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Research report

The association between suicidality and serotonergic dysfunction in depressed patients

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ABSTRACT

The loudness dependence of auditory evoked potentials (LDAEP) has been proposed as a reliable indicator of central serotonin system activity in animal and some human studies. Since low central serotonergic activity is related to suicidality, it is possible that the LDAEP can be used to predict suicidality. The aim of the present study was to determine whether there is an association between suicidality and LDAEP in a depressed Korean population. Data from 38 depressive subjects (10 males, 28 females; mean age: 40.79 years) were analyzed. The subjects were divided into two groups: with prior suicide attempts (SA; $n=17$) and no prior suicide attempts (NSA; $n=21$). The LDAEP was evaluated by measuring auditory event-related potentials. Peak-to-peak N1/P2 amplitudes were calculated at five stimulus intensities, and the LDAEP was calculated as the slope of the linear-regression curve. The LDAEP values differed significantly between the SA and NSA groups. Depressed subjects with a history of suicide attempts seem to be characterized by large LDAEP values, indicating low serotonergic activity. The findings of the present study support the view that low serotonergic activity is related to the suicidality of depressed subjects. Thus, LDAEP, which can reflect serotonergic activity, may be a practical biological marker for suicidality.

1. Introduction

Suicide in patients with depression is a particularly unfortunate cause of death. One survey performed in U.S.A found an average of 420,000 annual emergency department visits for suicide attempts and self-inflicted injuries over a 16-year period (during 1993–2008); that is, 1.5 visits per 1000 of the population (Ting et al., 2012). Another study showed that a total of 14,441 unnatural deaths (suicide, traffic accidents, and homicide) were reported in 2010 in Germany, of which suicide death rates were by far the highest: 10,021 subjects (69.4%) died by suicide. It is therefore becoming crucial to find predictors of suicide risk (Lukaschek et al., 2012).

Whether biological markers for suicide attempts exist remains a matter of debate, but patients who have attempted suicide are found to have a variety of biological abnormalities (Bachus et al., 1997; Engstrom et al., 1999; Gross-Isseroff et al., 1998; Maris, 2002; Tripodianakis et al., 2000). Much of the available data suggests that central serotonergic activity plays a key role in the etiology and pathogenesis of suicide (Mann, 1998). Early evidence is based on the findings of postmortem brainstem specimens from depressive patients or suicide victims in the 1960s (Bourne et al., 1968; Shaw et al., 1967). It has been revealed that the cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid (5-HIAA), the main metabolite of serotonin, were reduced in suicide attempters (Asberg et al., 1986; Lester, 1995). There is also evidence that tryptophan hydroxylase, a rate-limiting enzyme in serotonin synthesis, is associated with suicide among depressive patients (Fudalej et al., 2010). Furthermore, the density of tryptophan-hydroxylase-immuno-reactive neurons in the dorsal raphe nucleus (Boldrini et al., 2005) and the expression of tryptophan-hydroxylase-2 (Bach-Mizrachi et al., 2006) were found to be higher in suicide attempters than in control groups. It was hypothesized that this reflects a 5-HT reduction. However, it is also possible that it reflect an upregulatory homeostatic response to deficient brain serotonergic neurotransmission. In addition, suicide attempters show not only a significant reduction of serotonin binding to its transporter in the ventral prefrontal cortex (Mann et al., 2000), but also a significant reduction of serotonin binding to the 5-hydroxytryptamine 2A receptor (Arora and Meltzer, 1989; Pandey et al., 2002). The prolactin response to fenfluramine may provide information about the suicidal risk. Fenfluramine facilitates the release of serotonin, and this leads to an increase in prolactin secretion. Depressive suicide attempters exhibit a more blunted response than depressive non-suicide attempters and normal healthy controls (Correa et al., 2000).

Based on these findings, measuring the activity of central serotonin function may help to predict the risk of suicide attempts in depressive patients. However, the methods used to measure central serotonergic activity have several practical

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limitations, such as taking a CSF sample or applying the fenfluramine challenge test for psychiatric outpatients. Therefore, simpler and noninvasive methods of determining the level of central serotonergic activity are needed.

The loudness dependence of auditory evoked potentials (LDAEP) is considered to be a reliable indicator of central serotonergic activity as indicated by preclinical/animal research. The LDAEP has been identified as being inversely associated with central serotonergic activity, with a weak LDAEP reflecting high serotonergic neurotransmission and vice versa (Buchsbaum and Silverman, 1968; Hegerl et al., 2001; Hegerl and Juckel, 1993; Juckel et al., 1999; Strobel et al., 2003). Patients with major depression who have a larger LDAEP before medication exhibited a favorable response to serotonergic antidepressants (Hegerl et al., 2001). In addition, a low pretreatment LDAEP was related to unresponsiveness and severe adverse effects in response to selective serotonin reuptake inhibitors (Park et al., 2012). Thus, measuring LDAEP appears to provide useful clinical information for predicting treatment responses relative to central serotonergic activity.

