Eur. J. Psychiat. Vol. 23, N.° 4, (225-233)
2009

Keywords: P300; *TaqI*-A1; Alcoholism; Event-related potentials; Abstinence; Endophenotype.

P300 in alcohol dependence: Effects of TaqI-A genotype

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ABSTRACT – *Background and Objectives*: TaqI-A polymorphism, related to D2 dopamine receptor (DRD2), and event-related P300 potentials have been considered markers of alcohol dependence. The effect of alcohol use variables and TaqI-A on P300 in a single sample have been hardly analysed previously. This study examined changes in P300 parameters after six months of abstinence in alcohol-dependent subjects classified by their TaqI-A genotype.

Methods: 102 men with alcohol dependence were studied at baseline and at 6 months of continued abstinence. P300 was recorded using an auditory paradigm. TaqI-A polymorphism was genotyped: 34.3% of sample was classified as A1[TaqI-A1/TaqI-A1and TaqI-A1/TaqI-A2] and 65.7% as A2 [TaqI-A2/TaqI-A2]. The association between P300 and TaqI-A and the correlation with age and alcohol consumption were considered.

Results: The abstinence period was not associated to differences in neither P300 latency ($F[1, 99] = 1.154$ $p = 0.285$) nor amplitude ($F[1, 99] = 1.453$, $p = 0.231$). A1 subgroup was related to a longer latency ($F[1, 99] = 5.055$ $p = 0.027$), an early abuse age onset ($F[1, 100] = 14.552$ $p < 0.001$) and close to be significant to an early dependence age onset ($F[1, 100] = 3.868$ $p = 0.052$). Other drinking pattern variables were not associated to p300 measures. Family history for alcoholism and TaqI-A were not related ($X[1] = 0.327$ $p = 0.568$) and no association was found with p300 measures. Current age correlated positively with P300 latency ($F[1, 99] = 26.082$, $p < 0,001$) and negatively with amplitude ($F[1, 99] = 5.297$ $p = 0.023$). P300 amplitude was not influenced by alcohol use variables nor TaqI-A polymorphism.

Conclusions: P300 latency could be a biological marker of vulnerability to alcohol dependence related to TaqI-A1 polymorphism, irrespective of alcohol use variables.

Received: 11 November 2008
Revised: 10 August 2009
Accepted: 14 September 2009

Background and Objectives

P300 is a positive electrical deflection recorded at maximal amplitudes over the midline centroparietal scalp in response to rare attended events within a sequence of similar, but discriminate, stimuli. Although the functional significance of P300 is still debated[1, 2], its amplitude indexes the allocation of resources for the evaluation of stimuli and its sensitivity to instrumental manipulation indicates that it reflects a neural substrate of controlled information processing strategies[3].

Reduced P300 amplitude has been reported in many psychiatric disorders, including schizophrenia[4], depression[5], and alcoholism[6]. Various studies have related the presence of lower P300 amplitude or longer P300 latency with alcoholism[7-10]. Many of these studies have been carried out on children of alcoholics, so P300 alterations have been considered a genetic marker of vulnerability to alcoholism[11] or an endophenotype of an alcoholism subtype[12-15].

The brain dopaminergic system, which is centrally involved in reward and learning, has been widely studied in substance use disorders. The TaqI-A single-nucleotide polymorphism (SNP) (rs1800497) located near the 3´region of the dopamine D2 receptor gene (*DRD2*; chromosome 11q22–q23) has been considered a genetic marker of alcoholism[16-19]. TaqI-A SNP consists of the substitution of C > T, also called the A2 and A1 alleles, respectively, which affects a previously unidentified protein kinase gene called *ANKK1* (ankyrin repeat and kinase domain containing 1)[20]. There is no consensus about the role of the A1 allele and A1 genotype (heterozygous or homozygous for A1 allele) in addictive behaviour, but three meta-analyses have shown a robust association between TaqI-A SNP and alcoholism[21, 22].

In addition, the P300 wave has been associated with dopaminergic activity[23] and TaqI-A polymorphism has been associated with P300-wave changes.

