NEUROPHARMACOLOGY

Ram Raghubir and C. Nath

Introduction

Neuropharmacology has received priority at various scientific institutions, universities and and at some medical colleges. It has undergone significant development in the past decade leading to a steady and balanced growth of this discipline. Efforts in this area have been mainly directed to study regulation of some basic neurophysiological processes in the central and autonomic functions, besides elucidating the mechanism of action of centrally acting drugs developed in India or drugs in clinical use. Drug targets and newer models more akin to clinical situation have been standardized or developed for some CNS disorders. Molecular biology techniques have been increasingly used in most of the institutions in the country, thus giving impetus to molecular neuropharmacology.

Research in these areas has involved use of several classical and sophisticated techniques like microinjection, microstimulation, perfusion and superfusion of drugs, implantation of neuronal tissue and or neural stem cells into localised brain areas, selective lesioning of brain nuclei and pathways, use of specific and selective ligands for receptor binding and neurotransmitter turnover studies in discrete brain nuclei and heart. Further, EEG, single unit studies and microiontophoresis into brain neurones (Verma, 1998) have been employed to investigate the neuronal activity in the central nervous system. Use of microsphere technique and direct measurement of vascular blood flow by electromagnetic flowmeter was being used to study the effect of drugs on cardiac output and peripheral blood flow. The present review covers the areas in which significant progress has been achieved, since the publication of last comprehensive neuropharmacology status report by Dhawan and Patnaik (1989). Updates have also been published subsequently by Bhattacharya and Chakrabarti (1993) and Murugensndam et al (2000) as part of Indian National Science Academy's Status Report of Parmacological Research in India during that period.

Central Nervous System

Stimulation Produced Analgesia

A mild and brief electrical stimulation of tiny sites in the pretectal nucleus of rat evoked potent and long lasting antinociception (Kumar et al., 1990). The pretectal stimulation produced analgesia (SPA) is naloxone sensitive (Kumar et al., 1992).

SPA seems to involve both cholinergic and adrenergic neuroreceptors as well (Kumar et al., 1991 a, b). There is evidence, which suggests involvement of NO in mediation of pretectal antinociception (Kumar et al., 1993a). Morphine micoinjection into pretectal nucleus also produced marked and long lasting

antinociception (Kumar et al., 1993b). Microinjection of adrenergic, cholinergic and opioidergic agonists into pretectal nucleus produced mild analgesia, which was prevented or reversed by their respective antagonists (Kumar et al., 1994). Nucleus raphe lesion did not affect but lesion of red nucleus attenuated pretectal antinociception. Interestingly, red nucleus stimulation produced analgesia is also NO mediated (Kumar et al., 1995). These observations strongly suggest that descending pretectal antinociceptive pathway may pass through red nucleus rather than through nucleus raphe magnus. Electrical stimulation and pharmacological tools have clearly identified various neuroreceptors and their ligands in the physiology of pretectal antinociception (Raghubir et al., 1994). Electrical stimulation of tiny sites in pretectal area of monkey also produced antinociception of long duration.

Opioid Receptors and Antinociception

New opioids receptor classification has been proposed by IUPHAR and the subtypes have been renamed following molecular approach as OP_1 for d, OP_2 for m and OP_3 for k opioid receptors (Dhawan et al 1996, 1998).

Derivatisation of metenkephalin at amino and corboxy terminals led to stable analogs, which produced potent analgesia of long duration involving central mu opioid receptors (Raghubir et al.,1990, Nath et al.,1995). Further combination of met and leu enkephalin in the ratio 4:1 produced more marked analgesia indicating their possible physiological synergy in endogenous analgesic mechanisms (Raghubir et al., 1999). Khosla et al (2000) reported that both the leaf extract and seed oil of *Azadirechta indica* possess antinociceptive activity in rat, however the leaf extract was more potent.

Jain et al. (2003) reported that sildenafil-induced analgesia is mediated via the inhibition of PDE-5. The results also indicate that the guanylate cyclase system is stimulated in the peripheral nociceptive reaction. Sildenafil produced analgesia can be potentiated by sodium nitroprusside and L-arginine, probably through the activation of the NO-cGMP pathway. Further, sildenafil increased the antinocicieptive response of morphine, probably through the inhibition of cGMP degradation (Jain et al 2001). Sumatriptan, a novel 5-HT_{1D} receptor agonist and anti-migraine drug was found to have antinociceptive effect in mice by possibly releasing acetylcholine (Jain et al., 1998).

Gupta Y.K. et al. (1997a, 2001) showed the analgesic effect without significant tolerance following co-administration of sub-maximal doses of trans resveratrol and morphine. The results suggest that trans resveratrol may interact with k-receptor and not with the μ-receptor. The study suggests the advantages of combination of trans-resveratrol and opioids in treating pain. There is dopaminergic involvement in adenosine A1 receptor-mediated antinociception suggesting that an interaction between adenosine and dopamine may be involved in nociception (Malhotra et al., 2000).

Gupta S. et al. (1997b, 2001) and Hanif et al. (2006) studied the effects of intracerebro-ventricularly administered chimeric peptide of met enkephalin and FMRFa—[D-Ala2] YFa-on antinociception and its modulation in mice.

An increase in expression of opioid receptor-like 1 (ORL1) and m-opioid receptors was seen in the spinal cord of morphine tolerant mice that may be a contributing factor to morphine tolerance (Ray et al., 2005). Up-regulation of μ-opioid receptors in the spinal cord of morphine-tolerant rats was found by *in vitro* tissue autoradiography using [3H]-DAMGO. This up-regulation of μ-receptors after morphine tolerance suggests that a fraction of the receptors have been desensitized, which in turn could lead to tolerance (Ray et al., 2004).

Blood-Brain Barrier

Blood brain barrier (BBB) is a physiological mechanism to protect the brain from potentially toxic substances circulating in the blood. Study of basic mechanisms involved in regulation of this barrier have given some interesting results with the possibility of using them therapeutically. The blood brain barrier was found to be modulated by toxic metals like cadmium (Shukla et al., 1996a). The role of free radicals and the status of their scavenging enzymes during normal physiological state and after its induced disruption as well as ageing were studied in rat (Shukla et al., 1993) and monkey (Shukla et al., 1995b). The permeability of the BBB is altered in several metabolic derangements, infections, poisoning and other pathological conditions. Induction of NOS activity after exposure to lipopolyssacharide (LPS) contributes to the increase in BBB permeability (Shukla et al., 1995a). These studies thus demonstrated the involvement of NO/Arginine pathway and ROS in the opening of the blood brain barrier (Shukla et al., 1996b).

Electrophysicological studies

Iontophoretic application of L-arginine or SNP to the vasoactive neurons in ventrolateral medulla produced significant inhibition of synaptic activity of these neurons by activating the cGMP pathway (Verma and Raghubir, 1997). However, anti-hypertensive drugs, clonidine and centhaquin also caused marked inhibition of the discharge rate of ventromedullary neurons without involving cGMP pathway (Verma, 1998).

Behavioral Responses

Role of central neurotransmitters like acetylcholine, GABA, dopamine and opioids in regulation of foot shock induced aggression was investigated (Dhawan et al., 1990). Central dopaminergic mechanism was found to be involved in facilitatory effect of piracetam on foot shock induced aggression (Pant et al., 1993). The thermal nociception based testing procedure for pain response was found to induce avoidance learning in mice on repeated exposure (Saxena et al., 1991). Receptor mechanism for morphine induced Straub's response in mice was delineated and

opioid μ-2 receptor mechanism was found to be involved (Nath et al., 1994). It was found that some calcium channel blockers, which have more accessibility to brain and exert significant influence on behavioral responses like depression and aggressive behavior in mice (Srivastava et al., 1997, Srivastava and Nath, 2000). Bhatwadekar et al., (1999) observed facilitatory effect of nicotine on behavioral effects mediated via monoamine neurotransmitters and potentiation of antidepressant activity of amitripytline.

Kulkarni and co-workers have investigated the role of $GABA_A$/Benzodizapine receptors in the actions of anxiolytics, anticonvulsants, alcohol, development of tolerance and dependence, psychotropic actions of herbal preparations have been extensively worked out using various behavioral paradigms (Aley et al., 1989, Kulkarni et al., 1991, Reddy et al., 1997c). These workers have found an important role of neuronal nitric oxide pathway in the behavioral effects of ACTH (Reddy et al., 1998a).

