

# Neurotransmitters Functional Balance in Neurodegenerative Disease Management: Recent Advances

C. S. Paulose\*, Ameer Krishnakumar and Anu Joseph

Molecular Neurobiology and Cell Biology Unit, Centre for Neuroscience, Head, Department of Biotechnology, Cochin University of Science and Technology, Cochin 682 022, Kerala, India.  
E-mail: cspaulose@cusat.ac.in

Received 1 October 2006; Accepted 25 October 2006

## Abstract

The recent developments in neurobiology have rendered new prominence and potential to study about the structure and function of brain and related disorders. Human behaviour is the net result of neural control of the communication between brain cells. Neurotransmitters are chemicals that are used to relay, amplify and modulate electrical signals between neurons and/or another cell. It mediates rapid intercellular communication through the nervous system by interacting with cell surface receptors. These receptors often trigger second messenger signaling pathways that regulate the activity of ion channels. The functional balance of different neurotransmitters such as Acetylcholine (Ach), Dopamine (DA), Serotonin (5-HT), Norepinephrine (NE), Epinephrine (EPI), Glutamate and Gamma amino butyric acid (GABA) regulates the growth, division and other vital functions of a normal cell / organism (Sudha, 1998). Any change in neurotransmitters' functional balance will result in the failure of cell function and may lead to the occurrence of diseases. Abnormalities in the production or functioning of neurotransmitters have been implicated in a number of neurological disorders like Schizophrenia, Alzheimer's, Epilepsy, Depression and Parkinson's disease. Changes in central and peripheral neuronal signaling system is also noted in diabetes, cancer, cell proliferation, alcoholism and aging. Elucidation of neurotransmitters receptor interaction pathways and gene expression regulation by second messengers and transcriptional factors in health and disease conditions can lead to new small molecules for development of therapeutic agents to improve neurological disease conditions. Increased awareness of the global effects of neurological disorders should help health care planners and the neurological community set appropriate priorities in research, prevention, and management of these diseases.

**Key Words:** Neurotransmitters, neurotransmission, neurological disorders and disease management.

## Introduction

Neurons are the basic cell of the brain and nervous system. Neurons communicate to each other by releasing neurotransmitters. Neurotransmitters are the chemicals which account for the transmission of signals from one neuron to the next across synapses. It transmits information within the brain and from the brain to all the parts of the body. Neurotransmitters exert their effect by binding to specific receptors on the neuronal postsynaptic membrane. The activity of a neuron depends on the balance between the number of excitatory and inhibitory processes affecting it, either processes occurring individually or simultaneously (Paulose et al, 1999). The consequences of the neurotransmitter receptor function can influence the regulation of metabolic manifestations in hypothyroidism, hypertension, diabetes and cell proliferation directly by central nervous system function or through the hypothalamic-pituitary-end organ axis. Hormones such as insulin, glucagon, thyroxine, tri-iodothyronine, glucocorticoids function as growth regulators. The functional difference of neurotransmitters and hormones through receptor subtypes can lead to differential gene expression. The

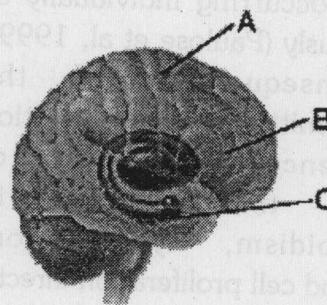
functional balance of different neurotransmitters such as acetylcholine (Ach), dopamine (DA), serotonin (5-HT), nor epinephrine (NE), epinephrine (EPI), glutamate and gamma amino butyric acid (GABA) and various hormones regulates the growth, division and other vital functions of a normal cell / organism (Paulose et al., 2005).

Most neurological and psychiatric disorders involve selective or preferential impairments of neurotransmitter systems. Therefore, studies of functional neurotransmitter pathophysiology in human brain are of unique importance in view of the development of effective, mechanism-based, therapeutic modalities. The use of neurosurgically removed fresh animal tissue samples in which receptors, transporters, ion channels, and enzymes essentially retain their natural environment, represents a unique experimental approach to enlarge our understanding of human brain processes. Using this experimental approach, many human brain functional proteins, in particular neurotransmitter receptors have been characterized in terms of localization, function, and pharmacological properties (Maurizio Raiteri, 2006).

