Alterations in phosphatidylinositol 3-kinase activity and PTEN phosphatase in the prefrontal cortex of depressed suicide victims

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Abstract
Recent studies have reported alterations in protein kinase B (PKB)/Akt and in its downstream target, glycogen synthase kinase 3β, in depression and suicide. The aim of the present study was to investigate possible impairment of the upstream regulators, namely phosphatidylinositol 3-kinase (PI3K) and PTEN.

Reference

DOI : 10.1159/000322145
PMID : 21422769
Alterations in Phosphatidylinositol 3-Kinase Activity and PTEN Phosphatase in the Prefrontal Cortex of Depressed Suicide Victims

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Abstract

Background: Recent studies have reported alterations in protein kinase B (PKB)/Akt and in its downstream target, glycogen synthase kinase 3β, in depression and suicide. The aim of the present study was to investigate possible impairment of the upstream regulators, namely phosphatidylinositol 3-kinase (PI3K) and PTEN. Methods: The ventral prefrontal cortex (Brodmann’s area 11) of 24 suicide victims and 24 drug-free nonsuicide subjects was used. The antemortem diagnoses of major depression disorder were obtained from the institutional records or psychological autopsy, and toxicological analyses were performed. Protein levels of PI3K and PTEN were assayed using the immunoblot method, and the kinase activity of PI3K and Akt were determined by phosphorylation of specific substrates. Results: A decrease was observed in the enzymatic activity of PI3K [ANOVA: F(3, 44) = 9.20; p < 0.001] and Akt1 [ANOVA: F(3, 44) = 13.59; p < 0.001], without any change in protein levels, in both depressed suicide victims and depressed nonsuicide subjects (p < 0.01 and p < 0.002, respectively). PTEN protein levels were increased in the same groups [ANOVA: F(3, 44) = 10.5; p < 0.001]. No change was observed in nondepressed suicide victims. Conclusion: This study concludes that attenuation of kinase activity of PKB/Akt in depressed suicide victims may be due to the combined dysregulation of PTEN and PI3K resulting in insufficient phosphorylation of lipid second messengers. The effect is associated with major depression rather than with suicide per se. Given the cellular deficits reported in major depression, the study of enzymes involved in cell survival and neuroplasticity is particularly relevant to neurotrophic factor dysregulation in depression.

Introduction

The role of serotonin in major depression and suicide has been recognized for decades, but its transduction signaling pathways still require thorough investigation. One serotonin receptor signaling pathway coupled to G proteins (5-HT1A) has been shown to activate phosphatidylinositol 3-kinase (PI3K) and the subsequent downstream effector protein kinase B (PKB), also called Akt [1, 2]. This signaling pathway, which essentially utilizes lipid signals as second messengers, is modulated by a
chain of protein and lipid kinases and phosphatases, the major members of which are PI3K, PTEN (phosphatase and tensin homolog deleted on chromosome 10), Akt/ PKB and glycogen synthase kinase 3β (GSK3β), the negative regulator of many transcription factors [3, 4] (fig. 1). According to recent reports, this pathway may be altered in major depression and suicide. Indeed, on the basis of the animal model of depression, it has been suggested that GSK3β inhibition contributes to antidepressant activity [5]. Moreover, an increase in GSK3β activity has been observed in depressed suicidal teenagers [6], while a decrease in Akt levels was reported in suicide subjects [7]. Interestingly, we have recently observed that the increase in GSK3β activity is associated with a decrease in Akt activity in depressed suicide subjects, suggesting an attenuation of the Akt/GSK3β signaling pathway [8].

On the basis of these previous results, we decided to go forward and explore the upstream elements which might be involved in this blunting. We hypothesized that changes in Akt signaling are probably due to the changes in upstream lipid kinase and phosphatase, which control the levels of the second messenger phosphorylatedinositol (3,4,5)-trisphosphate (PIP3). We then decided to measure PI3K activity and protein levels as well as the PTEN protein levels, and to replicate the Akt activity data.

