1. Introduction

Autacoids are the substances released from the cells in response to various types of stimulation to elicit normal physiological responses locally. An imbalance in their synthesis, release or in the transduction system contributes significantly to pathological conditions such as inflammation, allergy, hypersensitivity and ischaemia - reperfusion. Nitric oxide (NO) was recognized by Science magazine as the molecule of the year in 1992. It has led to a spurt in the research on NO and oxygen derived free radicals, which is very evident throughout the world and also in India. Research work carried out in India during the 'report period' on NO and reactive oxygen species (ROS) has also been included in this article. This review includes the papers published in this area during 1994-1998 but does not cover abstracts or conference proceedings.

2. Studies on central nervous system

Serotonin (5-HT) plays an important role in the regulation of various cognitive behavioural functions such as sleep, mood, learning, pain, depression and anxiety by binding to its receptors on the cell membranes. Alterations in the 5-HT synthesis, metabolism and in the receptor characteristics leads to various pathological conditions. Chattopadhyay et al. have worked on the solubility, absorbance and fluorescence characteristics of the 5-HT receptor purified from buffalo brain and its interaction with 5-HT. These studies might help further in understanding the interaction of 5-HT with its receptor.

The mouse 5-HT receptor, which is predominantly expressed in the cortex and hippocampus, is encoded by at least three transcripts as is also observed in the rat brain. The mouse 5-HT receptor clone shows the coding region to be intron less and an intron splice junction is seen in 5'-untranslated region that is conserved both in the rat and mouse.

Intracerebroventricular (icv) administration of serotonin antibodies (5-HTabs) in Balb/c mice leads to alteration in the behaviour as well as in the levels of 5-HT, dopamine (DA) and their metabolites in the substantia nigra (SN), nucleus raphe dorsalis (NRD) and caudate putamen. 5-HTabs inhibited tail flick latency but the tremor response to 5-methoxy N,N-dimethyl tryptamine was augmented. 5-HTabs also induced increase in the 5-HT turnover in all the nuclei studied; however, DA turnover was increased only in SN. This study helps in understanding the central neurotransmitter control on behaviour. It might also help in developing a 5-HT deficient model for studying clinical disorders but it may not help in delineating the underlying mechanism.

5-HT uptake inhibitor, fluoxetine, is metabolised in the brain by the enzyme flavin monooxygenase, thus this enzyme might be involved in local metabolism and modulation of the pharmacological effects of the psycho-active drugs. It metabolises fluoxetine to its respective N-oxide and S-oxides. Extirpation of the adrenal glands per se did not alter the responses to noxious stimuli but it increased the anti-nociceptive potency of imipramine in the rat. The anticonvulsant activity of the sepia shell might be due to the elevation of the seizure threshold rather than the prevention of the seizure spread. This action seems to be mediated by the serotonergic transmission. Panax ginseng and diazepam both attenuated stress induced elevation in brain and hypothalamus 5-HT level and in the plasma corticosterone levels. Pyrimidine thiols exhibit anticonvulsant activity, which seems to be mediated by enhancing the GABA-ergic activity and opening the chloride channels. Twenty patients of depression treated with imipramine as well as centroprazine did not exhibit significant changes in the blood pressure, heart rate, PR, QRS, Q-Tc intervals.
Oil extract of *Celastrus paniculatus* seeds improved the retention ability in rats. NE, dopamine, 5-HT and their metabolites in brain and urine were significantly decreased in the treated group suggesting a decrease in their turnover to improve the learning and memory. The acetone soluble fraction of petroleum ether extract of *Lawsonia inermis* leaves exhibited prominent nootropic activity and modified the 5-HT and NE mediated behaviour, suggesting towards exploring its nootropic principle. Subordination induced decrease in the 5-HT and dopamine contents in the frontal cortex have been observed in the rats.