Parkinson's disease, a neurological disorder involves the degeneration of dopaminergic neurons in the nigrostriatal tract, which projects from the substantia nigra pars compacta in the midbrain to the striatum and is essential for the control of movement. The disease leads to tremor, rigidity and hyperkinesias. Reports show a vulnerability of parkin gene to modification by dopamine, the principal neurotransmitter lost in Parkinson disease, suggesting a mechanism for the progressive loss of parkin function in dopaminergic neurons during aging and sporadic Parkinson disease (Matthew et al., 2005).

Epilepsy is syndrome of episodic brain dysfunction characterized by recurrent unpredictable spontaneous seizures. Temporal-lobe epilepsy is characterized by a loss of glutamate-stimulated GABA release that is secondary to a reduction in the number of GABA transporters (Matthew et al., 2002). Electrophysiological studies of human temporal-lobe epilepsy suggest that a loss of hippocampal GABA-mediated inhibition may underlie the neuronal hyperexcitability (Knowles, 1992). Glutamate or analogue excitatory amino acids are the

principal excitatory neurotransmitters in the mammalian CNS (Watkins & Evans, 1981), which is also involved in this disease. In the hippocampus, two different types of glutamate receptors, the *N*-methyl-D-aspartate (NMDA) and  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, each linked to different classes of ion channels are coactivated on the release of glutamate from presynaptic terminals (Bekkers & Stevens, 1989). The dentate granule from human epileptic hippocampus cells, which were acutely dissociated, showed prolonged NMDA receptor channel openings (Lieberman, et al., 1996).



- A = Cerebral Cortex
- B = Basal Forebrain
- C = Hippocampus

Fig: 1 Areas of the brain affected by AD

Alzheimer's disease (AD) is an irreversible, progressive disorder in which brain cells (neurons)

## Introduction

Neurons are the basic cell of the brain and nervous system. Neurons communicate to each other by releasing neurotransmitters. Neurotransmitters are the chemicals which account for the transmission of signals from one neuron to the next across synapses. It transmits information within the brain and from the brain to all the parts of the body. Neurotransmitters exert their effect by binding to specific receptors on the neuronal postsynaptic membrane. The activity of a neuron depends on the balance between the number of excitatory and inhibitory processes affecting it, either processes occurring individually or simultaneously (Paulose et al, 1999). The consequences of the neurotransmitter receptor function can influence the regulation of metabolic manifestations in hypothyroidism, hypertension, diabetes and cell proliferation directly by central nervous system function or through the hypothalamic-pituitary-end organ axis. Hormones such as insulin, glucagon, thyroxine, tri-iodothyronine, glucocorticoids function as growth regulators. The functional difference of neurotransmitters and hormones through receptor subtypes can lead to differential gene expression. The

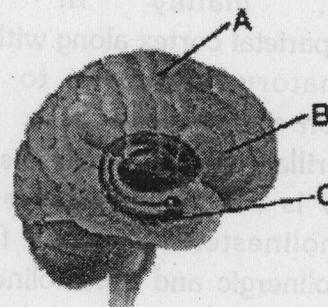
functional balance of different neurotransmitters such as acetylcholine (Ach), dopamine (DA), serotonin (5-HT), nor epinephrine (NE), epinephrine (EPI), glutamate and gamma amino butyric acid (GABA) and various hormones regulates the growth, division and other vital functions of a normal cell / organism (Paulose et al., 2005).

Most neurological and psychiatric disorders involve selective or preferential impairments of neurotransmitter systems. Therefore, studies of functional neurotransmitter pathophysiology in human brain are of unique importance in view of the development of effective, mechanism-based, therapeutic modalities. The use of neurosurgically removed fresh animal tissue samples in which receptors, transporters, ion channels, and enzymes essentially retain their natural environment, represents a unique experimental approach to enlarge our understanding of human brain processes. Using this experimental approach, many human brain functional proteins, in particular neurotransmitter receptors have been characterized in terms of localization, function, and pharmacological properties (Maurizio Raiteri, 2006).