PI3K is a heterodimer lipid and protein serine kinase comprising an 85-kDa regulatory subunit and a 110-kDa catalytic subunit [9]. This enzyme was shown to be required for the growth-factor-dependent survival of a wide variety of cultured cells, including neurons [10]. Biochemically, PI3K phosphorylates phosphoinositides at the D-3 position of the inositol ring to generate the lipid second messengers PI3-phosphate, PIP(3,4)-bisphosphate and PIP3 [11]. The lipid kinase is involved in regulating numerous physiological functions (cell survival and proliferation, growth, cell motility, apoptosis, etc.) after activation by a variety of stimuli. PI3K activation and the subsequent phosphorylation of the phosphoinositides leading to the phospholipid products are currently thought to stimulate the serine-threonine Akt/PKB [12, 13]. The latter is a crucial enzyme, the major role of which is to facilitate growth-factor-mediated cell survival and to block apoptotic cell death [12, 13]. Akt is activated by the direct binding of the PI3K-generated PIP3 to its pleckstrin homology domain [14, 15]. The main substrate of Akt is GSK3β, a serine-threonine kinase, originally known as a negative regulator in glycogen synthesis, subsequently described as a target of lithium and recently reported for its possible involvement in antidepressant activity [4, 5, 16]. Upstream of this signaling pathway, PTEN is another enzyme which has recently also attracted attention because of its crucial role in cell proliferation and neuronal survival and in mediating Akt activation in a number of cell functions [17, 18]. It is one of the frequently mutated tumor suppressors in human cancer, which functions primarily as a lipid phosphatase to regulate crucial signal transduction pathways. Its main target is PIP3 [17, 18]. PTEN has also been reported to be a modulator of cell signaling, growth and apoptosis. By operating via the reduction of PIP3 levels, it opposes the actions of PI3K-dependent pathways and behaves as a negative regulator of Akt. Although substantial progress has been made in understanding its role in suppressing malignancy, much less is known about its involvement in neurobiological processes and serotonin downstream signaling. However, recent studies have reported critical alterations in Alzheimer’s disease patients and in depressed suicide victims [7, 19]. The prefrontal cortex (PFC), in particular the ventral PFC (vPFC), is of great interest because it is innervated by serotonergic neurons [20]. Moreover, an early study revealed deficits in executive functions linked to the PFC in depressed patients with suicidal behavior [21]. Lastly, the impairment of vPFC-related function is also known to contrib-

![Fig. 1. Simplified representation of 5-HT1A signaling via PI3K/Akt (bold arrows). Depending on cell type or brain tissue, different pathways and often complex crosstalk have been reported. Also shown is an alternative activation by neurotrophic factors such as brain-derived neurotrophic factor (BDNF) via TrkB receptors. cAMP = Cyclic AMP; PKA = protein kinase A; ERK1/2 = extracellular-signal-regulated kinases 1 and 2; PIP3 = phosphatidylinositol (3,4,5)-trisphosphate; PIP2 = phosphatidylinositol 4,5-bisphosphate; NF-κB = nuclear factor-κB.](image-url)
Table 1. Diagnosis groups and demographic features of suicide victims and nonsuicide subjects

<table>
<thead>
<tr>
<th>Subjects (M/F), n</th>
<th>12 (6/6)</th>
<th>12 (6/6)</th>
<th>12 (6/6)</th>
<th>12 (6/6)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>43 ± 14</td>
<td>44 ± 17</td>
<td>45 ± 18</td>
<td>46 ± 17</td>
</tr>
<tr>
<td>PMI, h</td>
<td>24 ± 17</td>
<td>25 ± 19</td>
<td>28 ± 16</td>
<td>25 ± 13</td>
</tr>
</tbody>
</table>

Data are expressed as means ± SD. The group of nonsuicide subjects without MDD was used as control. MDD = Major depression disorder; PMI = postmortem interval; M = male; F = female.

The study of the protein kinases and protein phosphatases involved in cell proliferation and antiapoptotic processes is particularly relevant because recent studies have demonstrated abnormal structural changes, including neuronal atrophy and changes in cell numbers, in the brains of depressed and suicide victims [22].

The materials and methods

Collection and Dissection of Postmortem Brains

Human brains were collected at autopsy from the Institute of Forensic Medicine, Geneva, Switzerland. This study was approved by the research and ethics review board of the Department of Psychiatry, Faculty of Medicine, in Geneva. The brain collection was carried out following legal procedures by the Republic and Canton of Geneva, which, in some cases, requires family consent.

