Curriculum Vitae

Ravi-Shankar Akundi

Born on 02 July 1977, Secunderabad, India.

Education

Year Conferred	Degree	Grade	Authorising Institute
1994	Senior School Examination	77 %	Central Board of Secondary Education (C.B.S.E), New Delhi, India
1998	Bachelor of Science (B.Sc.) (Chemistry, Biochemistry & Biotechnology)	77.8 %	Andhra University, Visakhapatnam, India
2000	Master of Science (M.Sc.) (Biotechnology)	GPA 8.23 (out of 10)	Indian Institute of Technology (I.I.T), Bombay, India
Since 2000	Graduate Student		University of Freiburg Medical School Freiburg, Germany

Research Experience

October 2000 - Present : Graduate Student, Prof. Dr. E. Wagner / Dr. Bernd L. Fiebich, Neurochemistry Lab, Dept of Psychiatry, Uniklinik-Freiburg. Research involves studies on the signal transduction pathways in neuronal and glial cells with particular emphasis on neuronal apoptosis and neuro-inflammation.

August 1999 - April 2000 : Undergraduate Project, Dr. Sanjay Sonar, Biotechnology Centre, Indian Institute of Technology (Bombay). Studied the structural features of the protein bacteriorhodopsin through its chemical modification (cysteine incorporation & biotinylation) for studies in biomolecular electronics. (Title : "Site-specific non-native amino acid incorporation via cysteine chemical modification").

May 1999 - July 1999 : Internship, Dr. Dilip Bandyopadhyay, Tata Memorial Center, Bombay. Studied the expression of c-myc transcript in proliferating tissue culture cells.

Awards

2000 Ranked All-India 10th (Percentile 99.37 in Life Sciences) at the **Graduate Aptitude Test in Engineering** (GATE) conducted by the Indian Institutes of Technology and Indian Institute of Science, Bangalore, on behalf of the Department of Science & Technology, Govt. Of India.

1990 Awarded a Certificate of Learning in a preliminary course in Homoeopathy held by the World Teacher Trust, Visakhapatnam, India.

Co-curricular Activities

- Designed web-pages for the current lab (http://www.uniklinik-freiburg.de/k/psy/appt/de/auw/schwerpunkte/labpages/lab.html).
- Worked at a local dispensary (Master E.K. Homeopathy Vaidyalayam, Visakhapatnam, India) for two years and have actively participated in village tours conducted by the same.
- Trained in Indian Classical (Carnatic) music. Occasionally write poems and short stories (http://www.geocities.com/arshankar1977).

Publications

Akundi RS, Macho A, Munoz E, Lieb K, Bringmann G, Clement H-W, Hüll M, Fiebich BL. 1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline (TaClo) induced apoptosis in the human neuroblastoma cell-line SK-N-SH. *J Neurochem.* (in press)

Fiebich BL, **Akundi RS**, Seidel M, Geyer V, Haus U, Müller W, Stratz T, Candelario-Jalil E. Expression of 5-HT_{3A} receptors in cells of the immune system. *Scand J Rheumatol*. (in press)

Akundi RS, Hull M, Clement HW, Fiebich BL. 1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline (TaClo) induces apoptosis in human neuroblastoma cell lines. *Ann N Y Acad Sci*. 2003 Dec;1010:304-6.

Lieb K, Treffurth Y, Hamke M, **Akundi RS**, von Kleinsorgen M, Fiebich BL. Valproic acid inhibits substance P-induced activation of protein kinase C epsilon and expression of the substance P receptor. *J Neurochem*. 2003 Jul;86(1):69-76.

Fiebich BL, Waschbisch A, **Akundi RS**, Candelario-Jalil E, Schmitz ML, Hoozemans JJM, Virtainen N, Veerhuis R, Slawik H, Yrjänheikki J, Hüll M. Interleukin-1β–induced expression of the prostaglandin E_2 receptor type 3 (EP3) in astrocytes depends on protein kinase C and NF-κB. *J Immunol* (in revision)

Fiebich BL, **Akundi RS**, Lieb K, Candelario-Jalil E, Geyer V, Orlikowsky S, Haus U, Müller W, Stratz T, Munoz E. 5-HT_3 receptor antagonists inhibit the release of pro-inflammatory cytokines and p38 MAP kinase activation in primary human monocytes. *J Pharmacol Exptl Therap* (in revision)

Lieb K, Biersack L, Waschbisch A, Orlikowski S, **Akundi RS**, Candelario-Jalil E, Hüll M, Fiebich BL. Serotonin via 5-HT_7 receptors activates p38 MAP kinase and protein kinase C epsilon resulting in interleukin-6 synthesis in human U373MG astrocytoma cells. *J Neurochem* (submitted)

