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Reduced expression profile of neurotrophins and their cognitive receptors in the hippocampal region of postmortem suicidal brain

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ABSTRACT

Suicide is a major public health concern. Although the authors of many studies have examined the neurobiological aspects of suicide, the molecular mechanisms associated with suicidal behavior remain poorly understood, there is increasing evidence that brain-derived neurotrophic factor (BDNF) and Nerve growth factor (NGF) are involved in the pathophysiology and treatment of depression through binding and activating their cognate receptors trk B and trk A respectively. The present study was performed to examine whether the expression profiles of BDNF and/or trk B as well as NGF and/or trk A were altered in postmortem brain in subjects who commit suicide and whether these alterations were associated with specific psychopathologic conditions. These studies were performed in hippocampus obtained in 20 suicide subjects and 20 non-psychiatric control subjects. The protein and mRNA levels of BDNF, trk B and NGF, trk A were determined with Western Blot and RT PCR respectively. Given the importance of BDNF and NGF along with their cognate receptors in mediating physiological functions, including cell survival and synaptic plasticity, our findings of reduced expression of BDNF, Trk B and NGF, Trk A in both protein and mRNA levels of postmortem brain in suicide subjects suggest that these molecules may play an important role in the pathophysiological aspects of suicidal behavior. An unique parallel decrease of the mRNA and protein levels of BDNF, TrkB, NGF and TrkA in suicide victims might be of relevance to its pathophysiology of depression.

Keywords: derived neurotrophic factor (BDNF), Nerve growth factor (NGF), TrkB, TrkA, RT PCR.

Abbreviations: TrkB- Receptor Tyrosine Kinase B, TrkA- Receptor Tyrosine Kinase A, RT PCR- Real Time Polymerase Chain Reaction.

1. INTRODUCTION

Like everywhere else in the world suicide attempts in India have been increasing progressively. Despite of dramatic improvements in the medication treatment of psychiatric disorders, there has been relatively little change in suicide rates over the last quarter of a century. India, the second most populous country, is known today as one of the fastest developing nations in the world. Along with the increase in economy, there is also increasing number of people who are dying from suicide every year. As per estimation of WHO's latest suicide rate, India along with China, holds the dubious distinction of having the highest suicide rates in the world. In India 98 out of every 100,000 people commit suicide annually (David, 2009). Despite the devastating effect of suicide on numerous lives, there is still a dearth of knowledge concerning its underlying cause and pathologic mechanism. Several clinical and epidemiological studies have identified stress as an important risk factor in suicide (Pykel, 1976; Westrin, 2000). The role of neurotrophins in directing brain growth and neuronal functioning is being increasingly recognized. Neurotrophins not only play an important role in cellular proliferation, migration, and phenotypic differentiation and/or maintenance in the developing central nervous system (McAllister, 2001), but also their presence is required in the adult central nervous system for maintenance of neuronal functions, structural integrity of neurons, and neurogenesis (Cooper et al., 1996; Sofroniew et al., 1990), which suggests that neurotrophins are biologically significant over the entire lifespan. In addition, a number of studies have demonstrated that neurotrophic factors regulate structural and synaptic and morphological plasticity to modulate the strength or number of synaptic connections and neurotransmission (McAllister, Katz and Lo, 1991; Thoenen, 2000). Neurotrophins are structurally related homo dimeric proteins that include brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin (NT)-3, and NT-4/5. They exert their effects after binding to receptor tyrosine kinases (Trk), such as TrkA, TrkB, TrkC, and p75NGFR, in a specific manner (Huang and Reichardt, 2001). We therefore, investigated the correlation of neurotrophins and their respective receptors at the level of both protein and mRNA in hippocampus obtained from suicide victims and matched non-psychiatric control subjects. The results of the present study demonstrate reduced expression of neurotrophins and their receptors at both protein and mRNA level in postmortem brain of suicide victims, indicating a significant association of suicide and down regulation of neurotrophins and their cognate receptors at translational level in hippocampal region of the brain. This result indicates a significant defective brain neurotrophin milieu in Indian suicide victims and strengthens role of neurotrophins in the pathophysiology of suicide.