Parkinson's disease, a neurological disorder involves the degeneration of dopaminergic neurons in the nigrostriatal tract, which projects from the substantia nigra pars compacta in the midbrain to the striatum and is essential for the control of movement. The disease leads to tremor, rigidity and hyperkinesias. Reports show a vulnerability of parkin gene to modification by dopamine, the principal neurotransmitter lost in Parkinson disease, suggesting a mechanism for the progressive loss of parkin function in dopaminergic neurons during aging and sporadic Parkinson disease (Matthew et al., 2005).

Epilepsy is syndrome of episodic brain dysfunction characterized by recurrent unpredictable spontaneous seizures. Temporal-lobe epilepsy is characterized by a loss of glutamate-stimulated GABA release that is secondary to a reduction in the number of GABA transporters (Matthew et al., 2002). Electrophysiological studies of human temporal-lobe epilepsy suggest that a loss of hippocampal GABA-mediated inhibition may underlie the neuronal hyperexcitability (Knowles, 1992). Glutamate or analogue excitatory amino acids are the

principal excitatory neurotransmitters in the mammalian CNS (Watkins & Evans, 1981), which is also involved in this disease. In the hippocampus, two different types of glutamate receptors, the *N*-methyl-D-aspartate (NMDA) and  $\alpha$ -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors, each linked to different classes of ion channels are coactivated on the release of glutamate from presynaptic terminals (Bekkers & Stevens, 1989). The dentate granule from human epileptic hippocampus cells, which were acutely dissociated, showed prolonged NMDA receptor channel openings (Lieberman, et al., 1996).



- A = Cerebral Cortex
- B = Basal Forebrain
- C = Hippocampus

Fig: 1 Areas of the brain affected by AD

Alzheimer's disease (AD) is an irreversible, progressive disorder in which brain cells (neurons)

deteriorate, resulting in the loss of cognitive functions, primarily memory, judgment and reasoning, movement coordination, and pattern recognition. In advanced stages of the disease, all memory and mental functioning may be lost. It is the most common cause of dementia.

Patients also frequently have noncognitive symptoms, such as anxiety, depression, apathy, and psychosis that impair daily living. The condition predominantly affects the cerebral cortex and hippocampus, which lose mass and shrink (atrophy) as the disease advances. Mudher & Lovestone, (2002) reported neuronal loss or atrophy, mainly in the temporoparietal cortex along with an inflammatory response to the deposition of amyloid plaques and neurofibrillary tangles. The loss of memory is related to the loss of acetylcholinesterase (AChE) from both cholinergic and noncholinergic neurons of the diseased brain. However, AChE activity is increased around amyloid plaques. This increase in AChE is of significance for therapeutic strategies using AChE inhibitors. With no cure in sight for Alzheimer's disease, efforts are undertaken to lessen the symptoms once it is diagnosed. Glycosylation of AChE may be a useful diagnostic

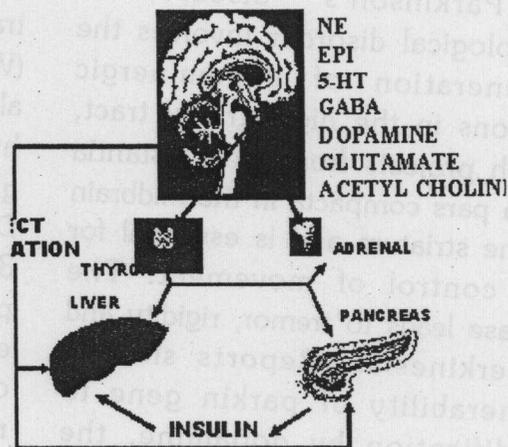


Fig: 2 Neuroendocrine Regulation of Insulin Secretion and cell proliferation

marker for AD (Sáez-Valero et al., 1999). There are medications that can lessen agitation, anxiety, unpredictable behavior, improve sleeping patterns, and treat depression.