The relationship between P300 wave and TaqI-A has been examined in non alcoholic sons of alcoholics. Longer latencies[24] and amplitude attenuation have been observed in A1 subjects[25, 26]. We found that A1 alcohol-dependent males had longer P300 latencies than A2 alcohol dependents and healthy controls[27].

Nonetheless, other studies have not found any differences between the A1 and A2 subgroups[28].

To further examine P300 capability to measure possible differences associated to the TaqI A1 and A2 subgroups and to ethanol toxic effect in alcohol dependence, we studied changes in the P300 wave after a period of abstinence in a sample of alcohol-dependent males classified by TaqI-A genotype. There have been published several works that had taken into account an abstinency period and the influence of family history for alcoholism on P300wave measures but not the TaqI A polymorphism[29-32].

Methods

This longitudinal study compared P300 amplitude and latency in a group of patients with alcohol dependence at two different times: (T1) baseline (after the detoxification period) and (T2) after six months of abstinence from alcohol. The sample was classified according to the presence or absence of TaqI-A1.

Study population

Our sample consisted of 115 adult males with alcohol dependence consecutively recruited in the Alcoholism programme of *Hospital Universitario 12 de Octubre*, of Madrid, Spain. The recruitment period included 66 days. Thirteen subjects relapsed in the 6 months after detoxification, so the group finally included had 102 patients. Sample demographic and clinical variables are summarised in Table 1.

The *inclusion criteria* were male patients, age range 18 to 65 years, who met DSM-IV criteria for alcohol dependence and had completed a detoxification period (at least 3 weeks), and who signed a written informed consent form. The *exclusion criteria* were the presence of other associated DSM-IV axis I psychiatric diagnoses, current neurologic disorder, auditory deficit, serious or chronic somatic illness unrelated to alcoholism and requiring treatment, presence of consanguinity or ancestors in the three previous generations that could cause genetic stratification. Alcohol abstinence was measured by patient self-reports, information gathered from families, ALT (alanine aminotransferase), AST (aspartate aminotransferase) and gamma-glutamyl-transpeptidase (GGT) values.

Instruments

A semi-structured interview was used to collect sociodemographic data. The Structured Clinical Interview (SCID)[33] from the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) was used to diagnose substance abuse or dependence. The Severity of Alcohol Dependence Scale (SADS) was also used.

Information about family history of alcoholism was collected by interviewing first-degree relatives. The subject was considered to have positive family antecedents of alcoholism if there was a first-degree relative with a history of alcohol dependence. When it was not possible to interview relatives the diagnosis was made by applying the Research Diagnostic Criteria-Family History (RDC-FH).

Genotyping

Genotyping was performed using a polymerase chain reaction (PCR), as described elsewhere[34]. Twenty microlitres of the PCR product were digested with 2 units of TaqI restriction enzyme (Boehringer Mannheim) for 4 hours at 65°C. The resulting fragments were 310, 185 and 125 bp for the A2/A1 genotype, 185 and 125 bp for the A1/A1 genotype and 310 bp for the A2/A2 genotype. Patients were grouped according to the presence of the *TaqI*-A1 allele (n = 35, A1(+): genotypes *TaqI*-A1/*TaqI*-A1 and *TaqI*-A1/*TaqI*-A2) or absence of the *TaqI*-A1 allele (n = 67, A2: genotype*TaqI*-A2/*TaqI*-A2).

Electrophysiologic recording and event-related potentials

The P300 study was carried out in the Event-Related Potentials (ERP) Unit of *Hospital Universitario 12 de Octubre* after verifying the absence of any auditory deficit in patients by tonal audiometry. A *MED-ELEC* brand *Sapphire* model ERP device, type 2, was used. The bioelectric cerebral activity of long latency was registered after an unexpected and infrequent stimulation (*odd-ball*). The stimulation was a high-pitched (2000 Hz, 70dB) aleatory target sound with a presence of 10% in a sequence of regular sounds (1000 Hz, 70 dB). Time interstimuli was 2 sec for regular sound. Both regular and randomised sounds had a duration of 100 ms.

