Reduced Frontal Cortex Inositol Levels in Postmortem Brain of Suicide Victims and Patients With Bipolar Disorder

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Objective: *This study aimed to evaluate aspects of second messenger function in the brain of suicide victims and patients with bipolar disorder.* *Method:* *Inositol and its synthetic enzyme, inositol monophosphatase, were measured in postmortem brain samples of 10 suicide victims, eight patients with bipolar affective disorder, and 10 normal comparison subjects.* *Results:* *The frontal cortex inositol levels of the suicide victims and the patients with bipolar disorder were significantly less than those of the normal comparison group. No differences in cerebellum or occipital cortex inositol levels were found among the three groups. The groups also showed no differences in inositol monophosphatase activity in any brain area.* *Conclusions:* *These results could suggest a deficiency of second messenger precursor in patients with bipolar disorder and suicide victims.*

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Inositol is a simple polyol isomer of glucose that serves as a precursor in the phosphatidylinositol second messenger cycle (1). Barkai et al. (2) reported that inositol is reduced in cerebrospinal fluid in patients with bipolar and unipolar depression, although others could not replicate this finding (3). In a double-blind, controlled study (4), Levine et al. administered 12 g/day of inositol or placebo to 28 depressed patients for 4 weeks. Inositol treatment reduced scores on the Hamilton Depression Rating Scale significantly more than placebo.

We were able to measure inositol and inositol monophosphatase, the enzyme that forms inositol in brain, in postmortem brain specimens from patients with bipolar affective disorder, suicide victims, and normal comparison subjects.

METHOD

Brain specimens of eight patients with bipolar disorder (six women and two men), 10 suicide victims (six women and four men), and 10 normal comparison subjects (four women and six men) were obtained at autopsy from the Medical Examiner's Office of Washington, D.C. Blood and urine samples were collected at the same time for toxicological analysis and for neuroleptic level determination. None of the subjects had measurable levels at the time of death. Level of lithium in the brains of the patients with bipolar disorder and the suicide victims was measured by flame emission spectroscopy; lithium was undetectable in all subjects except for three of the patients with bipolar disorder (levels of 0.35, 0.48, and 0.23 mmol/kg wet weight). Most of the patients with bipolar disorder had ceased taking psychoactive medication in the week before death; however, two had injested alcohol, and one had been taking thioridazine in addition to lithium. One suicide victim had a history of barbiturate use, and another had been taking codeine.

Psychiatric diagnosis was determined by independent review of medical records by at least two psychiatrists. This review revealed that seven suicide victims had evidence of depression, and one may have suffered from delusional disorder; no information was available for the remaining two suicide victims. Methods of suicide were jumping (N=3), hanging (N=3), gunshot (N=1), and overdose (N=3). Causes of death for the patients with bipolar disorder were drowning (N=1), hanging (N=1), car accident (N=1), cancer (N=1), and cardiopulmonary arrest (N=4). One normal comparison subject had died as a result of a fall, and another was a homicide victim; the rest had died of cardiovascular disease. Two patients with bipolar disorder were black, and six were white; two of the suicide victims were black, and eight were white; and nine of the 10 normal comparison subjects were black.

After collection from autopsy, brain tissue was stored at –70°C until dissection for this study. Postmortem interval was defined as the time from death until the brain was removed and frozen. The mean ages of the patients with bipolar disorder, the suicide victims, and the normal comparison subjects were 51.4 (range=31–83), 53.6 (range=29–86), and 53.6 years (range=34–84), respectively. The postmortem intervals for the three groups were as follows: patients with bipolar disorder: mean=25.5 hours (range=16–46; the interval was unknown for two patients); suicide victims: mean=20.5 hours (range=7–28); normal comparison group: mean=23.3 hours (range=14–41).

Human brain free myo-inositol levels were analyzed by gas chromatography as previously described (5). Enzyme activity was mea-

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sured by the release of inorganic phosphate as previously described (6). Assays were performed in a balanced design such that each run included samples from each clinical group and all available brain areas. To evaluate possible effects of postmortem decay, rats were killed by decapitation and the heads were left out at room temperature for 0, 1, 2, 4, 6, 7, 16, or 24 hours (eight rats at each time point). After the specified times the brains were removed from the skull and frozen at –70°C until assay. Analysis of variance (ANOVA) revealed no significant effect of postmortem interval on rat brain inositol level (F=0.24, df=7, 48) or inositol monophosphatase activity (F=1.0, df=7, 48).