Heinzmann M, Candelario-Jalil E, **Akundi RS**, Hüll M, Knörle R, Schneirle P, Aicher B, Finkenzeller G, Fiebich BL. The combination of acetylsalicylic acid, paracetamol and caffeine reduces extracellular dopamine by the inhibition of tyrosine hydroxylase expression. *Naunyn Schmiedeberg Arch Pharmacol* (submitted)

Fiebich BL, **Akundi RS**, Hamke M, Schmidt C, Butcher RD, van Calker D, Willmroth F. IL-6 expression induced by adenosine A_{2b} stimulation in U373MG cells depends on p38 MAPK and PKC. *Neurochem Intl*. (submitted)

Akundi RS, Hüll M, Lieb K, Gebicke-Haerter P, Fiebich BL. Regulation of cyclooxygenase in rat microglia : role of MAPK and sphingomyelinases. (in process)

Hüll M, Mueksch B, **Akundi RS**, Waschbisch A, Fiebich BL. Amyloid β-peptide (25-35) activate protein kinase C leading to cyclooxygenase-2 induction and prostaglandin E_2 release in primary midbrain astrocytes. (in process)

Akundi RS, Candelario-Jalil E, Clement HW, Hüll M, Fiebich BL. 1-trichloromethyl-1,2,3,4-tetrahydro-beta-carboline ('TaClo') – mediated inhibition of prostaglandin E_2 synthesis : *in vitro* and *in vivo* evidences. (in process)

Fiebich BL, Lieb K, Appel K, Candelario-Jalil E, **Akundi RS**, Hüll M. Ascorbic acid enhances the inhibitory effect of acetylsalicylic acid on neuronal cyclooxygenase-2-mediated prostaglandin E_2 release. (in process)

Communications – Posters

- XIth Annual Meeting of the Psychoneuroimmunology Research Society (May 26 - 29, 2004), Titisee (Germany) :
  1. Amyloid beta peptides (25-35) activate protein kinase C leading to cyclooxygenase-2 induction and prostaglandin E2 release in primary midbrain astrocytes. **Akundi RS**, Hüll M, Mueksch B, Waschbisch A, Fiebich BL. (Poster)
  2. Signal transduction pathways in activated microglia. **Akundi RS**, Hüll M, Lieb K, Fiebich BL. (Poster)

- Neurex Annual Meeting (23 Apr 2004), Freiburg (Germany) : Interleukin-1 beta induces the expression of the prostaglandin E2 receptor type 3 in astrocytes - the involvement of protein kinase C and NF-kappaB. Waschbisch A, Hüll M, **Akundi RS**, Schmitz ML, Hoozemans JJM, Virtainen N, Veerhuis R, Slawik H, Yrjänheikki J, Fiebich BL. (Poster)

- XIth Euroconference on Apoptosis organised by the European Cell Death Organisation (ECDO) (Oct 25 - 28, 2003), Ghent (Belgium) : 1-trichloromethyl-1,2,3,4-tetrahydro-beta-ccarboline induced apoptosis in the human neuroblastoma cell-line SK-N-SH. **Akundi RS**, Macho A, Munoz E, Clement H-W, Hüll M, Fiebich BL. (Poster)

- IVth International Meeting on Apoptosis (Jan 29 - Feb 1, 2003), Luxembourg : TaClo - induced cell - death in Human Neuroblastoma Cells. **Ravi, A**., Clement, H.-W. and Fiebich, B.L. (Poster)

- Vth European Meeting on Glial Cell Function in Health and Disease (May, 21-25, 2002), Rome : Sodium Valproate inhibits Substance P-induced interleukin-6 synthesis in human astrocytoma cells. Treffurth, Y., Hamke, M., **Akundi, R.S**., Fiebich, B.L., Lieb, K. (Poster)

Research Interests

My research interests lie in the field of neuroscience's, and in particular, the mechanisms of neurodegeneration. As part of my doctoral thesis, my work involved in identifying the signal transduction pathways regulating the synthesis of prostaglandin E_2 (PGE_2) during neuronal apoptosis and glial activation. I would like to continue further in this exciting field of research and expand these findings on the regulation of inflammatory cytokines such as interleukin-1β and TNF-α. Evidences for neuronal apoptosis in various neurodegenerative disorders, including Parkinson's disease, has been reported. However, the regulation of inflammatory factors, such as cytokines and PGE_2, their synthesis and associated signal transduction mechanisms are not completely understood. Following the lead identification of PKC and ATP in the regulation of PGE_2 synthesis in neuronal and microglial cells, further elucidation of their involvement in neurodegeneration presents a target for intervention. In addition, the role of growth factor mediated neuronal differentiation and its effects on cytokine / PGE_2 synthesis is of particular interest.