Apart from the central nervous system, neurotransmitters also play an important role in diseases associated with the peripheral system. Diabetes Mellitus is a metabolic disorder associated with insulin deficiency, which affects the carbohydrate metabolism linked with various central and peripheral complications. The pancreatic islets are innervated by parasympathetic, sympathetic and sensory nerves. Several neurotransmitters are stored within the terminals of these nerves. The central nervous system (CNS) neurotransmitters play an important

role in the regulation of glucose homeostasis. Lesions in the substantia nigra caused a reduction in the size and number of islet cell populations and decreased the content of insulin and glucagon in the pancreas (Smith, & Davis 1985). Diabetes is reported to damage the dopaminergic function. An increased turnover of DA to norepinephrine has been reported in the pancreatic islets, which could damage the stimulatory effect of DA (Morgan & Montagu, 1985). NE, a stress hormone at higher concentration not only inhibited the DA uptake but also its stimulatory effect on insulin secretion in the pancreatic islets (Eswar et al., 2006).

Insulin pathways in the brain play an important role in regulating dopamine transporter (DAT) activity. DAT regulates DA levels and their number is found to be decreased during diabetes due to hypoinsulinemia, which damages the dopaminergic activity (Figleicz et al., 2003). Chronic hyperglycemia during diabetes mellitus is a major initiator of diabetic microvascular complications like retinopathy, neuropathy and nephropathy (Sheetz & King, 2002). Neurotransmitter receptor studies (Dakshinamurthi, et al., 1985, 1988; Vishvanathan et al., 1988, 1990; Paulose &

Dakshinamurthi., 1985) and its regulation of hyperthyroidism (Dakshinamurthi, et al., 1986; Tessy et al., 1997) leading to sympathetic stimulation and hypertension in pyridoxine deficient rats (Paulose et al., 1988 & Dakshinamurthi, et al., 1990a, b) which in turn leads to diabetes have been reported. Studies from our laboratory have also established the central neurotransmitter subtypes functional regulation during pancreatic regeneration and cell proliferation (Mohanam et al., 2005; Ani et al., 2006; Renuka et al., 2006).

Endogenous progenitor cells can be harnessed to replace neurons lost in neurodegenerative diseases but requires the development of methods to stimulate their proliferation and differentiation. Researchers are also exploring a process called trans-differentiation – “tricking” cells of the bone marrow to produce brain cells or muscle cells. Experiments are done using pluripotent cells extracted from the bones along with different neurotransmitters individually and in combination to be infused to the site of damage in animal model using stereotaxic equipment in Epilepsy and Parkinson's disease.