It has been shown that melatonin, a pineal hormone and a regulator of biological clock as a modulator of $GABA_A$ receptors, affects behavioral paradigms (Shaji et al., 1998 a). The role of melatonin in depression has been also studied by these workers (Shaji et al., 1998 b). Further, benzodiazepine inverse agonist FG 7142 induced delayed behavioural depression in mice (Chopra et al., 1988).

Hyperforin, a prenylated phloroglucinol present in *Hypericum perforatum* (HP), has been suggested to be primarily responsible for the antidepressant activity of HP. Many of the experimental and clinical studies have confirmed the antidepressant activity of hyperforin. Indian *Hypericum perforatum* (IHp) extract standardised for hyperforin lacked MAO-A and B inhibitory activity. Additionally, IHp showed antidepressant, anti-amnestic, anxiolytic, anti-inflammatory and analgesic, and anti-stress activities in various animal models (Kumar et al., 1999a, 1999b, 2000a, 2000b, 2000c, 2001a, 2001b, 2002, 2003, 2004).

Memory Functions

A comparative profile of acetylcholinesterase (AChE) enzyme on the basis of age and gender in rats was obtained. The salt soluble fraction (G1 molecular form) of AChE and detergent soluble fraction (G4 molecular form) of AChE showed significant differences in distribution between the brain areas in male and female rats of the same age group. There was significant decrease in AChE activity with age in male and female rats (Das et al 2001). It was observed that acute immobilization stress in mice decreased activity of AChE (G4 molecular form) in the brain and improved cognition in passive avoidance test, while chronic stress failed to induce any significant change on the observed parameters (Das et al., 2000). These workers also studied the estrogenic influence on AChE activity. It was found that ovariectomy increased acetylcholinesterase activity in the brain areas but not in a uniform manner and only affects qualitative (no transfer response)

aspects of memory function, which could be improved by estrogen supplementation (Das et al 2002 a).

The study of activity of G_4 and G_1 molecular isoforms of AChE on learning and memory functions suggest that hippocampal G_4 isoform play a predominant role in learning and memory, as the changes in its activity correlate with events of training, dementia and anti-dementic tacrine treatment (Das et al., 2005).

Further efforts were made to correlate the anticholinesterase activity as possible mechanism for anti-dementic properties of *Ginkgo biloba*, a drug used in the treatment of dementia (Das et al 2002 b). A memory enhancing property has been demonstrated in gugulipid, an ethyl acetate extract of the resin of plant *Commiphora whighitii*. It is an established hypolipidemic agent and major constituent of gugulipid is guggulsterone [4, 17 (20)-pregnadiene-3, 16-dione]. Gugulipid showed primary anti-dementic activity in Streptozotocin (ICV) induced model of memory impairment. A US patent for gugulipid, as memory enhancer has also been obtained (Nath, 2006). Antiamnesic activity of scopolamine was investigated on different stages of memory and it was found that it does not affect recall process (Das et al., 2003). The extracts of *Evolvulus alsinoides* showed significant anti-amnesic activity alongwith anti-stress property (Kiran Babu et al., 2005).

Sharma et al. (2001a) and Veerendra et al. (2002a) demonstrated the significance of oxidative stress in the development of experimental models for dementia by intracerebroventricular streptozotocin and colchicine. These co-workers also evaluated the effect of antioxidants, melatonin (Sharma et al., 2001b), trans-resveratrol (Sharma et al., 2002)., alpha lipoic acid (Sharma et al., 2003 and 2005) as well as indigenous Indian medicinal plants such as *Centella Asiatica* (Veerendra et al., 2002b and 2003) and *Hypericum perforatum* (Kumar et. al., 2004) in these models of dementia.

Roychoudary et al., (1996) reported that 5-HT receptor system, particularly 5-HT_3 receptors, may play a modulating role in learning and memory in animal models. Kulakrni et al., have demonstrated the memory enhancing prevention of opioid tolerance of BR-16A, a herbal formulation available in the market (Kulkarni et al., 1992a, 1992b and 1993).

Drug Dependence

Neuropharmacological aspects of dependence induced by several psychoactive substances have been investigated. Diazepam, diphenhydramine, haloperidol and chlorpheniramine attenuated withdrawal signs of methaqualone (Gupta et al., 1990). A comparative study on physical dependence due to benzodiazepines suggested an inverse relationship between half-life and severity of physical dependence (Gupta et al., 1993). Concomitant administration of diphenydramine potentiated physical dependence of lorazepam and methaqualone but inhibited that of cannabis. Cannabis (leaves extract) induced physical

dependence was less severe in comparison to benzodiazepine and methaqualone (Nath et al., 1994). Complete suppression of withdrawal signs of lorazepam was observed following administration of diphenhydramine, verapamil or nimodipine during the withdrawal period (Gupta et al., 1996, Nath et al., 1997). These observations indicate usefulness of these drugs in the therapy of benzodiazepine methaqualone and cannabis withdrawal syndrome. Central dopaminergic (D1 and D2), histaminergic (H1 and H3) and serotonergic (5-HT2) receptors were found to play facilitatory role in development of benzodiazepine dependence (Nath et al., 2000). Possible role of peripheral benzodiazepine receptors in anti-addictive profile of melatonin has been reported by Raghavendra et al., (1999).

It was observed clinically that nitrazepam has similar abuse liability as diazepam (Prasad et al., 2001). Kulkarni and co-worker investigated central effects of neurosteroids. The studies conducted on immobilization and hypoxic stress suggested the pivotel anti-stress role of neurosteroids (Reddy et al., 1996 and 1997b). Studies on dependence and tolerance by morphine and benzodiazepines suggested the role of dihydropyridine-sensitive Ca^{2+} channels and mitochondrial DBI receptors in the anti-addictive action of neurosteroids and further potential utility of specific neurosteroids in the management of tolerance and dependence (Reddy et al., 1997a and 1998b). Detailed investigation of neurosteroids on new animal models of anxiety demonstrated the differential effects of neurosteroids in anxiety (Reddy et al., 1997c). Many of the neurosteroids induce hyperphagia by acting on $GABA_A$ and mitochondrial DBI receptors (Reddy et al., 1998d). Chronic studies have shown oestrus cycle and gender dependent effect of both neurosteroids and benzodiazepines (Reddy et al., 1998e). Neurosteroids modulated learning and memory behavior by acting at sigma receptors and neuronal nitric oxide pathway (Reddy et al., 1998a). Neurosteroids pregnenolone sulfate and dehydroepiandrosterone sulfate were shown to have pro-convulsant effects (Reddy et al., 1998c). The studies on neurosteroids are a pioneering approach and have opened up a new concept in the central modulation of behavioral disorders.

Kulkarni and co-workers found that pretreatment with rofecoxib or nimesulide displayed significant protection against ethanol-induced withdrawal symptoms, while naproxen was not effective, suggesting the role of COX-2 isoforms (Dhir et al., 2005 b).

Primate behavior

The profile of behavioral effects of various centrally acting drugs like antipsychotic, antidepresant, antianxiety and calcium channel blockers on rhesus monkey has been studied (Kumar, 1999a, Kumar et al. 1999b, Palit et al., 1992, 1997a, 2001). Haloperidol significantly reversed amphetamine induced hypervigilance stereotypy and oral hyperkinesias suggesting positive role of dopamine in these behavioral effects (Palit et al., 1995). A primate model of anxiety using sub-convulsant dose of pentylenetetrazol has been developed (Palit et al., 1998). The behavioral

effects of isatin, a postulated endocoid marker of stress and anxiety, were blocked by diazepam (Palit et al., 1997b).

Parkinsonism

Centrally administered GABA, 5-HT and histamine exerted significant modulatory influence on tremor, hypokinesia, rigidity and catatonia in rodent models of parkinsonism (Nath et al.,1990). MPTP - a neurotoxin producing parkinsonism, was also studied for its behavioral effects in monkeys and rodents. Opioidergic effects including, antinociception 'and Straub tail were produced by MPTP in mice and these effects were not linked to its conversion to MPP ((Nath et al., 1991; Srimal and Nath 1992). Injection of 6-hydroxydopamine (6-OHDA) into the striatum led to a significant reduction in dopamine and its metabolities in the striatum in a time dependent manner. Interestingly iNOS induction was observed 72 hours after 6-OHDA injection (Barthwal 2000).