Contact Addresses of Referees

1. Dr. Bernd L. Fiebich, Ph.D.
   Head, Neurochemistry Laboratory I,
   Dept. of Psychiatry,
   University of Freiburg Medical School,
   Hauptstrasse 5,
   Freiburg D79104.
   e-mail : bernd_fiebich@psyallg.ukl.uni-freiburg.de
   phone : +49 – 761 – 270 6898
   fax : + 49 – 761 – 270 6917

2. PD Dr. Michael Hüll, M.D.
   Head, Centre for Geriatrics and Gerontology,
   Dept. of Psychiatry,
   University of Freiburg Medical School,
   Hauptstrasse 5,
   Freiburg D79104.
   e-mail : michael_huell@psyallg.ukl.uni-freiburg.de
   phone : +49 – 761 – 270 6619
   fax : +49 – 761 – 270 6917

3. Prof. G. Subrahmanyam
   Associate Professor,
   Signal Transduction Lab,
   School of Biosciences and Bioengineering,
   Indian Institute of Technology,
   Powai, Mumbai – 400 076. India.
   e-mail : gsm@iitb.ac.in
   phone : +91 – 22 – 2576 7777
   fax : +49 – 22 – 2572 3480

Current Research Summary

"Signal Transduction Mechanisms in Neuro-inflammation : Regulation of Prostaglandin (PG) E_2 Synthesis in Neuronal Apoptosis and Glial Activation – the Role of Protein Kinase C (PKC) and Cellular or Extracellular ATP"

My work at the Neurochemitsry Research Group at the Department of Psychiatry, University of Freiburg Medical School, comprises of identifying the signal transduction pathways that are involved in neurodegenerative disorders with particular emphasis on the inflammatory parameters of these disorders.

In the study of neurodegeneration, we employed a relatively recently discovered environmental toxin - 1-trichloromethyl-1,2,3,4-tetrahydro-β-carboline (TaClo). It is synthesised *in vivo* through the condensation of the biogenic amine, tryptamine, with the still used hypnotic, chloral hydrate, or its metabolic precursor, the industrial solvent, trichloroethylene. Owing to its structural similarity to MPTP, and its ability to inhibit mitochondrial complex I, TaClo has previously been implicated in the etiology of Parkinson's disease. Our studies showed that TaClo causes a cytochrome c-dependent apoptosis in the human neuroblastoma cell-line, SK-N-SH. TaClo mediated a strong inhibition of metabolic ATP that rendered the apoptotic pathway largely irreversible. Though the use of a protein kinase C (PKC) inhibitor, Gö 6983, transiently elevated the levels of cellular ATP and caused an inhibition of caspase 3 activity, suggesting a role of mitochondrial K^+ channels in the pathway; TaClo-mediated DNA fragmentation could not be prevented.

In contrast to reports on MPP^+, TaClo dose-dependently inhibited the synthesis of prostaglandin E_2 (PGE_2) in interleukin-1β–stimulated SK-N-SH cells. At higher doses, TaClo inhibited the PG rate-limiting enzyme, cyclooxygenase-2 (COX-2). Further, when 0.4 mg/kg TaClo was injected in male Lewis rats for 24 h, inhibition of COX-2 expression and PGE_2 synthesis was observed in the hippocampus, corresponding to a decrease in hippocampal ATP ($P < 0.05$, n = 5).

Microglial activation and the corresponding synthesis and release of PGE_2 play an important role in the pathophysiology of neurodegenerative disorders. We used rat primary microglia stimulated with bacterial lipopolysaccharide (LPS) as a model. We found a primary role of ceramides in LPS-mediated PGE_2 release. LPS strongly induced acidic sphingomyelinase (A-SMase) that further activated the p38 mitogen-activated protein kinase (MAPK), but not the extracellular signal-regulated kinases (p42/44). However, both the MAPKs were shown to be important in LPS-mediated PGE_2 release.

The PKC inhibitors played a differential role in microglial PGE_2 synthesis. Though GF109203X inhibits LPS-induced PGE_2 synthesis, only Gö 6976 strongly inhibits in the nanomolar range. This inhibition could be reversed by the application of extracellular ATP to the medium. The characterisation of various purinergic receptors on rat microglia was performed. Through the use of selective agonists and antagonists for various purinergic receptors, a role for P_{2X7} and P_{2Y} have been implicated; and the signal transduction pathways are being studied.

The role of PKC in the inflammatory pathway has also been studied in primary astrocytes. Of particular interest is the phosphorylation and membrane translocation of PKC upon stimulation by amyloid peptides ($\beta A4_{25-35}$) in both human and rat primary astrocytes.

In summary, my work at the Neurochemistry Research Group helps understand the regulation of PGE_2 synthesis in various pathophysiological conditions such as neuronal apoptosis and microglial activation. The central role of PKC in the synthesis of PGE_2 in both astrocytes and microglia makes it a good choice for therapeutic intervention. The availability of various PKC inhibitors, with differing IC_{50} values, have made the identification of specific isoforms of PKC easier. Similarly, the addition of extracellular ATP in reversing the inhibitory role of PKC inhibitors on PGE_2 synthesis also presents a useful target for intervention.