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Table 1

Demographic characteristics of Suicide and Control Subjects

Subject No.	Group	Sex (M/F)	Age (Yr.)	PMI (h)	Brain pH	Cause of death	Psychiatric Diagnosis
1	MDD	M	45	17.9	6.91	Acid Poisoning	Familial dyshermony
2	MDD	F	21	24.8	6.23	Hanging	Familial dyshermony
3	MDD	M	65	13.9	6.72	Wrist cutting	Major depression, alcohol abuse
4	MDD	F	20	21.6	6.92	CuSO4 Poisoning	Major depression, adjustment disorder
5	MDD	M	59	15.6	6.95	Hanging	Schizophrenia
6	MDD	M	53	23	6.1	Jumped	Major depression
7	MDD	M	32	26.3	6.4	Hanging	Drug and alcohol abuse
8	MDD	F	36	18.8	5.69	Acid Poisoning	Major depression
9	MDD	M	34	24.3	6.44	Hanging	Major depression, adjustment disorder
10	MDD	M	38	24	6.3	Wrist cutting	Major depression, alcohol abuse
11	MDD	M	27	24.8	6.65	Acid Poisoning	Familial dyshermony
12	MDD	M	54	26.1	6.77	Multiple injuries	Drug and alcohol abuse
13	MDD	F	18	22	6.55	Jumped	Marital dyshermony
14	MDD	F	26	15.5	6.32	Hanging	Marital dyshermony
15	MDD	F	62	27	6.2	Hanging	No Psychiatric illness
16	MDD	F	46	20.1	6.52	Jumped	Major depression, agoraphobia
17	MDD	M	39	11.5	7	Run over in Metro rail	Familial dyshermony
18	MDD	M	29	24.7	6.66	Hanging	Bipolar disorder
19	MDD	M	44	19.3	7.06	Multiple injuries	Schizoaffective disorder
20	MDD	M	23	24.8	6.71	Wrist cutting	Major depression, adjustment disorder
21	MDD	M	72	24.5	6.25	Run over in Metro rail	Familial dyshermony
22	Control	M	30	22	5.8	Atherosclerotic cardiovascular disease	_
23	Control	M	22	19.24	7.33	Accidental trauma	_
24	Control	F	23	18.34	6.23	Cadiac arrhythmia	_
25	Control	M	43	26.13	5.69	Hypertensive heart	_
26	Control	M	67	27.23	5.89	Liver cirrhosis	_
27	Control	M	34	15.5	6.35	Hypoplastic coronary artery	_
28	Control	F	29	23	6.64	Cadiac arrhythmia	_
29	Control	M	47	26.3	6.22	Atherosclerotic cardiovascular disease	_
30	Control	F	54	18.8	5.98	Atherosclerotic cardiovascular disease	_
31	Control	M	27	24.3	6.43	Pneumonia	_
32	Control	M	32	29.13	5.33	Subarachnoid haemorrhage	_
33	Control	F	29	18	7.17	Anaphylaxis	_
34	Control	F	32	9.5	6.11	Mitral valve prolapse	_
35	Control	M	45	17	5.44	Hypertensive heart	_
36	Control	M	65	16	6.7	Hypoplastic coronary	_

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						artery	
37	Control	M	19	10.32	6	Accidental trauma	_
38	Control	M	50	17.5	6.11	Hypertrophic cardiomyopathy	_
39	Control	M	28	21	5.7	Accidental trauma	_
40	Control	F	40	24	6.47	Ovarian cancer	_

2. MATERIALS AND METHODS

2.1. Subjects

Post-mortem brain samples from suicide subjects with major depression and non-psychiatric control subjects were obtained from the Calcutta Medical College Hospital, The hippocampal region of the brains were dissected and stored at -80 ºC. We determined the selected neurotrophins and their respective receptors mRNA and protein expression in the hippocampal and cerebellum brain areas obtained from 20 non-psychiatric control subjects (referred as control subjects) and 20 depressed suicide subjects. Detailed demographic characteristics of the control and depressed suicide subjects are provided in Table 1. The brain samples were free of any neuropathological abnormalities and HIV. This study was approved by the Institutional Review Board (Ref. No. 06/B/IEC/MCH) of the Calcutta Medical College Hospital under West Bengal University of Health Sciences.