Mathur et al. (1999) studied the effect of adenosine modulating drugs in the $FeCl_3$-induced model of Parkinsonism in rats. In animals bearing unilateral $FeCl_3$ induced lesion of the dopaminergic nigrostriatal pathway, stimulation of adenosine receptors with adenosine, dose-dependently reduced the ipsilateral rotations induced by apomorphine. A specific agonist of adenosine A2A receptor, CGS-21680, also completely blocked the rotations induced by apomorphine, while the specific A2 receptor antagonist, CGS-15943A, potentiated it indicating a negative postsynaptic interaction between dopamine and adenosine receptors.

Kulkarni and co-workers developed a new animal model for tardive dyskinesia (Naidu et al., 2000 and Jain et al., 2001) Haloperidol-induced orofacial dyskinesia, has been shown to be similar to the symptoms of tardive dyskinesia and the involvement of different neurotransmitter systems such as dopamine, GABA, serotonin, glutamate and their interactions has been demonstrated (Naidu et al., 2000 and 2001 a,b,c). They also revealed the possible role of cyclooxygenase cascade as mediator in the pathophysiology of Parkinsonism and the potential therapeutic usefulness of COX inhibitors in these disorders (Naidu et al., 2002). Further, role of oxidative stress and neurotoxic mechanisms in the pathogenesis of neuroleptic-induced tardive dyskinesia was experimentally validated in some of their recent studies. The studies have explored the role of certain natural products such as quercetin, a bioflavonoid (Naidu et al., 2003 a, b).

Convulsive Disorders

Pretreatment with COX-inhibitors aspirin, naproxen, nimesulide or rofecoxib showed dose dependent protection against pentylenetetrazol (PTZ) induced convulsions. COX-2 inhibitors were more effective as compared to non-selective COX-inhibitors. COX-2 inhibitors were ineffective against maximal electroshock-induced convulsions (Dhir et al., 2005 a,b, 2006b). Pretreatment with nonselective COX-inhibitor naproxen or selective COX-2 inhibitor rofecoxib showed significant

protection against PTZ-induced kindling in mice. Chronic treatment with COX-2 inhibitors significantly reversed the PTZ-induced biochemical alterations (Dhir et al., 2006a). Chronic treatment with naproxen or rofecoxib significantly attenuated the immobilization stress-induced behavioral and biochemical alterations (Dhir et al., 2006b).

Gupta and co-workers have developed and validated lithium – pilocarpine induced seizures as an experimental model for status epilepticus. The wide range of lithium pretreatment time adds flexibility to the experimental schedule (Chaudhary et al., 1999, 2001). They have also standardized an indigenous device for continuos recording of seizure activity in rats. The device cannot only record the different seizure components, but also quantifies the latency and duration of seizure activity (Malhotra et al., 1997).

Gupta and co-workers have made efforts to identify endogenous anticonvulsant substances. The role of adenosinergic system was studied in experimental seizures in rats. Adenosine and stable adenosine analog 2-CADO pre-treatment offered significant protection against PTZ-induced seizures. Adenosine and the A1 agonist CPA, in doses that protected against seizures after acute PTZ-administration, offered only incomplete protection when tested against PTZ-kindled seizures (Gupta et al., 1997b and Malhotra and Gupta et al., 1997). Combination of subconvulsant doses of adenosine and the conventional antiepileptic drugs, afforded greater protection than either drug alone (Malhotra et al., 1999, Srivastava et al., 2001a, 2001b). However, adenosinergic agents failed to provide any protection against theophylline-induced seizures.

This suggests non-involvement of adenosinergic system in theophylline-induced seizures (Gupta et al., 1998). Melatonin, an endogenous antioxidant substance, and naturally occurring bioflavonoids from grapes (vineatrol and trans resveratrol) showed antiepileptic activity against kainic acid, PTZ and FeCl3 seizures (Srivastava et al., 2002a, Gupta et al., 1997a, 2001; Saxena et al., 1999).

The encouraging results and wide therapeutic margin led to the first clinical trials of melatonin as add-on treatment in children with epilepsy. The trial also evaluated the effect of add-on melatonin on the sleep behavior as well as quality of life of these children on sodium valproate/carbamazepine monotherapy using a parental questionnaire (Gupta et al., 2006).

Somani et al (1999) investigated dopaminergic mechanism in seizures. Haploperidol inhibited bicuculline-induced seizures probably by reducing the excitatory input to the cerebral cortex and bicuculline potentiated haloperidol-induced catalepsy in mice by reducing dopaminergic transmission in susbstantia nigra. Khanna et al (2000) showed that both nifedipine and nimodipine, the calcium channels blockers, possess, anticonvulsant activity (Khanna et al., 2000).

Ambawade et al. (2002) reported inhibitory effect of ethanolic extract of *Glycyrrhiza glabra* on PTZ and lithium-pilocarpine-induced but not on MES induced convulsions. Kulakarni and co-workers showed that *Withania somnifera* root extract was effective against PTZ-induced kindling epilepsy in mice and amygdaloid kindling in rats (Kulkarni et al., 1995). The functional and receptor assays have demonstrated that it has $GABA_A$ receptor facilitatory action (Kulkarni et al., 1993).

Cerebral Stroke

Gupta et al., (2004) and Raghubir and colleagues [Manhas et al., (2004), Manhas (2007), Sharma (2008), Mehta (2008) and Nakka (2008)] validated middle cerebral artery occlusion (MCAO) model of acute ischemic stroke in rats. Melatonin (Sinha et al., 2001), adenosine (Gupta et al., 2002), a-tocopherol (Chaudhary et al., 2003a), naturally occurring bioflavonoids i.e. vineatrol and trans resveratrol (Sinha et al., 2002) endothelin antagonist [TAK-044] (Gupta et al., 2005) were found to be effective against MCAO induced reperfusion injury in rats. The combination of melatonin (potent antioxidant) and meloxicam (preferential inhibitor of cyclooxygenase-2, did not show significant difference as compared to the effect of individual drug alone. *Withania somnifera* a well-known anti-inflammatory, antistress, hemopoeitic immunomodulatory and antioxidant herbal drug showed anti-stroke property in MCAO model (Gupta et al., 2004 and Chaudhary et al., 2003b).

The CDRI scientists led to the development of an antistroke herbal medicament, which has been licenced to Themis Medicare Limited, Mumbai. Raghubir and coworkers have done extensive work to understand the pathophysiology of cerebral ischemia. The heat shock proteins offer significant neuroprotective effects following cerebral ischemia (Manhas et al., 2004). An understanding of molecular mechanisms modulating the chain of events leading to cellular survival / damage may help to generate potential strategies for neuroprotection (Nakka et al., 2008). The current status on the molecular mechanisms of stroke pathophysiology with an endeavour to identify potential meolecular targets has been reviewed. Hence, selecting promising targets from various signaling cascades, for drug discovery and development is very challenging. Nevertheless such approaches may lead to the emergence of new avenues for therapeutic intervention in cerebral ischemia (Mehta et al 2007). A time dependent increase in mitochondrial membrane potential was found during reflow after ischemia in the Mongolian gerbil by treatment with NOS inhibitors and the blocker of the fast sodium channel. The ischaemic damage aggravated by a sodium ionophore was attenuated by specific NOS inhibitor indicating the prime role played by neuronal NO and sodium ion (Chaudhary et al., 1999).

Changes in Peripheral NO in CNS diseases

Studies undertaken to identify peripheral markers in various constituents of blood of patients of Parkinson's disease (PD), migraine, schizophrenia and

depression showed tha increase in nitrite content was specific to polymorphonuclear leukocytes (PMNLs) and no such changes were observed in the platelets or plasma. These findings suggest involvement of NO in PD (Barthwal et al., 1999). During headache free period platelet nitrite content and aggregation response were altered in migraine patients (Barthwal 2000). Patients of schizophrenia and depression on the other hand exhibited a significant decrease in the PMNLs nitrite content (Srivastava et al., 2001c) while beta-adrenergic receptor binding sites were decreased only in the patients of depression (Srivastava et. al., 2002b). Migraine patients did not demonstrate change in the PMNs nitrite content but increase in the platelet NOS activity was reverted back to the normal level within few days after the migraine attack (Shukla et al., 2001, 2004). Nitrite level in the CSF of motor neuron disease patients were also investigated (Shukla et al., 2003). Centpropazine inhibited inositol phosphate but not cyclic AMP accumulation in cerebral cortical slices of the rat. It also displaced the binding of prazosin but had no effect on adrenergic receptor binding to the rat cortical membranes (Dikshit et al., 1993).

