

Relationship between Serotonergic Dysfunction Based on Loudness Dependence of Auditory-Evoked Potentials and Suicide in Patients with Major Depressive Disorder

Young-Min Park[✉]

Department of Psychiatry, Inje University College of Medicine, Ilsan Paik Hospital, Goyang, Republic of Korea

The relationship between suicidality and the loudness dependence of auditory-evoked potentials (LDAEP) remains controversial. This article reviews the literature related to the LDAEP and suicide in patients with major depressive disorder, and suggests future research directions. Serotonergic dysfunction in suicidality seems to be more complicated than was originally thought. Studies of suicide based on the LDAEP have produced controversial results, but it is possible that these are due to differences in study designs and the smallness of samples. For example, some studies have evaluated suicide ideation and the LDAEP, while others have evaluated suicide attempts and the LDAEP. Furthermore, some of the latter studies enrolled acute suicide attempters, while others enrolled those with the history of previous suicide attempts, irrespective of whether these were acute or chronic. Thus, a more robust study design is needed in future studies, for example by evaluating the LDAEP immediately after a suicide attempt rather than in those with a history of suicide attempts and suicide ideation in order to reduce bias. Moreover, genuine suicide attempt, self-injurious behaviors, and faked suicide attempt need to be discriminated in the future.

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Key Words LDAEP, Major depressive disorder, Suicide, Suicide attempt.

INTRODUCTION

Individuals who have committed or attempted suicide are thought to have some biological abnormalities, but the biological markers for suicide remain unclear.¹ Most of the available evidence indicates that reduced serotonin plays an essential role in the pathogenesis of suicide.² Early studies showed that the cerebrospinal fluid (CSF) levels of 5-hydroxyindoleacetic acid (5-HIAA), which is the metabolite of serotonin and serotonin, were reduced in depressive patients and suicide victims.^{3,4} In addition, suicide attempters show not only a significant reduction of serotonin binding to its transporter in the ventral prefrontal cortex,⁵ but also a significant reduction of serotonin binding to the 5-hydroxytryptamine 2A receptor.^{6,7} Some genetic studies have found a relationship between serotonin-related genes and suicide.^{8,9} The prolactin

response in the fenfluramine test was found to be smaller in depressive suicide attempters than in depressive non-suicide-attempters and normal healthy controls.¹⁰ This means that serotonin activity was lower in depressive suicide attempters, since fenfluramine facilitates the release of serotonin that leads to an increase in prolactin secretion.

Serotonergic activity may help to predict the risk of suicide attempts in depressive patients. However, the methods, such as taking a CSF sample or applying the fenfluramine challenge test, are invasive and/or complicated for psychiatric outpatients. Therefore, easy and noninvasive methods of measuring the central serotonergic activity are needed. Both pre-clinical and animal research indicates that the loudness dependence of auditory-evoked potentials (LDAEP) is a reliable indicator of central serotonergic activity.^{11,12} The LDAEP has been identified as being inversely associated with central serotonergic activity, with a small LDAEP reflecting strong serotonergic neurotransmission.¹²⁻¹⁶ Patients with major depression who have a larger LDAEP before taking medication exhibited a more favorable response to serotonergic antidepressants.¹⁵ In addition, a small pretreatment LDAEP was related to unresponsiveness and severe adverse effects in response to selective serotonin-reuptake inhibitors.^{17,18} Thus, measuring the

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✉ Correspondence: Young-Min Park, MD, PhD

Department of Neuropsychiatry, Inje University College of Medicine, Ilsan Paik Hospital, 170 Juhwa-ro, Ilsanseo-gu, Goyang 10380, Republic of Korea
Tel: +82-31-910-7260, Fax: +82-31-910-7268, E-mail: medipark@hanmail.net

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LDAEP appears to provide useful clinical information for predicting treatment responses relative to central serotonergic activity.

Many studies have measured evoked potentials in patients with major depressive disorder (MDD), but only a few have focused on electrophysiological aberrance associated with suicide attempts. A recent study yielded electrophysiological evidence that the serotonergic activity was even lower (i.e., a larger LDAEP) in unmedicated depressive suicide attempters than in their depressive counterparts who did not attempt suicide.¹⁹ In contrast, Uhl and colleagues reported that patients with a history of suicide attempts exhibit a small LDAEP; however, the drug washout period allowed in that study was only 3 days.²⁰

The relationship between suicidality and the LDAEP therefore remains controversial. In this article we review the literature related to the LDAEP and suicide in patients with MDD, and suggests future research directions.

LDAEP AND SUICIDE IDEATION IN PATIENTS WITH MAJOR DEPRESSIVE DISORDER

A previous study found that patients who had acute suicidal ideas, as found in item 3 of the Hamilton Depression Rating Scale (HAM-D), were mainly present in the group with strong intensity dependences, when 22 patients with MDD were divided into 2 groups based on the median LDAEP value.²¹ Another study found that the LDAEP did not differ significantly between 73 depressive outpatients with or without suicide ideation, as dichotomized based on the score for HAM-D item 3 or Beck Depression Inventory (BDI) item 9.²² A recent study investigating the LDAEP and suicidality related to the subtype of MDD found a significant negative correlation between the LDAEP and the Beck Scale for Suicide Ideation (BSS) score in the atypical depression group (n=53), but no significant correlations between the LDAEP and scores on psychological scales in the non-atypical depression group (n=68).²³ In addition, the LDAEP was higher in patients with atypical depression than in those with non-atypical depression. A recent small study (n=16) found that the BSS score did not differ significantly between small- and large-LDAEP groups based on a dichotomized stratification at the median LDAEP, whereas the score on the Barratt Impulsiveness Scale (BIS) did differ significantly between the two groups.²⁴