Neurotransmitters are believed

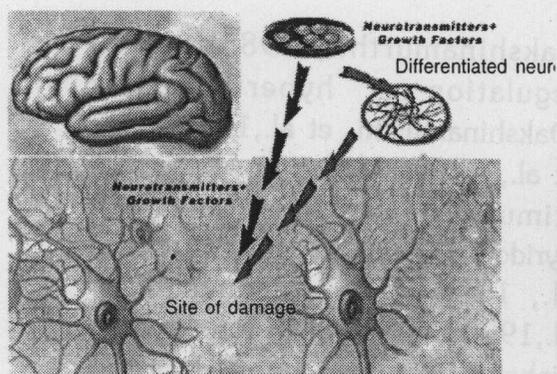


Fig 3a: Neurotransmitters + pluripotent cell infusion at site of injury

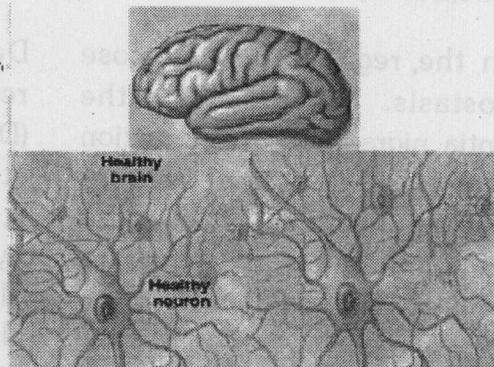


Fig 3b: Neuronal network re-established after treatment at the damaged site

to play a regulatory role during cell proliferation. Scientists are developing a number of strategies for producing dopamine neurons from human stem cells in the laboratory for transplantation into humans with Parkinson's disease. Dopaminergic neurons derived from embryonic stem cells can re-innervate the brain and restore dopaminergic neurotransmission. This has been shown by dopamine release, correction of a behavioral motor syndrome and functional integration as shown by the restoration of blood flow and activity in cerebral cortex after transplantation (Bjorklund, et al., 2002). The successful generation of an unlimited supply of dopamine neurons could make neuro transplantation widely available for Parkinson's patients at some point in the future. Researchers are now examining the possibility of

transplanting GABAergic neurons in the hippocampal region for the treatment of epilepsy. It is suggested that pluripotent bone marrow cells can be used directly with different neurotransmitter combination or differentiated neuronal cells directly to the site of damage to re-establish the neuronal connection (Fig: 3a, 3b) for the better management of the disease. A detailed study at the molecular level on the mechanism involved in role of neurotransmitters during stem cell therapy in neurodegenerative diseases and its functional modification could lead to therapeutic intervention which will have immense clinical significance in disease management.

## Conclusion

As the world's aged population increases, the relative effects of many disorders of the nervous system,

including stroke and dementia, are numerous. Increased awareness of the global effects of neurological disorders should help health care planners and the neurological community to set up appropriate priorities in research, prevention, and management of these diseased conditions. Neuropharmacology has transformed the management of Parkinsonism and epilepsy. New imaging techniques such as CT, NMR, PET and ultrasonic scanning have presented us with remarkable images of the nervous system in health and disease. Positive results help in diagnostic tests to enable the individualization of treatment and thus present new targets for drug development and better management of neurological disorders.

### Acknowledgements

C. S. Paulose thanks DAE, DBT, DST, ICMR, UGC, Govt. of India and STEC, Kerala for providing necessary facilities.

### References

- Ani V. D., Finla C and Paulose C. S. 2006. Decreased  $\alpha_2$  adrenergic receptor in the brainstem and pancreatic islets during pancreatic regeneration in weanling rats. *Life Sciences* 79: pp. 1507- 1513.
- Bekkers J. M. and Stevens C. F. 1989. NMDA and non-NMDA receptors are co-localized at individual excitatory synapses in cultured rat hippocampus. *Nature Lond* 341: pp. 230-233.
- Bjorklund L. M., Pernaute R. S and Chung S. 2002. Embryonic stem cells develop into functional dopaminergic neurons after transplantation in a Parkinson rat model. *Proc Natl Acad Sci USA* 99: pp. 2344-49.
- Boulton A. J. M., Gries F. A., Jervell J. 1998. Guidelines for the diagnosis and out patient management of diabetic peripheral neuropathy. *Diabet Med* 15: pp. 917-31.
- Dakshinamurthi K., Paulose C. S, Thliveris J. A. and Vriend J. 1984. Thyroid function in pyridoxine deficient rats *J. Endocr* 104: pp. 345- 345.
- Dakshinamurthi K., Paulose C. S. and Vriend J. 1985. Hypothyroidism of hypothalamic origin in pyridoxine deficient rats. *J. Endocr* 104: pp. 345- 345.
- Dakshinamurthi K., Paulose C. S, Vishwanathan M, Siow Y. L. 1988. Neuroendocrinology of Pyridoxine deficiency. *Neurosci & Behavioural Review*. 12: pp. 189- 193.
- Dakshinamurthi K., Paulose C. S, Vishwanathan M, Siow Y. L and Sharma K. 1990. Alterations in the brainstem  $\alpha_2$  adrenoreceptor activity in pyridoxine deficient rat model of hypertension. *Ann New York Acad of Science* 585: pp. 128- 144.
- Eswar Shankar P. N., Santhosh K. T., and Paulose C. S. 2006. DArgic Regulation of Glucose-induced Insulin Secretion through DA D2 Receptors in the Pancreatic Islets In Vitro. *IUBMB Life* 58, 157-163.
- Ficlewicz D. P., Brot M. D., McCall A. L, Szot P 1996. *Brain Res* 964: pp. 107- 115.
- Knowles W. D., Awad I. A. and Nayel M. H. 1992. Differences of in vitro electrophysiology of hippocampal neurons from epileptic patients with mesiotemporal sclerosis versus structural lesions. *Epilepsia* 33, pp. 601-609.
- Lieberman D. N., Isokawa M., Fried I., and Mody I. 1996. Properties of single NMDA channels in dentate granule cells of temporal lobe epilepsy patients. *Epilepsia* 37, Suppl. 5: 79.
- Matthew J., Ostaszewski B. L., Weihofen A, Schlossmacher M. G., and Selkoe D. J. 2005. Dopamine covalently modifies and functionally inactivates parkin. *Nature Medicine* 11, pp. 1214 - 1221
- Matthew, J., Kathryn M. R. & Dennis, D. S. 2002. Hippocampal GABA transporter function in temporal-lobe epilepsy.