Anorexia

Anorexia induced by quipazine is largely mediated through 5-HT2 receptors, while fenfluramine effect is mediated through 5-HT1 - receptors (Shukla et al., 1990). The growth hormone releasing hexapeptides-6 (GHRP-6), besides exhibiting orexigenic profile, has potent antianorexigenic effect as well (Tripathi, 2000).

Central Modulation of Gastric Motility

Gupta and co-workers (Kacker & Gupta 1996, Kacker et al., 1999) showed the protective effect of carbachol and cisapride against raised intracranial pressure induced gastric emptying and suggested that suppression of vagal activity due to increased ICP may play an important role in the inhibition of gastric emptying due to intracranial hypertension (Kacker et al., 1996 and 1999). Gupta and co-worker also reported antiemetic effect of the acetone and ethanolic extract of ginger (*Zingiber officinale*) against cisplatin-induced emesis in dogs (Sharma et al., 1997, 1998; Gupta et al., 2002).

Central adrenergic and cholinergic systems showed facilitatory influence on stress induced gastric ulcer in rats. Verapamil and Polyl -PolyC were effective in suppressing stress-induced gastric ulcer (Nath et al 1998). Various amino acid derivatives were found to moderate the proton pump activity and ulcer induced increase in the gastric acid content (Rastogi; 1997 and Dixit; 2000).

Central Cardiovascular Control

Studies have been conducted to gain insight into the central mechanisms involved in the onset and maintenance of blood pressure, cardiac arrhythmias, and myocardial ischemia.

Blood Pressure

Effect of chronic pretreatment of rats with anti-hypertensive drugs like reserpine, hydralazine, clonidine and centhaquin was investigated on 5-HT1, 5-HT2, alpha adrenergic, beta adrenergic, dopaminergic and cholinergic receptors in the cortex, caudate, hypothalamus and medulla (Gulati et al., 1991a, b).

Topical application of sodium nitropruside (SNP) to the exposed surface of ventro-lateral medulla in the cat also produced hypotension and bradycardia, which was reversed by methylene blue suggesting role of NO in the central modulation of circulation (Verma and Raghubir, 1997).

Involvement of nitric oxide (NO), arginine and cyclic guanosine monophosphate (cGMP) pathways in the central regulation of blood pressure has been demonstrated in normotensive cats and hypertensive rats (Hegde et al., 1994).

Further, relationship between blood pressure level and brain nitric oxide synthase (NOS) activity has been investigated in the aortic-banded rats. NOS activity was significantly reduced in the medulla and hypothalamus of hypertensive rats. Moreover, anti-hypertensive drugs, captopril, nifedipine or centhaquin normalized the blood pressure and brain NOS activity in these animals (Hegde et al., 1997).

Endothelin, a vasoactive peptide blocked the hypotensive and bradycardiac effect of clonidine administered by intracerebroventricular or intravenous routes. However, hypertensive effect of clonidine was potentiated (Gulati and Srimal 1992, 1993).

Thermoregulation

Cyclo (His-Pro) modulates body temperature and its analogs attenuated ethanol induced hypothermia in *Mastomys natalensis* (Shukla et al 1994, Carlton et al., 1995).

Biogenic Amines

The ontogeny of biogenic amines in various brain structures and peripheral tissues in *Mastomys natalensis* has been studied during parasitic infections. The results suggest that functional maturations of the brain is accompanied by a progressive increase in the levels of biogenic amines. Pharmacological studies related to drug indicate that changes in body temperature may be associated with changes in certain neurotransmitter levels in specific brain regions. Furthermore, filaria infection induced marked alterations in histamine levels in brain structures and lungs of *Mastomys natelensis* (Pandey et al., 1991).

Evidence for involvement of N-type calcium channels on presynaptic nerve terminal in the release of acetylcholine and L-type calcium channels on chromaffin cells in the secretion of catecholamines has been suggested (Shukla et al., 1991, Lopez et al., 1992).

Acknowledgement

The authors are extremely grateful to Prof. B.N. Dhawan, Former Director, Central Drug Research Institute, Lucknow for critical evaluation and encouragement in the preparation of this review.

References

Aley KO, Kulkarni SK: GABA-mediated modification of despair behavior in mice. Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 339, 306-311.

Ambawade S D, Kasture V S, Kasture S B: Anticonvulsant activity of roots and rhizomes of *Glycyrrhiza glabra*. Ind J Pharmacol. (2002) 34, 251-255.

Barthwal MK: PhD. Thesis: A study on the status of nitric oxide and free radicals in central nervous system disorders. (2000) Lucknow University, Lucknow.

Barthwal MK, Srivatava N, Shukla R, Nag D, Seth PK, Srimal RC, Diskhit M: Polymorphonuclear leukocyte nitrite content and antioxidant enzymes in Parkinson's disease patients. Acta Neurol Scand. (1999) 100, 300-304.

Bhattaccharya SK, Chakrabarti A: Neuropharmacology In: CK Chauhan ed. Review of Research in Pharmacology in India. Published by CK Chauhan, Ind. J. Pharmacol., LTM Medical College, Mumbai. (1993) 84-114.

Bhatwadekar AD, Logade NA, Shirsat AM, Kasture V S, Kasture SB: Effects of nicotine on behavioral mediates via monoamine neurotransmitters. Ind J Pharmacol. (1999) 31, 410-415.

Carlton J, Khan SI, Haq W, Mizuma H, Ragan FA, Mathur KB, Shukla R, Srimal RC, Prasad C: Attenuation of alcohal induced hypothermia by cyclo (his-pro) and its analogs. Neuropeptides. (1995) 28, 351-355.

Chaudhary G, Malhotra J, Chaudhari JD, Gopinath G, Gupta YK: Effect of different lithium priming schedule on pilocarpine-induced status epilepticus in rats. Methods Find Exp Clin Pharmacol. (1999) 21, 21-24.

Chaudhary G, Gupta YK: Lithium does not synergize the peripheral action of cholinomimetics as seen in the central nervous system. Life Sci. (2001) 68, 2115-2121.

Chaudhary G, Sharma U, Jagannathan NR, Gupta YK: Evaluation of *Withania somnifera* in a middle cerebral artery occlusion model of stroke in rats. Clin Exp Pharmacol Physiol. (2003a) 30, 399-404.

Chaudhary G, Sinha K, Gupta YK: Protective effect of exogenous administration of alpha-tocopherol in middle cerebral artery occlusion model of cerebral ischemia in rats. Fundam Clin Pharmacol. (2003b) 17,703-707.

Chopra K, Kunchandy J, Kulkarni SK: Benzodiazepine inverse agonist FG 7142 induced delayed behavioral depression in mice. Arch. Int. Pharmacodyn. (1988) 294, 56-63.

Das A, Kapoor K, Sayeepriyadarshni AT, Dikshit M, Palit G, Nath C: Immobilizatgion stress induced changes in brain acetylcholinesterase activity and cognitive function in mice. Pharmacological Res. (2000) 42,213-217.

Das A, Dikshit M, Nath C: Profile of acetylcholinesterase in brain areas of male and female rats of adult and old ages. Life Sci. (2001) 68, 1545-1555.

Das A, Dikshit M, Srivastava SR, Srivastava UK, Nath C: Effect of ovariectomy and estrogen supplementation on brain acetylcholinesterase activity and passive avoidance learning in rats, Canad J Physiol Pharamacol. (2002a) 80,907-914.

Das A, Shanker G, Nath C, Pal R, Singh S, Singh HK: A comparative study in rodents of standardized extracts of *Bacopa monniera* and *Ginkgo biloba:* Anticholinesterase and cognitive enhancing activities, Pharmacol Biochem Behav. (2002b) 73, 893-900.

Das A, Dikshit M, Singh HK, Nath C: Evaluation of effect of scopolamine on stages of active avoidance learning in rats. Ind J Pharmacal. (2003) 35, 47-50.

Das A, Dikshit M, Nath C: Role of molecular isoforms of acetylcholinesterase in learning and memory functions. Pharmacol Biochem Behav. (2005) 81, 89-99.

Dhawan BN, Patnaik GK: Neuropharmacology. In: SK Pandya Ed. Neuroscience in India. Retrospect and Prospect. Neuropharmcological Society of India, Trivandrum & Council of Scientific & Industrial Research, New Delhi. (1989) 231-295.

Dhawan KN, Nath C, Kumar A, Gupta GP: A study of some neurotransmitters in foot shock induced aggregation. Eur J Pharmacol. (1990) 183, 1385.