There have been many evoked-potential studies in depressive patients, but only a few have focused on electrophysiological aberrance associated with suicide attempts. A recent study provided electrophysiological evidence of even lower serotonergic activity (i.e., a larger LDAEP) in unmedicated depressive suicide attempters compared with their depressive counterparts who did not attempt suicide (Chen et al., 2005). In contrast, Juckel and Hegerl (1994) reported that patients with a history of suicide attempts exhibited a weak LDAEP, although the drug wash-out period allowed in that study was only 3days. The relationship between suicidality and the LDAEP remains a matter of controversy. Thus, in the present study, we explored differences in the LDAEP between unmedicated depressive patients with and without suicide attempts to test the serotonin dysfunction hypothesis. Our hypothesis was that depressive subjects with a history of suicide attempts would be characterized by large LDAEP values, indicating low serotonergic activity.

2. Subjects and methods

2.1. Subjects

In total, 38 outpatients who met the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria for major depressive disorder were enrolled in this study. The patients were recruited from psychiatric outpatients at Ilsan Paik Hospital (Republic of Korea) by a trained psychiatrist, and were not diagnosed with any additional mental disorders on axis I or axis II of the DSM-IV (including schizophrenia, substance abuse, bipolar disorder, anxiety disorder, eating disorder, sleep disorder, and borderline personality disorder) or major medical and/or neurological disorders. Patients taking psychotropic agents other than hypnotic drugs (benzodiazepine or zolpidem) were excluded. They were divided into two groups: with prior suicide attempts (SA; $n=17$) and no prior suicide attempts (NSA; $n=21$). Patients who had psychotic symptoms were also excluded in order to remove contamination from psychosis-related suicide attempts. Depression severity was assessed using the clinician-administered 17-item Hamilton Depression Rating Scale (HDRS-17) (Hamilton, 1960) and the self-reported Beck Depression Inventory (BDI) (Beck et al., 1961). Furthermore, the Beck Hopelessness Scale (BHS) (Beck et al., 1974), Barratt Impulsiveness Scale (BIS) (Patton et al., 1995), Hamilton Anxiety Scale (HAMA) (Maier et al., 1988), and Beck Scale for Suicidal Ideation (BSS) (Beck et al., 1979) were applied.

Written informed consent to participate was obtained from all patients before beginning the investigation.

2.2. EEG methods

The potential confounding influences of drugs were minimized by measuring the LDAEP before treatment with antidepressants or serotonergic agents. None of the patients had taken any psychotropic agent other than a hypnotic drug (benzodiazepine or zolpidem) for a minimum 3 months before visiting our hospital.

Each patient was seated in a comfortable chair in a sound-attenuated room. The auditory stimulation comprised 1000 stimuli with an interstimulus interval randomized to between 500 and 900 ms. Randomized tones of 1000 Hz and 80-ms duration (with a 10-ms rise and 10-ms fall) were presented at five intensities (55, 65, 75, 85, and 95 dB SPL) via headphones (MDR-D777, Sony, Tokyo, Japan). E-Prime software (Psychology Software Tools, Pittsburgh, PA, USA) generated the stimuli. EEG data were recorded from 32 scalp sites using silver/silver-chloride electrodes according to the international 10–20 system (impedance $<10\ k\Omega$), using an Auditory Neuroscan NuAmp amplifier (Compumedics USA, El Paso, TX, USA). Data were collected at a sampling rate of 1000 Hz, using a bandpass filter from 0.5 to 100 Hz. In addition, four electrodes were used to measure both horizontal and vertical electrooculograms.

Data were reanalyzed using Scan 4.3 software with a bandpass filter from 1 to 30 Hz, and ocular contamination was removed using standard blink-correction algorithms (Semlitsch et al. 1986). Event-related potential sweeps with artifacts exceeding 70 μV were rejected at all electrode sites. For each intensity and for each subject, the N1 peak (negative-most amplitude between 80 and 130 ms after the stimulus) and P2 peak (positive-most peak between 130 and 230 ms after the stimulus) were then determined at the Cz electrode.

The peak-to-peak N1/P2 amplitudes were calculated for the five stimulus intensities, and the LDAEP was calculated as the slope of the linear-regression curve.

2.3. Analysis

All statistical analyses were carried out using the SAS program (version 5.1) and all results are reported as mean ± SD values. The demographic, psychopathological, and LDAEP of the two groups were compared using Student's t test, the chi-square test, and correlation analysis (Pearson's correlation). Student's t test was used to know the mean value, the standard deviation value, and whether the difference between two groups was significant on age, LDAEP, and psychometric ratings of the patient groups. The chi-square test was used to know whether the difference between two groups was significant on gender. Correlation analysis using Pearson's correlation was carried to know clearly whether any significant correlation existed among gender, age, LDAEP, and psychometric ratings. In addition, logistic regression analysis was carried to adjust odds ratios for history of suicidal attempts by LDAEP when HAMA, HDRS, BDI, BIS, BHS were considered. All tests were two tailed, and group differences were tested at the $p<0.05$ level.

3. Results

In our sample of 38 patients with major depressive disorder, the age was 40.79 ± 15.12 years and the HDRS-17 score was 19.53 ± 4.83. There were no between-group differences in the gender distribution ($p=0.460$). These findings are summarized in Tables 1 and 2.

The age differed significantly between the SA group (33.35 ± 14.49 years) and the NSA group (46.81 ± 13.03 years; $p=0.005$). However, correlation analysis revealed no significant correlation between age and the LDAEP ($p=0.280$; Table 2). The LDAEP was significantly stronger in the SA group (1.45 ± 0.92) than in the