After the brain was removed from the cranial, it was examined for neuropathologic abnormalities. Tissue blocks from the vPFC (Brodmann's area 11) were dissected from the right hemisphere by forensic physicians and skilled technicians. The right hemisphere was used because of its reported association with suicidal tendencies and its functional insufficiency [25]. The samples were immediately stored at −80°C. During the fine dissection, tissue blocks were thawed from −80 to −20°C (approx. 30 min) to make them easier to dissect. Specimens were then carefully dissected on a glass surface with dry ice, in accordance with Brodmann’s Atlas. Only grey matter samples (0.5- to 1-cm coronal slices) were carefully isolated. No white matter was included. Samples were either stored at −80°C until used or immediately homogenized in appropriate buffers using a tissue grinder.

Subjects

Table 1 shows the characteristics of the subjects divided into 4 different groups, depending on diagnosis. The suicide victims consisted of a well-defined population of 24 subjects (12 male, 12 female) carefully determined by forensic physicians. A retrospective search for antemortem clinical diagnosis and drug treatment was performed by reviewing medical histories obtained from both psychiatric units and internal and surgical units. Where possible, a psychological autopsy was performed. Only subjects with or without the clinical diagnosis according to DSM-IV criteria were included, which meant that the suicide group consisted of 2 subgroups: 12 suicide victims with documented major depression disorder (MDD), and a subgroup of 12 without documented MDD. The causes of death were hanging (n = 5), drowning (n = 2), self-inflicted gunshot wound (n = 5), jumping (n = 4), carbon monoxide poisoning (n = 3), asphyxia (n = 2) and multiple trauma (n = 3). Data were collected from the first hospitalization or ambulatory follow-up until the subject’s death. Subjects were considered to be drug free if they had not taken any antidepressants, antipsychotics or anticonvulsants during at least a year before death. Toxicological data were obtained from analysis of urine and blood samples. Subjects with comorbidity in the form of other psychiatric diseases or with positive toxicology (antidepressants, antipsychotics or anticonvulsants) were excluded, and only a few subjects with traces of alcohol (n = 2) or benzdiazepines (n = 2) were included in the study.

The nonsuicide subjects consisted of 24 subjects (12 male, 12 female) whose cause of death had been determined. Only those subjects whose antemortem medical records were available were included. According to psychological autopsy and a retrospective search for antemortem clinical diagnosis (DSM-IV), the nonsuicide group consisted of 2 categories: a subgroup of 12 nonsuicide subjects with documented MDD, and a subgroup of 12 normal controls without any antecedents of MDD or any other psychiatric disease. The latter group was used as a control group. Subjects with other psychiatric or neurological disorders or positive toxicology were excluded from this control group. With respect to the suicide group, the ages and genders of the nonsuicide subjects were balanced, and no statistically significant difference was observed in postmortem intervals (PMI) between the 2 groups (table 1). The causes of death varied and included myocardial infarction (n = 5), bronchopneumonia (n = 1), homicide, gunshot wound (n = 3), road traffic accident (n = 6), hypothermia (n = 1), various somatic diseases (n = 5), accidental drowning (n = 1) and carbon monoxide poisoning (n = 2).

Quantification of PI3K, PTEN and Akt1 Using the Immunoblot Method

Coronal slices (approx. 50 mg fresh weight) were homogenized in an extraction buffer of 50 mM Tris-HCl (pH 7.4) containing 150 mM NaCl, 1% Triton X-100, 1% sodium deoxycholate, 0.01% SDS, 5 mM EDTA, 1 mM phenylmethylsulfonyl fluoride and 10 μg/ml of aprotinin, leupeptin and pepstatin, respectively. The homogenates were incubated for 20 min at 4°C with gentle rocking and then centrifuged (10,000 g for 10 min, 4°C). The supernatant was used for the assay samples. The loading buffer contained 0.125 mM Tris (pH 6.8), 20% glycerol, 10% mercaptoethanol, 4% SDS and 0.02% bromophenol blue. Samples were heated at 95°C for 10 min before gel loading. Protein concentrations were previously determined using the BCA kit (Pierce Chemical, Rockford, Ill., USA). Equal amounts of a soluble fraction of brain proteins (50 μg for PI3K, 25 μg for Akt1 and PTEN) were electrophoresed on 10% (w/v ratio) SDS-polyacrylamide gel with a Mini-Protein system (Bio-Rad Laboratories AG, Reinach, Switzerland) on precast Ready Gels (Criterion, Bio-Rad). The samples were electrotrans-
Enzymatic Assays for Akt and PI3K