Dhawan BN, Cesselin F, Raghubir R, Reisine T, Bradley PB, Portoghese PS, Hamon M: International union of pharmacology XII. Classification of opioid receptors. Pharmacological Reviews. (1996) 48, 567-592.

Dhawan BN, Raghubir R, Hamon M: Opioid receptors in IUPHAR Compendiumn of Receptor characterization and clsssification. IUPHAR Media, London, U.K. (1998) 218-226.

Dhir A, Naidu PS, Kulkarni SK: Effect of naproxen, a non-selective cyclooxygenase inhibitor, on pentylenetetrazol-induced kindling in mice. Clin. Exp. Pharmacol. Physiol. (2005a) 32, 579-584.

Dhir A, Naidu PS, Kulkarni SK: Protective effect of cyclooxygenase-2 (COX-2) inhibitors but not non-selective cyclooxygenase (COX)-inhibitors on ethanol withdrawal-induced behavioral changes. Addiction Biology. (2005b) 10, 329-335.

Dhir A, Naidu PS, Kulkarni SK: Effect of rofecoxib, a cyclo-oxygenase-2 inhibitor, on various biochemical parameters of brain associated with pentylenetetrazol-induced chemical kindling in mice. Fund. Clin. Pharmacol. (2006a) 20, 255-261.

Dhir A, Padi SS, Naidu PS, Kulkarni SK: Protective effect of naproxen (non-selective COX-inhibitor) or rofecoxib (selective COX-2 inhibitor) on immobilization stress-induced behavioral and biochemical alterations in mice. Eur. J. Pharmacol. (2006b) 535, 192-198.

Dikshit M, Chalecka-Frranaszek E, Nalepa I: Centpropazine affinity to cortical noradrenergic receptors and effect on their responsiveness. J Pharmacol. (1993) 45, 228-230.

Dixit C: PhD Thesis: A biochemical study on the mechanism of antiulcer agents. (2000) Lucknow University, Lucknow.

Gulati A, Hussain G, Srimal RC: Effect of repeated administration of clonidine on adrenergic, cholinergic (muscarinic), dopaminergic and serotonergic receptor in brain regions of rats. Drug Dev Res. (1991a) 22, 141-152.

Gulati A, Hussain G, Srimal RC: Effect of repeated administration of Centhaquin, a centrally acting hypotensive drug, on adrenergic, cholinergic (muscarinic), dopaminergic and serotonergic receptors in brain regions of rat. Drug Dev Res. (1991b) 24, 307-323.

Gulati A, Srimal RC: Endothelin mechanisms in CNS - a target for drug development. Drug Dev Res. (1992) 24, 361-388.

Gulati A, Srimal RC: Endothelin antagonizes the hypotension and potentiates the hypertension induced by clonidine. Eur J Pharmacol. (1993) 230, 293-300.

Gupta GP, Gupta MB, Nath C, Srimal RC, Dhawan BN: Effect of some CNS active drugs on methaqualone abstinence. Eur J Pharmacol. (1990) 183: 557.

Gupta MB, Nath C, Bhalla DN, Patnaik GK, Dhawan KN: Comparative evaluation of physical dependence of some benzodiazepines in rats. Annl Neurosci. (1993) 4, 12-17.

Gupta MB, Nath C, Patnaik GK, Saxena RC:) Effect of calcium channel blockers on withdrawal syndrome of lorazepam in rats. Ind J Med Res. (1996 103, 310-314.

Gupta S, Bhardwaj DK, Gupta YK, Pasha S; Role of hybrid peptide of met-enkephalin and FMRFamide in antinociception and its modulation. Neuropeptides. (1997) 31: 609-634.

Gupta YK, Malhotra J: Adenosinergic system as an endogenous anticonvulsant mechanism. Indian J Physiol Pharmacol. (1997a) 41,329-343.

Gupta YK, Malhotra J: Effect of theophylline on diazepam and sodium valproate protection in pentylenetetrazole - kindled seizures in rats. Indian J Physiol Pharmacol. (1997b) 41, 280-284.

Gupta YK, Malhotra J; Influence of adenosine agonists and antiepileptic drugs on theophylline-induced seizures in rats. Indian J Physiol Pharmacol. (1998) 42, 491-497.

Gupta YK, Chaudhary G, Sinha K, Srivastava AK: Protective effect of resveratrol against intracortical FeCl3-induced model of posttraumatic seizures in rats. Methods Find Exp Clin Pharmacol. (2001) 23, 241-244.

Gupta S, Pasha S, Gupta YK, Bhardwaj DK: Effects of intracerebroventricularly administered chimeric peptide of metenkephalin and FMRFa-[D-Ala2]YFa-on antinociception and its modulation in mice. Brain Res Bull. (2001) 55, 51-57.

Gupta YK, Sharma SS: Involvement of 5-HT1A and 5-HT2 receptor in cisplatin induced emesis in dogs. Indian J Physiol Pharmacol. (2002) 46, 463-467.

Gupta YK, Sinha K, Chaudhary G, Jagannathan NR: Protective effect of adenosine against neuronal injury induced by middle cerebral artery occlusion in rats as evidenced by diffusion-weighted imaging. Pharmacol Biochem Behav. (2002) 72,569-574.

Gupta YK, Briyal S: Animal models of cerebral ischemia for evaluation of drugs. Indian J Physiol Pharmacol. (2004) 48, 379-394.

Gupta YK, Sharma M, Briyal S: Antinociceptive effect of trans-resveratrol in rats: Involvement of an opioidergic mechanism. Methods Find Exp Clin Pharmacol. (2004) 26,667-672.

Gupta YK, Briyal S, Sharma U, Jagannathan NR, Gulati A: Effect of endothelin antagonist (TAK-044) on cerebral ischemic volume, oxidative stress markers and neurobehavioral parameters in the middle cerebral artery occlusion model of stroke in rats. Life Sci. (2005) 77, 15-27.

Gupta YK, Briyal S: Protective effect of vineatrol against kainic acid induced seizures, oxidative stress and on the expression of heat shock proteins in rats. Eur Neuropsychopharmacol. (2006) 16, 85-91.

Gupta YK, Gupta M: Post traumatic epilepsy: a review of scientific evidence. Indian J Physiol Pharmacol. (2006) 50: 7-16.

Hanif K, Gupta K, Gupta S, Gupta YK, Maiti S, Pasha S: Chimeric peptide of met-enkephalin and FMRFa: effect of chlorination on conformation and analgesia. Neurosci Lett. (2006) 403, 131-135.

Hegde, LG, Shukla R, Dikshit M, Srimal RC: Study on the involvement of the L-Arginine/Nitric oxide pathway in the central cardiovascular regulation in the chloralose anaesthetised cat. Arch. Int Pharmacodyn. (1994) 328, 155-164.

Hegde LG, Shukla R, Srimal RC, Dikshit M: Alteration in the brain nitric oxide synthase activity in coarctation model of hypertension in rats. Pharmacol Res. (1997) 36, 109-114.

Jain NK, Kulkarni SK: Antinociceptive effect of sumatriptan in mice. Ind. J. Exp. Biol. (1998) 36,973-979.

Jain NK, Patil CS, Singh A, Kulkarni SK: Sildenafil-induced peripheral analgesia and activation of the nitric oxide-cyclic GMP pathway. Brain Res. (2001) 909, 170-178.

Jain NK, Patil CS, Singh A, Kulkarni SK: Sildenafil, a phosphodiesterase-5 inhibitor, enhances the antinociceptive effect of morphine. Pharmacology. (2003) 67,150-156.

Kacker V, Gupta YK: An experimental model to study intracranial hypertension-induced vomiting in conscious dogs. Methods Find Exp Clin Pharmacol. (1996) 18, 315-320.

Kacker V, Mehta VS, Gupta YK: Acute intracranial hypertension-induced inhibition of gastric emptying: evaluation in conscious rats. Eur J Pharmacol. (1999) 369, 65-72.

Khanna N, Bhalla S, Verma V, Sharma KK: Modulatory effects of nifedipine and nimodipine in experimental convulsions. Ind J Pharmacol. (2000) 32,347-352.

Khosla P, Sangeeta B, Singh J, Srivastava R.K: Antinociceptive activity of *Azadirachta indica* (neem) in rats. Ind J Pharmacol. (2000) 32,372-374.

Kiran Babu S, Gupta P, Nath C, Maurya R, Palit G: Anti-stress and anti-amnesic activity of *Evolvulus alsinoides* in rodents. Pharmacol Biochem Behav. (2005) 81, 424-432.