Involvement of nitric oxide and oxygen derived free radicals has been suggested in the neurodegeneration observed in the Parkinson's disease and also in the cerebral ischaemia. Studies carried out in India have also investigated their role in the experimental models of chemical and ischaemia induced lesions. A significant decrease in the phospholipids and membrane fluidity was observed, following 6-hydroxy-dopamine (6-OHDA) induced bilateral lesions in the striatum. In addition, there was a significant increase in intracellular calcium and malondialdehyde (MDA) levels. However, glutathione content and the activity of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) was attenuated 72 hr after 6-OHDA injection into the striatum. Studies on another neurotoxic substance, methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) were performed in golden hamsters. These animals were resistant to the toxicity observed following both acute and chronic administration of MPTP as indicated by lack of any alteration in normal content of dopamine and its metabolites in the nucleus caudate putamen (NCP), limbic system and SN. Balb/c and C57/BL mice exhibited >50% and 70% depletion in DA following MPTP administration respectively. The content of total monoamine oxidase (MAO) in golden hamster was one third to one sixth of any nuclei or mitochondria of both strains of mice. Differences in the distribution and levels of MAO could be correlated with the MPTP neurotoxicity. NO by reacting with superoxide radicals (O$_2^-$) generates more toxic and reactive peroxynitrite, reactive nitrogen species, which on decompositions form more toxic and reactive hydroxyl radicals. This pathway has been found to mediate neurodegeneration and neurotoxic action. Rapid restoration of thiol homoeostasis in the brain during reperfusion following cerebral ischaemia helps in the recovery from reperfusion induced injury. It has been observed that glutathione is significantly decreased after the reperfusion for 1 hr following moderate or severe ischaemia for 30 min. Tertiary butyl hydroperoxide caused increase in the lipid peroxidation and decrease in the reduced glutathione content in the striatum, which was prevented by alpha tocopherol and nicotinamide.

Inhibition of endothelial nitric oxide synthase in the periphery is primarily known to be associated with hypertension. However, involvement of NO/Arginine/cGMP pathways in the central regulation of blood pressure is not very well understood. Studies on normotensive cats showed the involvement of NO/Arginine/cGMP pathways in the central regulation of blood pressure. Topical application of sodium nitroprusside (SNP) produced a significant hypotension and bradycardia, which was significantly blocked by methylene blue (MB), suggesting towards the possible involvement of NO-cGMP mechanism in the central cardiovascular regulation.

An interrelationship between blood pressure level and brain nitric oxide synthase (NOS) activity in hypertensive rats has also been indicated. NOS activity was significantly reduced in the medulla and hypothalamus of coarctation induced experimental model of hypertension in the rat. In the same study anti-hypertensive drugs, captopril, nifedipine, or centhaquin (a centrally acting antihypertensive compound developed at CDRI) normalised blood pressure and the brain NOS activity. Cyclosporin A, a potent immunosuppressive agent, by interfering with calcium/calmodulin, inhibited the brain NOS activity both in vitro and in vivo in the rat.

The permeability of the blood brain barrier (BBB) is altered in several metabolic derangements, infections, poisoning and other pathological conditions. NO mediated modulation of BBB permeability has been demonstrated by Shukla et al. Induction of NOS activity after exposure to lipopolysaccharide contributes to the increase in BBB permeability. Thus the results obtained demonstrated the involvement of NO/Arginine pathway and reactive oxygen species in the opening of the BBB.

*Ginkgo biloba*, a platelet activating factor (PAF) antagonist, potentiates the picrotoxin-induced convulsions, which might be due to the involvement of GABAergic system and chloride channel. While facilitation of the strychnine action suggests towards...
the modulating action of Ginkgo biloba on glycine39. Ginkgo biloba treatment decreased the protective effect of sodium valproate and carbamazepine against tonic convulsions in mice36.