Akt kinase activity was measured in brain lysates prepared as follows. Brain sections (approx. 50 mg; 1–2 mm depth) were homogenized in Phosphosafe™ Extraction buffer (www.novagen.com) at a ratio of 1/5 (w/v). This buffer offers significant advantages over a classical lysis buffer in that it preserves the phosphorylation state of proteins and maintains kinase activity [26]. The lysates were sonicated in Eppendorf tubes for 10 s on ice and centrifuged at 14,000 g for 15 min. The supernatant was saved for further use, while an aliquot of 50 µl was taken out for protein determination using the Micro BCA method (Pierce Chemical). The lysate was then immunoprecipitated with primary specific Akt antibody (Cell Signaling Technology). The immunoprecipitated Akt activity was determined by phosphorylating a specific Akt antibody (Cell Signaling Technology) and binding to protein A/G-agarose beads (30 µl). Quantiﬁcation of the immunoreactivities was performed by densitometric scanning, using an image analysis system (Molecular Analyst; Bio-Rad). The OD obtained from each band was normalized against the corresponding β-actin band. Test-retest stability in different samples, assayed twice with different antibodies, showed a significant correlation between tests.

Statistical Analysis

Data were analyzed by statistical software (StatViewV; BrainPower, Calabas, Calif., USA). The results are reported as means ± SD. Values of OD were expressed as a ratio to β-actin protein. PI3K and AktI enzymatic activity were expressed in picomoles per minute per milligram proteins. Assuming comparisons of 2 samples of 12 subjects each, our study had 90% power to detect a significant difference at an α level of 0.05, and 74% power at an α level of 0.01. Power was calculated using Rollin Brant’s Sample Size Calculators available at http://www.stat.ubc.ca/~rollin/stats/sizel.html.

Statistical comparisons between groups were made using ANOVA, with significant difference set at p < 0.05. As we compared 4 categories (MDD with and without history of suicide attempt (SA), and non-MDD with and without SA) and 2 protein levels, Bonferroni’s correction for multiple testing was applied and the α level for significance was set at 0.05/2 × 4 = 0.006. Ad hoc Fisher tests were used for multiple comparisons, and the significance was set at p < 0.01. To test the potential effect of the confounding variable of gender on various measures, a two-way ANOVA (gender and diagnosis) was used. Although PMI and age were matched as carefully as possible, and no difference between control and suicide victims was found (table 1), the influence of both parameters on protein levels and kinase activity were examined. ANCOVA was used with PMI and age as covariates for this purpose. The effect of suicide method on protein variations was tested by comparing violent and nonviolent methods of death, and an unpaired t test was used with significance set at p < 0.05. Autoradiographic exposure times were adjusted to protein levels. In most cases, the polyvinylidene fluoride membranes were stripped with Reprob Plus for a further protein immunodetection.
Results

For the immunoblot analyses, preliminary tests were performed to establish the linear range and accurate amount of each protein to be loaded in the routine assays. By way of example, figure 2 shows the case of PTEN, where a linear range was observed between 10 and 40 μg. Following these tests, 25 μg proteins for PTEN or Akt and 50 μg for PI3K samples were regularly used. Figure 3 shows the relative OD (ROD) of these protein bands, expressed in mean values ± SD of the ratio to β-actin OD. For Akt1 and PI3K protein levels, the mean values of ROD were not statistically different in the 4 diagnostic groups. For PTEN measures, ANOVA yielded statistically significant differences among diagnostic groups [F(3, 44) = 10.59; p < 0.001]. Ad hoc Fisher tests for multiple comparisons indicated that PTEN measures were significantly increased in 2 diagnostic groups, the suicide group with depression (S/D+; p < 0.02) and the nonsuicide group with a well-diagnosed history of depression (C/D+; p < 0.02), in comparison with the control group.