2.2. Diagnostic methodology

All subjects were diagnosed as follows: after giving written informed consent at least one family member was interviewed using procedures based on the Diagnostic Evaluation After Death (DEAD) and the Schedule for Clinical Interviews for the DSM-IV (SCID). Family members gave permission for clinical records to be obtained from mental health treatment providers when there was a prior history of mental health treatment, and in all cases of suicide. An attempt was made to collect all the available records on each case, from which the appropriate data were extracted and collected using the DEAD. Two senior psychiatrists provided independent DSM-III-R diagnoses; discrepancies were resolved by means of a consensus conference. Data on suicide cases were collected and the circumstances of the suicide were determined using the DEAD form during the same interview process. Cases were considered to be suicide only if the manner of death was determined to be suicide by the medical examiner. Similarly, controls were verified as free from mental illnesses using such consensus diagnostic procedures. This study was approved by the Institutional Review Board (Ref. No. 06/B/IEC/MCH), Calcutta Medical College Hospital under West Bengal University of Health Sciences.

2.3. Extraction of hippocampus and Western blotting

The brains of suicide subjects and control subjects were removed for isolating the hippocampal tissues. 50-100 mg hippocampal tissue of each subject was lysed in 1 ml lysate (50 mmol/L Tis-HCl pH 7.4, 50 mmol/L NaCl, 1%Triton-X 100, 1 mmol/L EDTA, 100 µg/ml PMSF) and centrifuged at 15000 rpm for 15 minutes at 4°C to obtain the supernatant. The proteins were separated by 12% SDS-PAGE and transferred to Nitro-Cellulose membranes. An Western blotting reaction was performed with anti-BDNF polyclonal antibodies (1:1000 dilution in 3% BSA, Chemicon, USA), anti-TrkB polyclonal antibodies (1:1000 dilution in 3% BSA, Chemicon, USA), NGF polyclonal antibodies (1:1000 dilution in 3% BSA, Chemicon, USA) and anti-TrkA polyclonal antibodies (1:400 dilution in 3% BSA, Santa Cruz, USA) overnight at 4°C. Anti-β-actin monoclonal antibody (1:10000 dilution in 3% BSA, Sigma, USA) was used as the internal control. Membranes were washed three times in TBST and incubated with HRP-conjugated anti-sheep IgG (1:1000) for 2 hours at room temperature. Immuno-reactive bands were visualized using the enhanced chemi-luminescence (ECL) [Santa Cruz, C.A, USA]. The optical density value (OD) of each band was analyzed with the biology electrophoresis image analysis system (Smartview 2001, S/N: SV-0002202, Japan). The expression of BDNF, NGF TrkB, and TrkA were determined by calculating the optical density ratio of each band to β-actin protein.

2.4. Isolation of total mRNA from the hippocampus and RT-PCR

Hippocampal tissues were isolated from all subjects. Total mRNA was extracted from the 50-100 mg hippocampus according to the instructions of TRIzol kit (Invitrogen, USA). BDNF, NGF, TrkB, and Trk A mRNA in each extraction were determined by Real Time-Polymerase Chain Reaction (RT-PCR). GAPDH, used as an internal control, was co-amplified with BDNF, NGF, TrkB, and Trk A mRNAs. The primers were designed by AuGCT-technology Company (Beijing, China) according to the serial number from Genebank as

follows: BDNF: 5′-ATTAGGTGGCTTCATAGGAGAC-3′(sense) and 5′-GAACAGAACAGAACAGAACAGG-3′(antisense); Trk B: 5′-TCTCTCGGTCTATGCCGTGGTGG-3′(sense) and 5′-TCCAGGCACTTCCTCGTTCAGT-3′(antisense); NGF: 5′- AGCGTAATGTCCATGTTGTTC TAC-3′(sense) and 5′-TGCTATCTGTGTACGGTTCTGC-3′(antisense); Trk A: 5′-CTTGCGCCGCATCCTGTCGT-3′ (sense) and 5′-GCAGGCCG CGGAGGGTATTC-3′ (antisense) and GAPDH: 5′-TTGCCATCAATGACCCCTTCA-3′ (sense) and 5′-CGCCCCACTTGATTTTGGA-3′ (antisense). The PCR products were observed after electrophoresis on 1.2% agarose gel and the density of each band was analyzed on the gel image analysis system (Smartview 2001, S/N: SV- 0002202, Japan). The level of the mRNA was determined by calculating the density ratio of each band of BDNF, TrkB, NGF and Trk A mRNA to GAPDH mRNA.