Kulkarni, SK, Sharma AC, Verma A: Strain differences bidirectional activity of benzodiazepine ligands in rodents subjected to elevated plus-maze. Ann. Natl. Acad. Med. Sci. (1991) 27, 61-68.

Kulkarni SK, Verma A: Evidence for nootropic effect of BR-16A, a herbal psychotropic preparation in mice. Indian J. Physiol. Pharmacol. (1992a) 36, 29-34.

Kulkarni SK, Verma A; Prevention of development of tolerance and dependence to opiate in mice by BR-16A (Mentat), a herbal psychotropic preparation. Ind. J. Exptl. Biol. (1992b) 30, 885-888.

Kulkarni SK, Verma A: BR-16A (Mentat), a herbal preparation, improves learning and memory performance in mice. Indian Drugs. (1993) 30, 97-107.

Kulkarni SK, Sharma A, Verma A, Ticku MK: GABA receptor mediated anticonvulsant action of *Withania somnifera* root extract. Indian Drugs. (1993) 30, 305-312.

Kulkarni SK, George B: Anticonvulsant action of *W. somnifera* root extract against PTZ-induced kindling in mice. Phytotherapy Res. (1995) 10, 447-449.

Kumar A, Raghubir R, Dhawan BN; Analysis of stimulation produced analgesia form pretectal nucleus in rat. Ann. Neurosci. (1990) 1, 9-15.

Kumar A, Raghubir R, Dhawan BN: Involvement of cholinergic mechanisms in electrically induced analgesia from pretectal nucleus of rat. Ind J Med Res. (1991a) 94, 1939-1942.

Kumar A, Raghubir R, Dhawan BN: Effects of monoamine anatagonists on pretectal evoked analgesia in rats. Ind J Exp Biol. (1991b) 29, 32-34.

Kumar A, Raghubir R, Dhawan BN: Atropine and naloxone sensitive stimulation produced analgesia for pretectal nucleus. Neuroreport. (1992) 3, 591-593.

Kumar A: PhD Thesis: Neuropharmacological investigations in stimulation produced analgesia from pretectal nuclei. (1993) Lucknow, Lucknow University.

Kumar A, Raghubir R, Dhawan BN: Evidence for the involvement of nitric oxide in pretectal anagesia in rat. Neuroreport. (1993a) 4, 706-708.

Kumar A, Raghubir R, Dhawan BN: Analgesic effects of morphine, clonidine and serotonin micro injected in pretectal nucleus. Neuroreport. (1993b) 4,944-946.

Kumar A, Raghubir R, Dhawan BN: Antinociception induced by neuro-transmitters agonists micorinjected into the pretreated nucleus of rat. In Recent Advances In The Study of Neurotransmitter Receptor (eds) Dhawan BN, Srimal RC, Raghubir R, Rapaka RS, CDRI, Lucknow. (1994) 275-281.

Kumar A, Raghubir R, Dhawan BN: Possible involvement of nitric oxide in red nucleus stimulation produced analgesia in the rat. Eur J Pharmacol. (1995) 279, 1-5.

Kumar R: PhD Thesis. Experimental studies in the efficacy of CNS active drugs on behaviour of Rhesus monkey (Pacala mulatto). (1999) RML Avadh University, Faizabad.

Kumar R, Palit G, Singh JR, Dhawan BN: Comparative behavioral effects of benzodiazepine and non-benzodiazipine anxiolytivcs in rhesus monkeys. Pharmacol Res. (1999a) 39, 437-444.

Kumar V, Singh PN, Jaiswal AK, Bhattacharya SK: Antidepressant activity of Indian *Hypericum perforatum* Linn in rodents, Indian J Exp Biol. (1999b) 37,1171-1176.

Kumar V, Singh PN, Muruganandam AV, Bhattacharya SK: Effect of Indian *Hypericum perforatum* Linn on animal models of cognitive dysfunction, J Ethnopharmacol. (2000a) 72,119-128.

Kumar V, Jaiswal AK, Singh PN, Bhattacharya SK: Anxiolytic activity of Indian *Hypericum perforatum* Linn: an experimental study, Indian J Exp Biol. (2000b) 38, 36-41.

Kumar V, Singh PN, Bhattacharya SK: *Hypericum perforatum*: nature's mood stabilizer, Indian J Exp Biol. (2000c) 38, 1077-1085.

Kumar V, Singh PN, Bhattacharya SK: Anti-inflammatory and analgesic activity of Indian *Hypericum perforatum* L. Ind J Exp Biol. (2001a) 39, 339-343.

Kumar V, Singh PN, Bhattacharya SK: Anti-stress activity of Indian *Hypericum perforatum* Linn, Indian J Exp Biol. (2001b) 39,344-349.

Kumar V, Singh PN, Bhattacharya SK: Neurochemical studies on Indian *Hypericum perforatum* Linn, Indian J Exp Biol. (2001c) 39,334-338.

Kumar MH, Gupta YK: Antioxidant property of *Celastrus paniculatus* Willd: a possible mechanism in enhancing cognition. Phytomedicine. (2002) 9, 302-311.

Kumar V, Khanna VK, Seth PK, Singh, PN, Bhattacharya SK: Brain neurotransmitter receptor binding and nootropic studies on Indian *Hypericum perforatum* Linn, Phytother Res. (2002) 16,210-216.

Kumar R, Palit G, Dhawan BN: Comparative behavioural effects of typical alytricla antiphychotic drugs in rhesus monkey. Euro. J Pharmacol. (2003) 462,133-138.

Kumar V, Agrawala SK, Bhattacharya SK: Behavioral studies on *Hypericum perforatum* formulations, Phytomedica. (2004) 5,19-30.

Lopez MG, Shukla R, Garcia AG, Wakade AR: A dihydropyridines - resistant component in the adrenal secretory response to splanchnic nerve stimulation. J Neuchem. (1992) 58, 2139-2144.

Malhotra J, Gupta YK: Effect of adenosine receptor modulation on pentylenetetrazole-induced seizures in rats. Br J Pharmacol. (1997) 120, 282-288.

Malhotra J, Velpandian T, Gupta YK : A simple device for recording seizure activity in rats. Methods Find Exp Clin Pharmacol. (1997) 19, 47-51.

Malhotra J, Gupta YK: Effect of adenosinergic modulation on the anticonvulsant effect of phenobarbitone and carbamazepine. Methods Find Exp Clin Pharmacol. (1999) 21, 79-83.

Malhotra J, Chaudhary G, Gupta YK: Dopaminergic involvement in adenosine A1 receptor-mediated antinociception in the tail flick latency model in mice. Methods Find Exp Clin Pharmacol. (2000) 22, 37-41.

Manhas N, Sharma R, Raghubir R: Heat shock proteins: TYheir functional role in cerebral ischemia, Curr R & D Highlights. (2004) 27, 7-10.

Mathur R, Gupta YK: Adenosinergic and dopaminergic interaction in nigrostriatum in FeCl3-induced model of parkinsonism in rats. Methods Find Exp Clin Pharmacol. (1999) 21, 435-439.

Mehta L, Manhas N, Raghubir, R: Molecular targets in cerebral ischemia for developing novel therapeutics. Brain Res Rev. (2007) 54, 34-66.

Mehta L: Studies on cellular and molecular mechanisms of stroke damage in diabetes, JNU, N Delhi. (2008).

Mungemandam AV, Kuamr V, Bhattacharya SK: Neuropharmacology. In C Adithan ed Status Report on Pharmacological Research in India 1994-1998. India National Science Academy, N Delhi. (2000) 119-133.

Naidu PS, Kulkarni SK: Differential role of dopamine D1 and D2 receptors in isoniazid-induced vacuous chewing movements. Methods Find. Exp. Clin. Phamacol. (2000) 22, 747-751.

Naidu PS, Kulkarni SK: Excitatory mechanisms in neuroleptic – induced vacuous chewing movements (VCMs): possible involvement of calcium and nitric oxide. Behavio. Pharmacolo. (2001a) 12, 209-216.

Naidu PS, Kulkarni SK: Possible involvement of prostaglandins in haloperidol-induced orofacial dyskinesia in rats. Eur J Pharmacol. (2001b) 430, 295-298.

Naidu PS, Kulkarni SK: Reversal of neuroleptic-induced orofacial dyskinesia by 5-HT3 receptor antagonists. Eur J Pharmacol. (2001c) 420, 113-117.