TABLE 1. Postmortem Inositol Levels of Eight Patients With Bipolar Disorder, 10 Suicide Victims, and 10 Normal Comparison Subjects

	Inositol Level (mmol/kg wet weight)					
	Patients With Bipolar Disorder		Suicide Victims		Normal Comparison Subjects	
Brain Region	Mean	SD	Mean	SD	Mean	SD
Frontal cortex	5.90	2.12	6.74	2.21	8.74	2.39
Occipital cortex	6.69	2.84	6.91	2.37	9.08	3.53
Cerebellum	7.22	2.58	7.72	3.73	7.69	2.98

RESULTS

Table 1 summarizes the inositol results. ANOVA revealed a significant difference among the groups for frontal cortex inositol levels (F=3.83, df=2, 25, p=0.04) but not for inositol levels in the occipital cortex (F=1.8, df=2, 24) or cerebellum (F=0.11, df=2, 21). Post hoc least significant difference test showed that the frontal cortex inositol levels of the patients with bipolar disorder were significantly lower than those of the normal comparison subjects (F=6.9, df=1, 16, p=0.02) and that the difference in inositol level between the suicide victims and the normal comparison subjects approached significance (F=3.61, df=1, 18, p=0.07). After omission of the subjects with postmortem interval unknown or greater than 30 hours, the difference among the groups for frontal cortex inositol levels remained significant (F=4.24, df=2, 21, p=0.03), and post hoc least significant difference test showed that the inositol levels of the normal comparison subjects were significantly different from those of both the patients with bipolar disorder (F=5.46, df=1, 12, p=0.04) and the suicide victims (F=6.97, df=1, 17, p=0.02).

Postmortem interval correlated with frontal cortex inositol level (r=–0.39, df=1, 24, p=0.05), but the ANOVA group difference in frontal cortex inositol level was still significant after covariance for postmortem interval (F=3.7, df=2, 22, p=0.04). After the two subjects with postmortem interval greater than 30 hours were excluded, correlation of postmortem interval and frontal cortex inositol level declined (r=–0.13, df=1, 22, n.s.). Age or sex had no significant effect on inositol levels in any brain region. ANOVA indicated that among the suicide victims, patients with bipolar disorder, and normal comparison subjects there was no difference in mean inositol monophosphatase activity (nmol/min × mg protein) in the frontal cortex (1.3 [SD=0.7], 1.0 [SD=0.7], and 1.1 [SD=0.5], respectively), occipital cortex (1.6 [SD=0.6], 1.5 [SD=1.2], and 1.5 [SD=0.9]), or cerebellum (0.7 [SD=0.6], 0.8 [SD= 0.7], and 0.8 [SD=0.4]).

DISCUSSION

These data suggest that patients with bipolar affective disorder and suicide victims have lower frontal cortex inositol levels than normal comparison subjects. There were no significant differences among the groups in inositol monophosphatase activity, which suggests that nonspecific degradation does not explain the frontal inositol reduction. Inositol is not metabolizable in brain (7), which argues against postmortem effects as the cause of the lower frontal cortex inositol levels. Inositol phosphates that could be metabolized to inositol postmortem are present in very small concentrations in comparison to inositol (7). High-dose acute lithium is reported to lower inositol in rat brain, but acute or chronic lithium levels of 0.23–0.48 mmol (as found in three of the patients with bipolar disorder) would lower cortical inositol by 10% or less (7). Hyponatremia lowers brain levels of inositol (8), and if the suicide victims or the patients with bipolar disorder were more likely than the normal comparison group to be hyponatremic for several days before death, this could have artifactually lowered brain inositol in the non-neurotransmitter related pool.

The pathophysiological implications of low frontal cortex inositol levels are not clear. Batty and Downes (9) have reported that inositol levels may regulate phospholipase C activity in a complex manner unrelated to levels of phosphatidylinositol. Low inositol levels could thus cause functionally deficient responses to one or more receptors linked to phosphatidylinositol. Deicken et al. (10) performed magnetic resonance spectroscopic imaging on unmedicated euthymic patients with bipolar disorder and reported changes in frontal lobe phosphomonoesters that were consistent with depressed phosphatidylinositol-linked function in this brain region.

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