitutes another approach to the study of the neurobiological substrates of P300. A recent study in demented patients showed a relationship between P300 amplitude and the concentrations of 5-hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin, but not with homovanillic acid (HVA), a metabolite of dopamine, in the cerebrospinal fluid (CSF) (Ito et al., 1990).

Neuroendocrine strategy may provide an indirect index of central neurotransmission. The release of anterior pituitary hormones depends on hypothalamic releasing factors controlled by neurotransmitters, such as norepinephrine and dopamine. In particular, clonidine stimulates growth hormone (GH) secretion through postsynaptic alpha-2-adrenergic receptors in the hypothalamus, whereas apomorphine stimulates GH by means of dopaminergic receptors. Then GH response to clonidine and to apomorphine can reflect respectively noradrenergic and dopaminergic central neurotransmission.

Many studies have shown a blunted response to both clonidine and apomorphine neuroendocrine tests in depression (Ansseau et al., 1988). Since P300 amplitude is also reported to be altered in depressive patients (Thier et al., 1986) the aim of this study was to investigate possible relationships between P300 amplitude and both noradrenergic and dopaminergic systems as assessed by GH response to clonidine and apomorphine challenge tests in major depression.

2. Methods

The study was conducted in 20 DSM-III-R major depressive inpatients admitted to the Psychiatric Unit of the University Hospital of Liège, Belgium. The sample comprised 10 men and 10 women with a mean age of 40.4 years (S.D. = 10.3 years). All patients had a score of at least 18 at the 17-item Hamilton depression scale and were free of medical illness, evidenced by clinical examination, history, EKG, EEG, chest X-ray, and routine laboratory tests.

Psychophysiological recording was performed at the end of a drug-free period of at least 2 weeks. The subjects were sitting in a sound-attenuated room. For the P300 paradigm, a series of 150 auditory stimuli was presented with interstimulus intervals varying between 2 and 4 sec. According to the classic oddball paradigm, 80% of the stimuli (frequent) were tones of 1470 Hz, 64 dB and 40 msec duration. The other 20% (rare) were tones of 900 Hz, 64 dB and 40 msec 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 the baseline and the higher point between 250 and 550 msec after the stimulus.

The EEG was recorded using silver-silver chloride disc electrodes attached at Cz and Pz using linked earlobes for reference and right

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forehead for ground. All sites were cleaned with acetone and abraded to maintain resistance below 3 kΩ. EOG was recorded from above the left eye. Amplifier gains were set at 10,000, with a bandpass of 0.05–30 Hz, and digitized at 250 samples/sec for 800 msec epochs (of which the first 200 msec were prestimulus activities).

Clonidine and apomorphine challenge tests were performed in the same week as the P300 recording, at 1 day intervals, both after an overnight fast using a procedure previously described (Ansseau et al., 1988). Briefly, at 07:00, a butterfly needle was inserted into a forearm vein. Blood samples of 10 ml were collected 20 min before and immediately before the injection of clonidine or apomorphine at 08:00. Successive blood samples were collected 20, 40, 60 and 120 min after injection. Clonidine (0.15 mg), diluted in saline to obtain 20 ml, and apomorphine (0.5 mg), diluted in saline to obtain 0.5 ml, were injected respectively intravenously in 10 min and subcutaneously.

GH was measured with a double antibody radioimmunoassay with intra-assay and inter-assay coefficients of variation of respectively 13.3 ± 4.7% and 14.8 ± 9.6% and a detection limit of 0.2 ng/ml. GH responses to clonidine and apomorphine were assessed by peak values following injection as well as by the area under the curve (AUC) situated between injection (t0) and the last blood sampling (t120). Analysis was performed using absolute GH values as well as differences related to basal level (relative values). Since the correlations between peak and AUC absolute and relative values were very high ($r > 0.98$), only the correlations using peak absolute values are reported here. Pearson's correlation coefficients were used to relate P300 and the two neuroendocrine challenge tests.

3. Results

Individual neuroendocrine and psychophysiological results are provided in Table 1. GH peak response to clonidine ranged from 0.10 to 21.60 with a mean value (S.D.) of 4.37 ng/ml (6.3), and GH peak responses to apomorphine ranged from 0.90 to 17.60 with a mean value (S.D.) of 5.73 ng/ml (4.23). P300 amplitudes ranged from 0.20 to 23.50 with a mean value (S.D.) of 10.09 μV (6.15) at Cz and ranged from 3.30 to 21.90 with a mean value (S.D.) of 9.6 μV (5.59) at Pz, and mean latencies of 335 msec ± 25 for Cz derivation and 338 ± 25 for Pz. Reaction time ranged from 309 to 645 with a mean value (S.D.) of 435.3 msec (96.7).

GH responses to apomorphine were positively correlated with P300 amplitude recorded at Cz ($r = 0.51$, $P = 0.02$), and Pz ($r = 0.54$, $P = 0.01$). In contrast, no significant relationships were exhibited between GH response to clonidine and P300 amplitude ($r = 0.16$, NS at Cz, and $r = 0.22$, NS at Pz).

P300 latency was not related to the GH response to either clonidine ($r = -0.30$, NS at Cz, $r = -0.28$, NS at Pz) or apomorphine ($r = 0.18$, NS at Cz, $r = 0.23$, NS at Pz). Moreover, reaction time (RT) did not exhibit any significant relationship with GH response to either clonidine ($r = -0.14$, NS) or apomorphine ($r = -0.09$, NS).