Table 1
Clinical and demographic characteristics of patients subtypes with alcohol dependence based on A1 and A2 allele classification

	A1 group n = 35	A2 group n = 67	Total (n = 102)	ANOVA	
Age, mean (SD)	39.89 (10.17)	42.94 (9.96)	41.89 (10.08)	F[1, 100] = 2.133	p = 0.147
Age at onset of alcohol abuse criterion, mean (SD)	19.26 (2.89)	24.31 (7.54)	22.58 (6.77)	F[1, 100] = 14.552	p < 0.001
Age at onset of alcohol dependence criterion, mean (SD)	27.57 (7.90)	31.25 (9.49)	29.99 (9.10)	F[1, 100] = 3.868	p = 0.052
Ethanol intake grs/ occasion, mean (SD)*	2.43 (1.71)	2.28 (1.44)	2.33 (1.53)	F[1, 100] = 0.199	p = 0.657
Ethanol intake grs/ week, mean (SD)**	14.65 (12.38)	13.35 (9.92)	13.79 (10.76)	F[1, 100] = 0.294	p = 0.589

* Grs/ocassion in grs/100
** Grs/week in gr/100

Table 2
P300 latency and amplitude measures and repeted measures ANOVA

	Preabstinency		Postabstinency		Abst Effect**	Abst*TaqI Effect	Abs*Age Effect	Age Effect	TaqI Effect***
	A1	A2	A1	A2					
Latency	369.54 (22.47)*	366.67 (25.38)	366.29 (20.13)	358.34 (22.70)	L = 0.988**** F[1, 99] = 1.154* p = 0.285	L = 0.995 F[1, 99] = 0.457 p = 0.501	L = 0.974 F[1, 99] = 2.691 p = 0.104	F[1, 99] = 26.08 p < 0.001	F[1, 99] = 5.06 p = 0.027
Amplitude	17.58 (2.04)	17.53 (2.06)	17.81 (1.86)	17.50 (2.62)	L = 0.986 F[1, 99] = 1.453 p = 0.231	L = 0.996 F[1, 99] = 0.424 p = 0.516	L = 0.982 F[1, 99] = 1.773 p = 0.186	F[1, 99] = 5.297 p = 0.023	F[1, 99] = 0.033 p = 0.855

* Average (sd)
** Represents within subjects effect
*** Represents between subjects effect
**** Statistic Wilks' Lambda

During the test, the patient was asked to remember the number of infrequent (1000 Hz) stimuli. The EEG was recorded at parietal (Pz) scalp location because of the highest amplitude distributed[35].

The reference electrode was placed on the nose tip, and the ground electrode on the forehead. The high-pass filter was 0,1 Hz and the low-pass, 30 Hz. The epochs were recorded from 100 ms prestimuli to 800 ms later. Any epochs with voltage above 70 were considered artifacts and rejected.

Statistical analysis

Analysis of variance has been used to test quantitative variables between TaqI-A subgroups (A1 vs. A2). Possible association between TaqI-A and family history for alcoholism were tested with Chi-square.

Differences between P300 variables at preabstinency versus postabstinency have been analysed using a repeated measures ANOVA. We have considered the abstinency period like within subject effect and TaqI-A like between subjects effect. Possible covariates were studied in the ANOVA.

The SPSS statistical package version 12 was used for analysis.

The Hardy–Weinberg equilibrium was satisfied in our sample ($c2 = 0.24$, $df = 1$, $p= 0.62$).

Results

The A1 subgroup (n = 35, 34.3%) had an age average of 39.89 (sd = 10.17) years, while it was 42.94 (sd = 9.96) for A2 subgroup (n = 67, 65.7%). A1 was related to a more severe drinking pattern, like an earlier abuse age onset [$F[1, 100] = 14.552$ $p < 0.001$] and almost significantly to an earlier dependence age onset ($F[1, 100] = 3.868$ $p = 0.052$]. Interestingly family history for alcoholism was not related neither to TaqI-A ($X[1] = 0.327$ $p = 0.568$) neither to alcohol dependence characteristics.

Regarding age and drinking pattern characteristics (see table 1), there were not differences between 102 and 115 patients sample.