Naidu PS, Kulkarni SK: Differential effects of cyclooxygenase inhibitors on haloperidol-induced catalepsy. Prog. Neurosychopharamcol. Biol. Psychiat. (2002) 26, 819-822.

Naidu PS, Singh A, Kulkarni SK: Quercetin, A bioflavonoid attenuates haloperidol-induced orofacial dyskinesia. Neuropharmacology. (2003a) 44, 1100-1106.

Naidu PS, Singh A, Kulkarni SK: Reversal of haloperidol-induced orofacial dyskinesia by quercetin, a bioflavonoid. Psychopharmacology (Berl.). (2003b) 167, 418-423.

Nakka VP, Gusain A, Mehta SL, Raghubir R: Molecualr mechanisms of apoptosis in cerebral ischemia: multiple neuroprotective opportunities. Mol Neurobiol. (2008) 37, 7-38.

Nath C, Gupta MB, Gupta GP, Srimal RC, Dhawan BN: Study of central putative neurotransmitters in rodent models of parkinsonism. In: Nagatsu T, Fisher A, Yoshida M eds Basic Clinical and Therapeutic aspects of Alzheimer's and Parkinson's disease. New York: Plenum Press. (1990) 503-507.

Nath C, Gurtu S, Gupta MB, Gupta GP, Srimal RC, Dhawan BN: Novel effects of MPTP: MAO-B unrelated activity in mice. Neuroreport. (1991) 2, 449-450.

Nath C, Gupta MB, Shanker K, Gupta GP, Srimal RC, Dhawan BN: Effect of diphenhydramine on withdrawal syndrome of some psychoactive drugs. In "Recent Advances in the Study of Neurotransmitter Receptors" Eds BN Dhawan, RC Srimal R, R Raghubir, RS Rapaka. CDRI, Lucknow. (1994) 310-318.

Nath C, Patnaik GK, Haq W, Mathur KB, Srimal RC, Dhawan BN, Porreca F: Novel Met-enkephalin analogue: A potent systemic mu agonist antinociceptive agent. Pharmacol Res. (1995) 31, 269-273.

Nath C, Patnaik GK, Saxena RC, Gupta MB: Evaluation of inhibitory effect of diphenhydramine on benzodiazepine withdrawal. Ind J Physiol Pharmacol. (1997) 41, 42-46.

Nath C, Rastogi L, Dikshit M and Patnaik GK, Saxena RC and Gupta MB: Interferon inducer. A potent antigastric ulcer agent and inhibitor of gastric proton pump in rats. Clin Expt Pharmacol Physiol. (1998) 25, 564-567.

Nath C, Saxena RC, Gupta MB: Effect of dopamine agonists and antagonists on lorazepam withdrawal syndrome in rats. Clin Exptl. Physiol Pharmacol. (2000) 27, 167-171.

Nath C: Herbal preparations as memory enhancer. Annals of Neurosci. (2006) 13: 25.

Palit G, Kumar R, Dhawan BN: Quantitative assessment of behavior in rhesus monkey. Lab Animals India. (1992) 3, 97-104.

Palit G: Quantitative assessment of amphetamine induced behavioral changes in rhesus monkey (*Macca mulatta*). Ind J Exp Biol. (1995) 33, 980-982.

Palit G, Kumar R, Gupta MB, Saxena RC, Patnaik GK, Dhawan BN: Quantafication of behavior in social colonies of rhesus monkey. Ind J Physiol Pharmacol. (1997a) 41, 229-226.

Palit G, Kumar R, Patnaik GK, Bhattacharya SK: Behavioral effects of Isatin, a putative biological factor in rhesus monkeys. Biogenic Amines. (1997b) 13, 131-142.

Palit G, Kumar R, Chowdhury SR, Gupta MB, Saxena RC, Srimal RC, Dhawan BN: A primate model of anxiety. Eur Neuropsychopharmacol. (1998) 8,195-201.

Palit G, Kalshotra A, Kumar R, Nath C, Dubey MP: Beahvioural and anti-psychotic effects of Ca2+ channel blockers in rhesus monkey. Eur J Pharmacol. (2001) 412, 189-44.

Pandey SC, Dubey MP, Misra S, Chatterjee RK, Dhawan BN: *Acanthocheilonema vitae* in *Mastomys natalensis*: Content of certain biogenic amines in brain and other peripheral tissues following diethylcarbamazine treatment. Trop. Med. (1991) 33, 7-13.

Pant KK, Nath C: Dopaminergic involvement in the effects of piracetion on foot shock induced aggression in mice. Ind J Med Res. (1993) 98, 155-159.

Prasad PS, Ray R, Jain R, Chavan B.S: Abuse liability of nitrazepam: A study among experienced drug users: Ind J Pharmacol. (2001) 33, 357-362.

Raghavendra V., Kulkarni, S.K: Reversal of morphine tolerance and dependence by melatonin: possible role of central and peripheral benzodiazepine receptors. Brain Res. (1999) 834, 178-181.

Raghubir R, Panaik GK, Sharma SD, W Haq, Mathur KB, Dhawan BN: Morphine like activity of hydrazide derivatives of D-Ala2, Met5-enkephalin. Asia Pacific J Pharmacol. (1990) 5, 3-8.

Raghubir R, Kumar A, Dhawan BN: Nature of neurotransmitters involved in pretectal stimulation produced analgesin in Recentt Advances In The Study Of Neurotransmitter Receptors, Ed Dhawan BN, Srimal RC, Raghubir R, Rapaka RS, CDRI, Lucknow. (1994) 282-288.

Raghubir R, Haq W, Kutty SB: Posssible significant of endogenous ratio of met and leu-enkephalins in antinociception. Pain Suppl. (1999) 8, 166-167.

Rastogi L: PhD Thesis, Biochemical changes during ulceration on experimental animals and their modification by antiulcer drugs. (1997). Dr. RML Avadh University, Faizabad.

Ray SB, Gupta H, Gupta YK: Up-regulation of μ-opioid receptors in the spinal cord of morphine-tolerant rats. J Biosci. (2004) 29,51-56.

Ray SB, Gupta YK, Wadhwa S: Expression of opioid receptor-like 1 (ORL1) and μ opioid receptors in the spinal cord of morphine tolerant mice. Ind J Med Res. (2005) 121,194-202.

Reddy DS, Kulkarni SK: Role of GABA-A and mitochondrial diazepam binding inhibitor receptor in the antistress activity of neurosteroids in mice. Psychopharmacology. (1996) 128, 280-292.

Reddy DS, Kulkarni SK: Chronic neurosteroid treatment prevents development of morphine tolerance and attenuates abstinence behavior in mice. Eur. J. Pharmacol. (1997a) 337, 19-25.

Reddy DS, Kulkarni SK: Neuroprotective effects of neurosteroids against hypoxic stress-induced neurotoxicity in naive and FG 7142-treated mice. Ind. J. Pharmacol. (1997b) 29, 381-392.

Reddy DS, Kulkarni SK: Differential anxiolytic effects of neurosteroids in the mirrored chamber behavior test in mice. Brain Res. (1997c) 752, 61-71.

Reddy DS, Kulkarni SK: Inhibition of neuronal nitric oxide synthase (n-NOS) reverses the corticotrophin induced behavioral effects in rats. Molecular and Cellular Biochem. (1998a) 183, 25-58.

Reddy DS, Kulkarni SK: Potential mechanisms of neurosteroid -induced attenuation of morphine tolerance and dependence. Ind. J. Pharmacol. (1998b) 30, 6-15.

Reddy DS, Kulkarni SK: Proconvulsant effects of neurosteroids pregnenolone sulfate and dehydroepiandrosterone sulfate in mice. Eur J Pharmacol. (1998c) 345, 55-59.

Reddy DS, Kulkarni SK: Role of GABA-A and mitochondrial diazepam binding inhibitor receptors on the effects of neurosteroids on food intake in mice. Psychopharmacology. (1998d) 137,391-400.

Reddy DS, Kulkarni SK: Sex and estrous cycle-dependent in neurosteroid and benzodiazepine effects on food consumption and plus-maze learning behaviors in rats. Pharmacol. Biochem. Behav. (1998e) 62, 53-60.

Roychoudary M, Kulkarni SK: Effect of ondansetron on short terms memory retrieval in mice. Meth. Find. Exptl. Clin. Pharmacol. (1996) 19, 43-46.