2.5. Statistical Analysis

The Statistical Package for the Social Science (SPSS) 15.0 was utilized for statistical analyses. All data are expressed as mean ± standard error of the mean (SEM) of n subjects, and have been statistically analyzed with the student's t- test. *P* values less than 0.001 were considered statistically significant

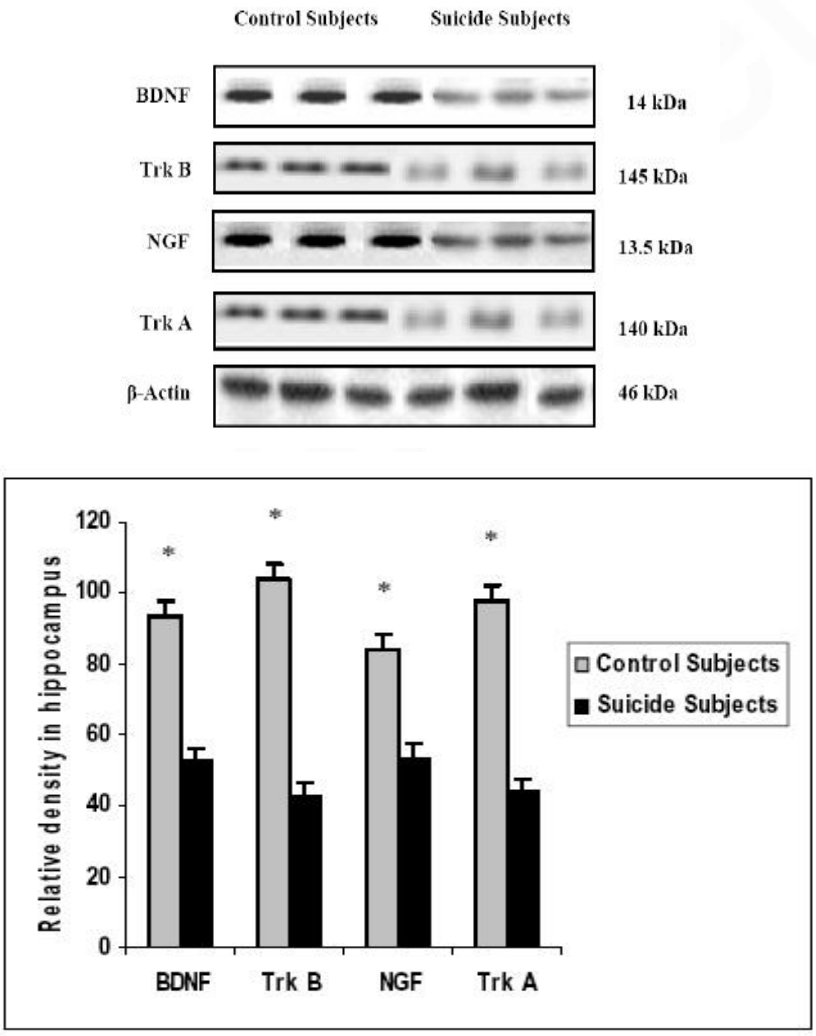

Figure 1

Representative bands of Western Blot showing the Protein levels of BDNF, Trk B, NGF and Trk A in hippocampus of suicide subjects and normal controls. Data are the mean ± S.D. Hippocampus samples were from 19 normal controls and 21 suicide subjects.

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3. RESULTS AND DISCUSSION

3.1. Comparison of Protein levels of BDNF, TrkB, NGF and TrkA between Normal Control Subjects and Suicide Victims in the hippocampus

The molecular weights of BDNF, TrkB, NGF, TrkA and β-actin were 14 kDa, 145 kDa, 13.5 kDa, 140 kDa and 46 kDa, respectively. The expression levels of BDNF, NGF, TrkB, and TrkA proteins were normalized against the β-actin protein level, which was used as an internal control. The results showed that the expression of BDNF, NGF, TrkB and TrkA in the hippocampus decreased significantly in the suicide subjects when compared to the control subjects ($P<0.05$, Fig. 1).