4. Discussion

The results of the present study show a positive relationship between dopaminergic activity, as assessed by the GH response to apomorphine and P300 amplitude in depressive patients. However, noradrenergic activity, as reflected by the GH response to clonidine, was not related to P300 amplitude in our sample. Moreover, both P300 latency and RT did not show any relationship with clonidine and apomorphine tests.

Several limitations in the design of this study should, however, be acknowledged. First, no controls were investigated. The variables, P300 amplitude and GH secretion, may vary without interdependence, if both measures are differently influenced by depression. Therefore, similar studies in controls as well as in other psychiatric disorders are clearly needed to validate our conclusions. Second, the pharmacologically induced GH response is an indirect index of neurotransmission and may well involve areas of the brain having nothing to do with the generation of P300. A more direct approach using the effects of drug treatment yielded mixed results for P300 latency following treatment with L-DOPA (Prasher and Findley, 1991; Stanzione et al., 1991). Third, the specificity of agents such as clonidine and apomorphine can be discussed. Clonidine exhibits some anticholinergic effects and an inverse relation has been observed between GH response to L-DOPA and to apomorphine, suggesting that mechanisms other than dopamine might be involved (Rotrosen et al., 1976); further, the GH response to apomorphine can be antagonized

Table 1
Individual values of the sample

	Sex	Age	P300 amplitude (μV)		P300 latency (msec)		RT (msec)	GH peak (ng/ml)	
			Cz	Pz	Cz	Pz		CLO	APO
1	m	41	17.7	17.2	380	380	408	2.5	5.9
2	m	21	16.9	20.3	332	309	309	0.1	9.1
3	m	47	19.3	23.5	388	343	343	0.2	9.2
4	m	22	7.4	9.8	312	360	360	16.5	4.4
5	f	37	12.3	8.2	328	348	348	0.3	4.3
6	f	34	3.3	9.6	324	326	421	1.5	4.0
7	f	51	4.3	0.2	328	328	547	2.1	0.9
8	f	42	4.2	4.1	290	296	332	0.7	4.8
9	m	35	4.7	2.3	360	376	435	1.6	4.9
10	f	38	8.2	7.6	312	312	385	8.0	3.0
11	f	40	3.7	4.4	320	336	574	1.4	5.5
12	f	50	10.1	9.1	360	360	645	1.3	2.7
13	f	42	11.2	11.6	312	316	376	1.8	1.0
14	m	45	8.6	10.9	352	364	398	1.4	11.4
15	f	48	4.1	5.3	320	320	514	1.2	1.8
16	m	54	6.0	4.5	332	336	621	0.7	6.5
17	m	33	7.4	9.8	326	332	420	16.5	4.4
18	f	35	21.9	18.5	312	320	438	21.6	17.6
19	m	60	9.1	10.5	360	360	458	7.6	11.8
20	m	63	12.5	14.4	348	348	374	0.5	1.4

RT = reaction time; GH = growth hormone; CLO = clonidine test; APO = apomorphine test.

by diazepam, atropine, and CCK peptides, emphasizing the difficulty of identifying specific neurotransmitter mechanisms. Fourth, our study using the standard oddball task was unable to differentiate between P300 sub-components (P3a, P3b, positive slow wave) which are likely to be differentially influenced by the various monoamine transmitter systems since they seem to differ with respect to stimulus- (noradrenergic?) or response-related (dopaminergic?) information processing. It should be noted, however, that the majority of the studies concerning the neurobiology of P300 only refer to the P3b sub-component.

This study investigated the relationship between psychophysiological and neuroendocrine parameters in depressed patients before antidepressant treatment. Similar data collected after antidepressant treatment could be of interest. However, the GH responses to clonidine and apomorphine appear to behave as "trait markers" of depressive illness. Indeed, depressive patients tested after complete remission of their episode still exhibit a blunted GH response (Mitchell et al., 1988).

P300 amplitude appears to be modulated by multiple neurotransmitter systems, especially dopaminergic, noradrenergic as well as cholinergic and GABAergic. A large body of findings favours a role for dopaminergic systems in the modulation of P300 amplitude (Callaway, 1991). For example, dopaminergic agonists like methylphenidate enhance P300 amplitude in normal subjects as well as hyperkinetic children (Klorman and Brumaghim, 1991) whereas dopaminergic antagonists like flupentixol reduce P300 amplitude in normal subjects (Rösler et al., 1985). Several negative results have, however, been reported (Glover et al., 1988; Ito et al., 1990). Our results, using neuroendocrine challenge tests, support a role for dopamine in the generation and modulation of P300.

Noradrenergic activity, and more specifically the integrity of the locus coeruleus-noradrenergic system, appears to be critical for the generation and the modulation of P300-like potentials recorded in monkeys (Pineda et al., 1991). The results of the present study do not confirm the implication of the noradrenergic system in the generation and the modulation of P300. These negative findings may depend on the limited range of GH responses to clonidine in our sample of depressive patients. These neuroendocrine data confirm the blunted GH response to clonidine reported in the large majority of depressed patients (Ansseau et al., 1988). For a more definitive answer on the role of noradrenergic neurotransmission in the modulation of P300 amplitude, the clonidine test should be performed in healthy subjects.

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