LDAEP AND HISTORY OF SUICIDE ATTEMPTS IN PATIENTS WITH MDD

Some investigators initially reported that a small intensity

dependence of somatosensory evoked potentials was related to suicidal attempts in patients with MDD.²⁵ These results were replicated for the intensity dependence of auditory-evoked potentials.²¹ That study found the intensity dependence to be smaller in patients with a history of suicide attempts (n=7) than in those with no suicide history (n=15). However, these results were consistent with most previous studies finding low serotonergic activity to be associated with suicide attempts (using different methods, such as postmortem CSF measurements).² This discrepancy might be attributable to the suicide attempts of these patients having occurred in the past and hence being unrelated to the current medical contact, and that the relationship between low serotonergic activity and suicide attempts was mainly found during the acute suicidal state.

A study involving Taiwan patients produced contradictory results,²⁶ finding that the LDAEP was larger in depressed patients who had attempted suicide (n=16) than in those who had not (n=50). These results were replicated in another study also involving subjects divided into those who had attempted suicide (n=17) and those who had not (n=21).¹⁹ The LDAEP was calculated by measuring auditory event-related potentials (ERP), and differed significantly between the two groups. Depressive patients with a history of suicide attempts seem to be characterized by a large LDAEP, indicating low serotonergic activity. Another study found that the LDAEP did not differ significantly between suicide attempts (n=11) and no suicide attempts (n=130).²⁷ However, that study was not originally designed to investigate the relationship between the LDAEP and suicide attempts, and the group with a suicide-attempts history was much smaller than the group without such a history.

The above-described results indicate that the relationship between suicide attempts and the LDAEP is still controversial. A key feature of all of the studies is that they have involved relatively small samples. In addition, almost all subjects included in the suicide-attempters group were not acute suicide attempters, instead having a history of suicide attempts. Thus, a more precise evaluation requires the application of different methodology. For example, the LDAEP should be measured immediately after the suicide attempts of patients with MDD, rather than simply assessing the history of suicide attempts. One recent study with a different design was performed by Uhl and colleagues,²⁰ in which the LDAEP was measured at about 2, 5, 9, and 16 days after attempted suicide or a suicide attempt. The LDAEP was significantly larger on day 9 than on days 2 and 16, and tended to be larger on day 9 than on day 5. Instability of central serotonergic function is suggested to result in reduced serotonergic activity at about 1 week after a suicide attempt. Thus, serotonergic dysfunction in suicidality seems to be more complicated than was originally thought. However, that study had several limitations, including 1) the

smallness of the sample, 2) the noninclusion of nonsuicidal controls, and 3) no control of medications such as antidepressants and antipsychotics. Another study investigated the relationship between the LDAEP and self-injurious behavior.²⁸ The LDAEP was measured in 41 men, who then completed the Suicidal Behaviors Questionnaire (SBQ) and the Deliberate Self-Harm Inventory (DSHI). The LDAEP was positively correlated with scores on the SBQ and DSHI. In addition, in subjects with a history of actual suicide attempts, a larger LDAEP was related to higher scores on measures of self-injurious behaviors across the spectrum of lethality. However, that study also had significant limitations: 1) the sample was relatively small (as is the case for most ERP studies), 2) the study exclusively relied on self-report behavioral measures of lifetime SIB, and 3) only men were included.

Juckel and Hegerl²¹ found that the LDAEP of the tangential dipole was smaller in alcoholic patients with a history of suicide attempts (n=10) than in those without such a history (n=15). However, the LDAEP of the radial dipole did not differ significantly between two groups. Park and Lee²⁹ evaluated the LDAEP in patients with acute major depressive episode. They divided 61 patients into 2 groups based on whether or not they achieved a positive score on the Mood Disorder Questionnaire (MDQ). The LDAEP was measured before beginning medication with serotonergic agents, and it was found that the LDAEP did not differ significantly between MDD patients with and without bipolarity. However, the BSS score (which reflects impulsivity) was higher in the MDD patients with bipolarity, and applying binary logistic regression analysis to bipolarity revealed that the relationship between the total MDQ score and the BIS or BSS score was also significant. It is therefore possible that suicidality in the presence of a mood disorder depends on impulsivity and bipolarity as well as the serotonin level.³⁰

DISCUSSION AND FUTURE DIRECTIONS

Serotonergic dysfunction in suicidality seems to be more complicated than was originally thought. Studies of suicide based on the LDAEP have produced controversial results, but it is possible that these discrepancies are due to differences in study designs and the smallness of the included samples. For example, some studies have evaluated suicide ideation and the LDAEP, while others have evaluated suicide attempts and the LDAEP. Furthermore, some of the latter studies enrolled acute suicide attempters, while others enrolled those with a history of previous suicide attempts, irrespective of whether these were acute or chronic. Thus, a robust study design is needed in future studies, such as by evaluating the LDAEP immediately after a suicide attempt rather than in those with

a history of suicide attempts and suicide ideation in order to reduce bias. Moreover, genuine suicide attempt, self-injurious behaviors, and faked suicide attempt need to be discriminated in the future. Medication can also affect the LDAEP, and so ERP has to be measured in a drug-naive state. Another consideration is the ERP methodology. All of studies reported in this article used only the scalp N1/P2 LDAEP as measured at Cz, and each N1 LDAEP and P2 LDAEP need to be analyzed in order to provide detail outcomes in the future. In addition to these analyses, source analysis such as standardized low-resolution brain electromagnetic tomography (sLORETA) should be performed in large samples in future studies because some studies have produced different findings according to the use of scalp analysis or source analysis.

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