3.2. Comparison of mRNA levels of BDNF, TrkB, NGF and TrkA between Normal Control Subjects and Suicide Victims in the hippocampus

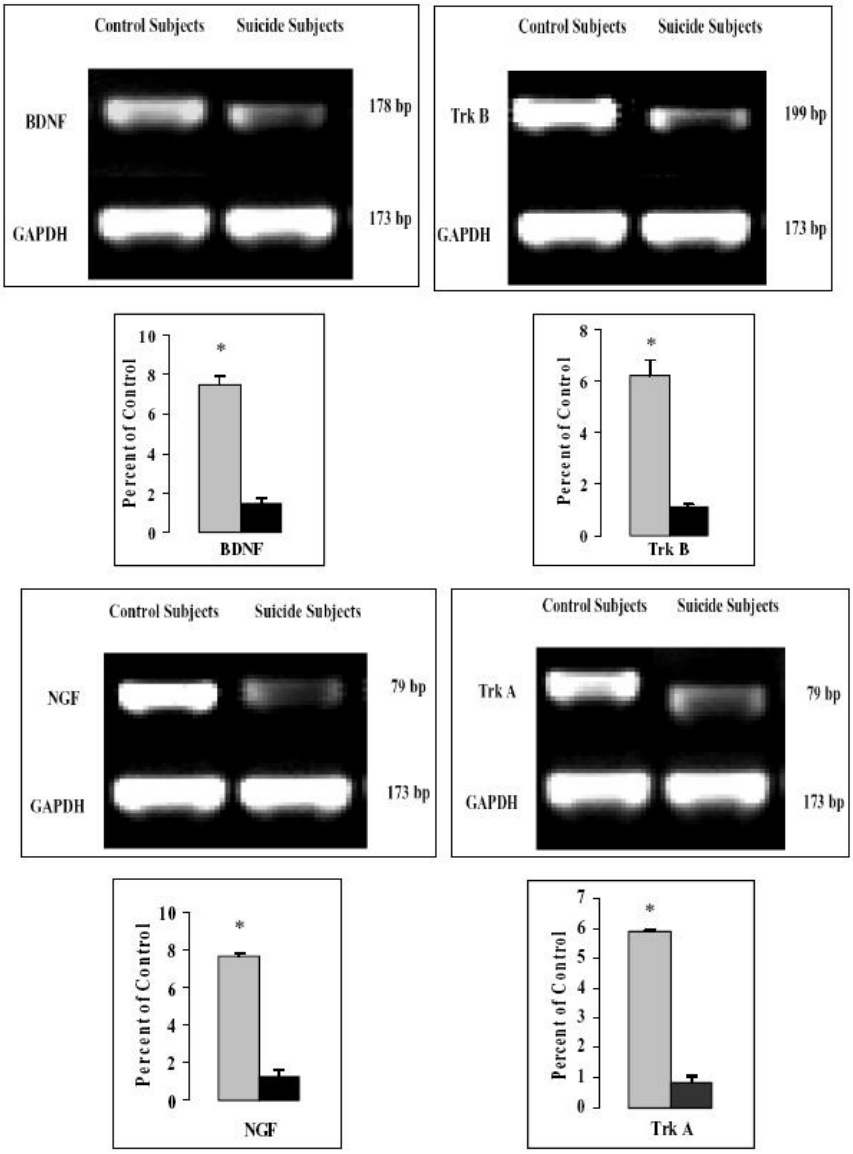

Figure 2

Representative gel electrophoreses showing the mRNA levels of BDNF, Trk B, NGF and Trk A in hippocampus of suicide subjects and normal controls. Data are the mean ± S.D. Hippocampus samples were from 19 normal controls and 21 suicide subjects. ☐ = Control subjects; ■ = Suicide Subjects.

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The lengths of BDNF, NGF, TrkB, TrkA and GAPDH amplified fragments were 178 bp, 199 bp, 79 bp, 96 bp and 173 bp respectively and the bands were clear (Fig. 2). The levels of BDNF, NGF, TrkB, and TrkA mRNA and were normalized against GAPDH mRNA levels as an internal control. Compared with the control group, the levels of BDNF, NGF TrkB and TrkA mRNA reduced in suicide subjects and the differences were statistically significant ($P<0.05$).