Table 2 shows the measures of kinase activities (expressed in pmol/min/mg protein) of PI3K and Akt1 in the different diagnostic groups. With respect to Akt kinase activity, significant variations between diagnostic groups were observed [ANOVA: F(3, 44) = 13.5; p < 0.001]. An ad hoc Fisher test for multiple comparisons showed a significant decrease in Akt1 activity in the depressed suicide group (p < 0.002) and in the depressed nonsuicide group (p < 0.01) in comparison with control subjects. The suicide group with an undocumented history of depression was not different from the control group (p = 0.713). Similar changes were observed in PI3K activity measures [ANOVA: F(3, 44) = 9.20; p < 0.001]. Ad hoc Fisher tests indicated increased activity in both the depressed suicide (S/D+) and depressed nonsuicide groups (C/D+), compared with the control group (C/D−; p < 0.01). Tests of the influence of the potential confounding factors of PMI.

Table 2. Enzyme activities

<table>
<thead>
<tr>
<th></th>
<th>Suicide victims</th>
<th>Nonsuicide subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>with MDD</td>
<td>without MDD</td>
</tr>
<tr>
<td>PI3K</td>
<td>7.5 ± 2.8*</td>
<td>11.8 ± 2.3</td>
</tr>
<tr>
<td>Akt/PKB</td>
<td>16.3 ± 3.6**</td>
<td>24.1 ± 5.5</td>
</tr>
</tbody>
</table>

 PI3K and Akt1 activities were measured in vPFC lysates from postmortem depressed suicide and nonsuicide subjects. The results are expressed in pmol/min/mg proteins of 32P transferred to substrates. Data from nonsuicide subjects without MDD were used as control subjects. ANOVA yielded F(3, 44) = 13.5, p < 0.001, and F(3, 44) = 9.20, p < 0.001 for Akt and PI3K, respectively. Ad hoc Fisher tests: * p < 0.01, ** p < 0.002.
and age yielded a nonsignificant effect on all proteins, whatever the subgroup. The effect of gender, analyzed by a two-way ANOVA (gender and diagnosis), was not significant. Likewise, there was no difference between violent and nonviolent methods of suicide.

Discussion

This study aimed to investigate the upstream regulators of Akt/PKB, an enzyme of major importance in mediating hormonal actions in neuronal survival [10, 12, 13]. The findings confirm previous reports on alterations in Akt1 activity, but the most interesting observation is the finding of decreased PI3K activity and increased protein levels of PTEN in depressed subjects, regardless of suicide. These findings suggest that alterations in Akt1 signaling might stem from changes in PI3K and PTEN.

To our knowledge, this is the first report to investigate the three proteins in one study encompassing suicide and MDD and to show such a specific dysregulation. The inclusion of nondepressed suicide victims and a depressed nonsuicide group in the study made it possible to analyze the specificity of this dysregulation. Interestingly, all those signaling factors, PI3K, PTEN and Akt1, constitute a series of sequentially activated protein or lipid kinases and phosphatases which are crucial to cell survival and neuroplasticity [10, 18, 27, 28]. Accordingly, these abnormalities in expression and function of the proteins implicated in neural plasticity and cell survival may be of importance in major depression. Indeed, following the hypotheses of structural alterations in affective disorders and suicide proposed during the last decade, a number of reports have continually been published on alterations in the molecules involved in neuroplasticity and cell survival [29–32]. It is now accepted that neurogenesis and synaptic remodeling are influenced by neurotrophic factors and the various kinases that participate in phosphorylation and functional characterization of critical proteins [33]. The aim of this study was to examine some of those proteins which play a major role in these processes. Moreover, by using a design matrix consisting of four diagnosed groups of suicide and nonsuicide subjects, with or without a history of major depression, the study has also attempted to reveal changes specific to suicide and depression diagnostics. The relationship between MDD and suicide has always been problematic and it is difficult to determine what effects are attributable to the presence of a major depression as opposed to a vulnerability to suicidal behavior. Many individuals in postmortem studies of one factor meet the criteria of the other. Suicide and suicide behavior are likely to involve specific neurochemical abnormalities that might partially overlap with major depression [34].