## Invited Articles

Science & Society

- Nature* 376 pp.174 – 177.
- Maurizio R. 2006. Functional Pharmacology in Human Brain. *Pharmacol Rev* 58: pp.162-193.
- Mudher A, Lovestone S. 2002. Alzheimer's disease-tauists and baptists finally shake hands? *Trends Neurosci* 25 (1): pp. 22-26.
- Mohan V. V, Finla C., and Paulose C. S. 2004. Decreased 5-HT<sub>2c</sub> receptor binding in the cerebral cortex and brainstem during pancreatic regeneration in rats. *Mol. and Cell. Biochem* 272: pp. 165- 170.
- Morgan N. G., and Montagu W. 1985. Studies on the mechanism of inhibition of glucose induced insulin secretion by noradrenalin in rat islets of langerhans. *Biochem. I.J.*, 226, pp. 571- 576.
- Paulose C. S. & Dakshinamurthi K. 1985. Effect of pyridoxine deficiency in young rats on high affinity serotonin and dopamine receptors. *J. Neurosci. Res* 14: pp. 263- 270.
- Renuka T. R., Remya R., and Paulose C. S. 2006. Increased insulin secretion by muscarinic M1 and M3 Receptor function from rat pancreatic islets in vitro. *Neurochem. Res* 1- 8.
- Sáez-Valero J., Sberna G., McLean C. A. and Small D. H. 1999. Molecular Isoform Distribution and Glycosylation of Acetylcholinesterase Are Altered in Brain and Cerebrospinal Fluid of Patients with Alzheimer's Disease. *J Neurochem* 72: pp. 1471-4159.
- Sheetz M. J, King G. L 2002. Molecular understanding of hyperglycemia's adverse effects for diabetic complications. *JAMA* 228: pp. 2579-2588.
- Smith P. H. and Davis B. J. 1985. Effect of substantia nigra lesions on the volume of A, B and D cells and the content of insulin and glucagon in the rat pancreas. *Diabetologi*, 28, pp. 756-762.
- Sudha B and Paulose C. S. 1998. Induction of DNA synthesis in primary cultures of rat hepatocytes by serotonin: Possible involvement of Serotonin S<sub>2</sub> receptor. *Journal of Hepatology* 27, pp. 62 - 66.
- Tessy T. M, Sudha B. and Paulose C. S. 1997 Kinetic parameters of thymidine kinase and DNA synthesis during liver regeneration: Role of thyroid hormones. *Life Sciences* 21: pp. 1867-1874.
- Vishwanathan M, Paulose C. S., Lal K. J., Sharma S. K. and Dakshinamurthi K. 1990. Enhancements of high affinity  $\gamma$ -aminobutyric acid receptor binding in cerebellum of pyridoxine deficient rats. *Neurosci. Letters* 111: pp. 201-205.
- Vishwanathan M, Paulose C. S., Siow Y. L, Dakshinamurthi K. 1998. Pineal indoleamine metabolism in pyridoxine deficient rats. *Brain Res* 473: pp. 37- 42.