The effect of the abstinence period on this alcoholic patients sample has not generate significant differences on neither p300 wave latency ($L = 0.988$ $F[1, 99] = 1.154$ $p = 0.285$) nor the amplitude ($L = 0.986$ $F[1, 99] = 1.453$, $p = 0.231$). However TaqI-A effect was statistically significant on latency. Hence, A1 subgroup showed higher latency values than A2 subgroup [$F[1, 99] = 5.055$ $p = 0.027$]. Amplitude results were irrespective of TaqI-A.

Age influenced in a significant manner to both latency and amplitude. Patients with a higher age have a longer latency ($F[1, 99] = 26.082$ $p < 0.001$) and a minor amplitude ($F[1, 99] = 5.297$ $p = 0.023$). None of the rest of variables were statistically significant.

Discussion

Our study supports that P300 wave measures are not influenced by a six months abstinence period. Others published works have offered similar data[30-32]. It is interesting that these authors arrive to the same conclusion from works methodologically different and taking into account very different sobriety length periods.

Chronic alcohol intake have been extensively associated to P300 amplitude reduction. However we did not find any correla-

tion between the amount of alcohol intake in the previous drinking period and changes in either P300 amplitude or latency, similar to other published results[31]. A possible explanation for this could be the presence of an idiosyncratic vulnerability to the ethanol, what has been sustained by some authors[36]. In other words, once subjects reach a certain level of alcohol intake, P300 values may not modify in a significant manner with a higher consumption what may obscure the association. Another possible explanation of the absence of correlation may be the presence of different metabolisation rates.

The absence of changes in P300 measures after an abstinence period and its lack of association with alcohol intake amount and with time consumption suggest a minor roll of the toxic effect in the alcohol dependence, idea sustained for different authors[16, 22]. An alternative explanation could be that chronic alcohol intake has a not reversible effect on P300 measures[31].

The association between TaqI-A polymorphism and P300 wave measures had been studied by several authors, mainly in non alcoholic young population. Considering that P300 performance has been associated to disrupted sensory gating[37, 38] and to dopamine dysfunction[39, 40], it could be hypothesised that TaqI-A is involved in dopamine disorders underlying P300 neurophysiologic substrates. It is congruent with it that the A1 genotype had been related to a hipodopaminergic state, with a reduced number of DRD2 in striatum[41]. Hence, dopamine dysfunction could contribute both to P300 wave changes and to a dysfunctional reward system. An earlier alcohol abuse age and others manifestations of a more severe alcoholism have been hypothesised to be consequences of it[42].

In this sample, TaqI-A1 subgroup is associated to a P300 longer latency, to an earlier alcohol abuse age onset and is very close to reach a statistic significant association with alcohol dependence age onset. It is similar to data from other studies[27, 42] and supports the presence of a genetic effect on alcoholism severity. Interestingly our study results show that family history for alcoholism is not related to neither TaqI-A polymorphism nor P300 measures nor drinking pattern variables. There are some published works that are congruent with this[43-45] and others that suggest a positive association among these variables[42, 46, 47]. Possibly there are different genotypes not sufficiently represented in the sample that could be related to different metabolitation rates. The absence of differences in P300 amplitude related to DRD2 genotype in our study may be due to this reason or even to the absence of a genetic effect.

On the other hand, our results also showed that the association between the TaqI-A genotype and P300 measures might be obscured if the age effect is not controlled. Age effect is observed in young people and adults[25], which suggests that must be controlled statistically even if the sample contains young people. It is important to note that some studies have included young people in the belief that age effect on P300 values is unappreciable in people under 50 years old[48]. It has been published that differences on P300 amplitude from alcoholic descendant adolescents respect controls tend to reduce with age. The high average age in our sample could have contributed to reduce the genetic effect on P300 values associated to TaqI-A.

In summary, our results suggest that P300 event related potentials are an useful instrument to detect the genetic effect associated to TaqI-A polymorphism. Latency could be

related to fact of alcohol consumption (possibly not to intake amount), inheritance, and age. They support the hypothesis that this association is related to the function of the brain dopaminergic circuit.

The fact that the sample was small and did not include women are limitations of our study. A sample with a lower average age could reveal more marked differences in P300-wave latency between A1 and A2 subgroups. More studies are needed to clarify the influence of genetic factors, age and alcohol intake on P300-wave changes.

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