3.3. Correlation between Protein and mRNA Levels of BDNF, NGF, TrkB, and TrkA

To examine whether the decreases in protein levels of neurotrophins were associated with their respective mRNA levels, we correlated mRNA and protein levels of neurotrophins in the combined control and suicide groups. Interestingly, we observed a significant correlation between mRNA and protein levels of BDNF ($r=0.38$, $p< 0.001$), TrkB ($r=0.42$, $p<0.001$), NGF($r=0.42$, $p<0.001$) and TrkA ($r=0.52$, $p<0.001$) in hippocampus. Using human-specific antibodies, we compared protein levels of neurotrophins and their cognitive receptors in the hippocampal regions in normal control subjects and suicide subjects. We observed that protein levels of BDNF, NGF, TrkB and TrkA were similar within hippocampus of all control subjects. In parallel observations the present results also showed similar findings on mRNA levels of these neurotrophins and their respective receptors in hippocampus, determined quantitatively with human-specific primers by Real Time PCR. In contrast, when we compared neurotrophin levels and their respective receptors status between suicide victims and normal control subjects, we observed significant differences in all suicide victims. Both protein and mRNA levels of BDNF, NGF, TrkB, and TrkA were significantly decreased in hippocampus of suicide victims as compared with normal control subjects. The changes in neurotrophins and their receptors levels were not correlated with gender, pH of the brain, PMI, or age (Results are not shown here). Our present study, provides the evidence for the first time that two major neurotrophins BDNF and NGF along with their cognitive TrkB and TrkA receptors are not only less expressed in their protein levels but also their transcription levels are also compromised in postmortem brains of suicide subjects as evident from the mRNA studies of the present experiment.

4. CONCLUSION

Different regions of the brain play a major role in mood regulation and have been implicated in the pathophysiology of affective disorders and suicide (George et al., 1994). Mainly the hippocampus is involved in cognition (Sweatt, 2004) and is the primary brain area affected by stress (Sala et al., 2004), one of the major factors in suicidal behavior (Clayton, 1985; Monk, 1987). Therefore, in the present study, the observed decreases in the levels of neurotrophins in hippocampus might be of relevance in suicidal behavior. Interestingly, structural abnormalities in cortical and hippocampal brain areas and reduced hippocampal plasticity have been demonstrated in affective disorder patients and during stress (MacQueen et al., 2003; Miguel-Hidalgo and Rajkowska, 2002; Rajkowska, 2000; Sheline et al., 2003). Some studies suggest structural abnormalities in brain of suicide victims (Gould et al., 2000; Rajkowska, 1997). The reduced expression of neurotrophins assayed, in the present experiments, could possibly be associated with such structural abnormalities and reduced hippocampal plasticity. Interestingly, we observed a unique parallel decrease of the mRNA and protein levels of BDNF, NGF, TrkB and TrkA in hippocampus of suicide victims. This suggests that the decrease in amount of these neurotrophins and their cognitive receptors could be due to reduced transcription. A number of studies suggest that neurotrophins are regulated in response to stress (Alfonso et al., 2004; Scaccianoce et al., 2000). Whether stress might have affected the levels of neurotrophins in the brain of the suicide victims in our cohort is not clear; however, such a possibility cannot be ruled out, because there is a strong relationship between stress and suicidal behavior (Lopez et al., 1997), and a dysregulated stress system has been demonstrated in suicide victims (Hiroi et al., 2001; Lopez et al., 1992). The precise mechanisms are still to be elucidated; however, our findings of decreased levels of BDNF and NGF in suicide might be of relevance to its pathophysiology of depression.

SUMMARY OF RESEARCH

1. Evaluation of the expression profile of neurotrophins BDNF, NGF and their cognitive receptors TrkB and TrkA in the hippocampal region of suicide victims compared to normal individuals.
2. Analysis of mRNA expressions of neurotrophins and their respective receptors in the hippocampal region of postmortem suicidal brains compared to normal control subjects.
3. In this study the significant reduction of neurotrophins and their cognitive receptors clearly correlated with the significant reduction of their mRNA levels in the postmortem suicide brains.

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FUTURE ISSUES

1. Whether the BDNF/TrkB and NGF/TrkA mediated signaling cascades are the key regulator of depression?

DISCLOSURE STATEMENT

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RELATED RESOURCES

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