Saxena AK, Gurtu S, Nath C: A method for rapid induction of avoidance learning through thermal nociception. Asia Pacfic J Pharmacol. (1991) 6, 15-18.

Saxena VS, Chaudhary G, Srivastava AK, Gupta YK: Seizure protective effect of melatonin in experimental model of status epilepticus in rats. Epilepsia. (1999) 40,115.

Shaji AV, Kulkarni SK: Evidence for GABA-ergic modulation of melatonin induced short-term memory deficits and food consumation. Meth. Find. Exp. Clin. Pharmacol. (1998a) 20, 311-319.

Shaji AV, Kulkarni SK: Central nervous system depressant activities of melatonin in rats and mice. Ind J Exp. Biol. (1998b) 36, 257-263.

Sharma SS, Kochupillai V, Gupta SK, Seth SD, Gupta YK: Antiemetic efficacy of ginger (*Zingiber officinale*) against cisplatin-induced emesis in dogs. J Ethnopharmacol. (1997) 57, 93-96.

Sharma SS, Gupta YK: Reversal of cisplatin-induced delay in gastric emptying in rats by ginger (*Zingiber officinale*). J Ethnopharmacol. (1998) 62, 49-55.

Sharma M, Gupta YK: Intracerebroventricular injection of streptozotocin in rats produces both oxidative stress in the brain and cognitive impairment. Life Sci. (2001a) 68,1021-1029.

Sharma M, Gupta YK: Effect of chronic treatment of melatonin on learning, memory and oxidative deficiencies induced by intracerebroventricular streptozotocin in rats. Pharmacol Biochem Behav. (2001b) 70, 325-331.

Sharma M, Gupta YK: Chronic treatment with trans resveratrol prevents intracerebroventricular streptozotocin induced cognitive impairment and oxidative stress in rats. Life Sci. (2002) 71, 2489-2498.

Sharma M, Gupta YK: Effect of alpha lipoic acid on intracerebroventricular streptozotocin model of cognitive impairment in rats. Eur Neuropsychopharmacol. (2003) 13, 241-247.

Sharma M, Briyal S, Gupta YK: Effect of alpha lipoic acid, melatonin and trans resveratrol on intracerebroventricular streptozotocin induced spatial memory deficit in rats. Ind J Physiol Pharmacol. (2005) 49, 395-402.

Sharma R: Molecular and cellular mechanism involved in neuroprotective effects of neurotrophins following cerebral ischemia – reperfusion unjury. JNU, N Delhi. (2008).

Shukla R, MacKenzie-Taylor DR, Rech RH: Evidcence for 5-HT2 receptor mediation in quipazine anorexia. Psychopharmacology. (1990) 100: 115-118.

Shukla R, Wakade AR: Differential effects of cadmium on calcium channels of splanchnic neurones and chromaffin cells of the rat adrenal medulla. J Neurochem. (1991) 56, 753-758.

Shukla A, Shukla R, Dikshit, Srimal RC: Alteration in free radical scavenging mechanisms following blood brain barrier disruption. Free Radical Biol Med. (1993) 15, 97-100.

Shukla R, Rahmani NH, Mizuma H, Srimal RC, Prasad C: Role of endogenous cyclo (his-pro) in cold induced hypothermia in the desert rat (*Mastomys natalensis*). Peptides. (1994) 15, 1471-1474.

Shukla A, Dikshit M, Srimal RC: Nitric oxide modulates blood brain barrier permeability during infections with an inactivated bacterium. Neuroreport. (1995a) 6, 1629-1632.

Shukla A, Dikshit M, Srimal RC: Status of antioxidants in brain microvessels of monkey and rat. Free Rad Res. (1995b) 22, 303-308.

Shukla A, Shukla GS, Srimal RC: Cadmium induced alterations in blood brain barreir permeability and its possible correlation with decreased microvessel antioxidant potential in rat. Human Experimental Toxicol. (1996a) 15, 400-404.

Shukla A, Dikshit M, Srimal RC: Nitric oxide dependent blood brain barrier alteration in the rat brain. Experientia. (1996b) 52, 136-140.

Shukla R, Barthwal MK, Srivastava N, Nag D, Seth PK, Srimal RC, Dikshit M: Blood nitrite levels in patients with migraine during headache-free period. Headache. (2001) 41, 475-81.

Shukla R, Rajani M, Barthwal MK, Srivatavava N, Dikshit M: Cerebral fluid nitrite and malondialdehyde levels in patients with motor neuron disease. Int J Neurosci. (2003) 113, 1043-1054.

Shukla R, Barthwal MK, Srivatavava N, Sharma P, Raghavan SA, Naga D, Srimal RC, Seth PK, Dikshit M: Neutrophil free radical feneration and enzymatic antioxidants in migraine patients. Cephalalgia. (2004) 24, 37-43.

Sinha K, Degaonkar MN, Jagannathan NR, Gupta YK: Effect of melatonin on ischemia reperfusion injury induced by middle cerebral artery occlusion in rats. Eur J Pharmacol. (2001) 428, 185-192.

Sinha K, Chaudhary G, Gupta YK: Protective effect of resveratrol against oxidative stress in middle cerebral artery occlusion model of stroke in rats. Life Sci. (2002) 71, 655-665.

Somani R S., Kasture V S,.Kasture S B: Haloperidol inhibits (-) bicuculline-induced seizures and bicuculline potentiates haloperidol-induced catalepsy in mice. Ind J Pharmacol. (1999) 31, 434-436.

Srimal RC, Nath C: The neurotoxicity of 1-methyl, 4-phenyl 1,2,3,6-terahydropyridine. In: Lectures in Neurobiology, Eds Tandon PN, Bijlani V, Wadhwa S, New Delhi: Willey Eastern Ltd. (1992) 157-162.

Srivastava SK, Nath C, Sinha JN: Evidence for antiaggressive property of some calcium channel blockers. Pharmacol Res. (1997) 35, 435-438.

Srivastava SK, Nath C: Differential effects of calcium channel blockers in the behavioural despair test in mice. Pharmacol Res. (2000) 42, 293-297.

Srivastava AK, Malhotra J, Gupta YK: Adenosine receptors do not mediate the melatonin protection against pentylenetetrazole induced seizures in rats. Neurobiology. (2001a) 9,147-152.

Srivastava AK, Gupta YK: Aspirin modulates the anticonvulsant effect of diazepam and sodium valproate in pentylenetetrazole and maximal electroshock induced seizures in mice. Indian J Physiol Pharmacol. (2001b) 45, 475-80.

Srivastava N, Barthwal MK, Dalal PK, Agarwal AK, Nag D, Seth PK, Srimal RC, Dikshit M: Nitric content and antioxidant enzyme levels in the blood of schizophrenia patients. Psychopharmacology. (2001c)158, 140-145.

Srivastava AK, Gupta SK, Jain S, Gupta YK: Effect of melatonin and phenytoin on an intracortical ferric chloride model of posttraumatic seizures in rats. Methods Find Exp Clin Pharmacol. (2002a) 24, 145-149.

Srivastava N, Barthwal MK, Dalal PK, Agarwal AK, Nag D, Seth PK, Srimal RC, Dikshit M: A study on nitric oxide, beta adrenergic receptors and antioxidant status in the polymorphonuclear leukocytes from the patients of depression. J Affective Dispoder. (2002b) 47, 45-52.

Tripathi A: PhD Thesis, Biological evaluation and mode of action of growth promoters. (2000) University of Lucknow, Lucknow.

Veerendra Kumar MH, Gupta YK: Intracerebroventricular administration of colchicine produces cognitive impairment associated with oxidative stress in rats. Pharmacol Biochem Behav. (2002a) 73, 565-571.

Veerendra Kumar MH, Gupta YK: Effect of different extracts of *Centella asiatica* on cognition and markers of oxidative stress in rats. J Ethnopharmacol. (2002b) 79, 253-260.

Veerendra Kumar MH, Gupta YK: Effect of *Centella asiatica* on cognition and oxidative stress in an intracerebroventricular streptozotocin model of Alzheimer's disease in rats. Clin Exp Pharmacol Physiol. (2003) 30, 336-342.

Verma S, Raghubir R: Nitric oxide modulation of cardiovascular responses from ventral surface of medulla in cat. Ind J Pharmacol. (1997) 29,125-128.

Verma S: Ph.D. Thesis, Neuropharmacological investigation of the role of nitric oxide in central cardiovascular regulation from the ventral surface of medulla in cat. (1998) Dr. RML Avadh University Faizabad, U.P.