Our study demonstrated that only subjects who presented an antemortem diagnosis of MDD, whether victims of suicide or not, were affected. The data indicate that protein levels and enzyme activities of PI3K and Akt1 are not affected in the vPFC of suicide victims with no documented history of MDD. This suggests that, rather than being an indicator of suicide, the compromised PI3K/Akt signaling pathway is an indicator of depression. Therefore, without necessarily testing a new hypothesis on depression or suicide, the merit of our study was to allow for discrimination between elements specific to depression. This is an interesting observation, but research should be extended to other limbic areas such as the hippocampus as selective changes across limbic circuits have been demonstrated [35]. In a recent study on gene ontology analysis, differentially expressed genes revealed specific patterns in the limbic system for suicide and depression [36]. In this report, the authors suggested that suicide may be more likely to be associated with regulation of transcription factors, while depression would be mainly related to second messenger systems like G-protein-coupled receptors. However, other evidence has indicated that, in the cyclic AMP-protein kinase A pathways, various catalytic and regulatory subunits were selectively decreased in postmortem suicide victims, and that decreases were specific to depressed suicide, while in extracellular-signal-regulated kinases 1 and 2 (ERK1/2), decreases were observed in all suicide subjects, irrespective of psychiatric diagnosis [34]. The difficult lies in that most studies on depressed suicide victims did not include depressed nonsuicide subjects and/or nondepressed suicide victims as did the present one. Therefore, our report represents a significant advance in that it shows neurochemical signals specific to depression in depressed suicide subjects.

What could be the remote cause of this PI3K/Akt dysregulation in the PFC of depressed persons? In other words, is there any connection with the serotonergic system? A wealth of evidence from neuropsychology-neuropathology and functional imaging studies performed in both animals and humans indicates that the PFC is a key component of the corticostriatal circuits which are thought to generate pathological emotional behavior and accompany physiological disturbance [37]. The vPFC is of particular interest because it is one of the brain regions whose activity positively correlates with the
Hamilton Depression Rating Scale score, and a number of studies indicate abnormalities of structure and function in this region [23, 38]. Moreover, deficits in executive functions linked to the PFC in depressed patients with suicidal behavior were observed [20], and the impairment of vPFC-related function is also known to contribute to impulsivity, a behavior which is linked to suicidal behavior [22]. But more interestingly, 5-HT systems have been shown to have anatomical connections with the vPFC and to contain a high density of 5-HT receptor sites, including 5-HT1A subtypes [20, 39]. The role of serotonin receptors (5-HT1A) in PI3K/Akt signaling has been highlighted in recent years. It appears that, although 5-HT1A receptor activation stimulates multiple signals such as ERK1/2, PI3K/Akt and nuclear transcription factor-kB, only PI3/Akt activation is required for 5-HT1A-receptor-dependent cell survival [40]. Other evidence has recently indicated that 5-HT1A receptors couple to Akt activation, but not ERK, in cultured hippocampus neurons [2]. This implies that the relative distribution of signals between competing transduction pathways determines the functional outcome of 5-HT1A receptor activation. The alteration in the PI3K/Akt signaling pathway, therefore, may be relevant to the mediation of cell-survival-associated responses by 5-HT1A receptors. Alternatively, PI3K/Akt dysregulation could stem from some impaired neurotrophic factor systems such as brain-derived neurotrophic factor, which is also altered in major depression and suicide [28, 29]. A number of reports have indeed indicated that brain-derived neurotrophic factor can signal through PI3K [41, 42].

However, this study has limitations. The subsample size (12 per group) was small, but it is relatively difficult to obtain drug-free, correctly diagnosed deceased subjects. Secondly, some antemortem medical records might have ignored depressive episodes that could have occurred at the time of death. However, in a major contribution to postmortem studies, Kelly and Mann [43] demonstrated the close agreement between informant-based retrospective psychological assessment of deceased subjects and diagnoses by clinicians treating the subjects before their deaths. Lastly, it would have been interesting to analyze other brain regions, and we are considering to do this in our research group.

In conclusion, our study observed a decrease in Akt and PI3K enzymatic activity and an increase in PTEN protein levels in the vPFC of depressed suicide victims and nonsuicide subjects with a documented history of major depression. The protein levels of PTEN, as well as the enzymatic activities of PI3K and Akt1, were not altered in suicide victims who had not been depressed ante mortem. We conclude that the alteration in PI3K/Akt signaling is associated with MDD rather than with suicide per se. The results are consistent with the role of these proteins, lipid kinases and phosphatases, formerly described as regulators of neuron survival and of neuroplasticity in general. This might be of relevance for the further development of new drugs on the basis of PI3K/Akt signal transduction boosting.

**Acknowledgment**

This study was partly supported by the Swiss National Science Foundation, grant No. 31-120471.

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