3. Studies on peripheral system

Calcium channel blockers (CCBs) significantly reduced the 5-HT induced contractions and completely blocked histamine induced contractions in the rat aortic rings. Similarly histamine and 5-HT induced contractions were also attenuated in aortic rings obtained from DOCA saline hypertensive rats in presence of these blockers31. In DOCA saline hypertensive rats chronic treatment with prazosin reduced the pD2 value for norepinephrine (NE) and abolished the phenylephrine (PE) response in isolated aortic strips. However, chronic treatment with thyroxine and prazosin significantly augmented the pD2 value for NE but it was attenuated in PE in comparison to the thyroxine treated controls32. Furthermore chronic treatment with ethinyl oestradiol for 3 weeks did not alter the pD2 values of NE in the rat isolated aortic strips, however, pD2 values of NE in the portal vein preparation was significantly increased33.

Role of central serotonergic system in various pathologies has been reported. Changes in the serotonergic systems in the central nervous system have been reflected in the platelets as shown by many investigators. A significant low basal platelet 5-HT and cerebrospinal fluid 5-hydroxy indole acetic acid (5-HIAA) concentration in epileptic patients suggests the involvement of 5-HT in epilepsy34. Platelet 5-HT2 receptors have also been found to be associated with severe social phobia35. Platelet 5-HT basal level uptake and efflux was not significantly different from the 8 untreated depressive adolescents from age and sex matched controls. However, fluoxetine, a 5-HT uptake inhibitor produced clinical recovery in all the patients and reduced the 5-HT content and uptake as compared to the control and pre-treatment level36. Increased sympathetic activity seems to be responsible for an increase in the platelet 5-HT, epinephrine and norepinephrine content in the diabetic patients and also in the streptozotocin treated rats37. Increase in the 5-HT levels seems to be associated with toxemia of pregnancy38. In the patients of essential hypertension an increase in the platelet intracellular calcium level seems to be due to a decrease in the Ca++ ATPase activity39.

Central serotonergic system seems to play a critical role in the immunomodulation40. Immune-21, a polyherbal product significantly potentiated humoral immunity in rabbits41. Ascorbic acid stimulates the humoral immunity by increasing synthesis of IgG, IgA and IgM and it also activates the macrophages42. Benzodiazepine-GABA A and B receptors appear to regulate the restraint stress induced modulation in release/activity of leucocyte migration inhibition factor, a lymphokine released from the sensitized lymphocytes43. In another study human aqueous placental extract was found to be immunostimulant for humoral and cell mediated immunity in animals as well as in humans44.

The response to 5-HT was inhibited while that of NE was potentiated in the anococcygeus muscle and vas deferens after 30-min incubation with fluoxetine. Treatment of rats with fluoxetine for seven days suggests towards the depletion of catecholamines45. Contractile activity of Alstonia boonei (used in West Africa to treat fever and malaria) extract observed in the isolated rat stomach strip and guinea pig ileum was antagonized by methysergide suggesting the role of 5-HT in the biological effect of the extract46. Nifedipine offered significant protection against the 5-HT induced increase in the paw oedema and reduced the volume of the fluid and weight of the granulation tissue in the granuloma pouch but verapamil and diltiazem exhibited no protection47. Nifedipine, verapamil and diltiazem produced significant and dose dependent anti-inflammatory effect in rat hind paw oedema produced by prostaglandin E1 (PGE1) and bradykinin48, which was better than aspirin. These inhibitors were ineffective against the histamine-induced increase in the paw volume49,50.

NO donor, 3-morpholinosydnonimine (SIN-1) induced a concentration dependent relaxation in the coronary artery rings precontracted with 30 mM K+. Pretreatment of the rings with methylene blue, a guanylate cyclase inhibitor, shifted the SIN-1 induced response curve towards right. Glibenclamide, a K+-channel blocker blocked the pinacidil induced response but it had no effect on SIN-1 induced response49, suggesting that NO mediated relaxation is not mediated by K+-ATP channels. On the other hand pinacidil induced vasorelaxation in 30 mM K+ preconstricted rings was blocked by NOS inhibitor L-NAME, MB and by endothelium denudement. However, levocromakalim
(another K^-\text{ATP} channel opener) induced relaxation was potentiated in the absence of basal NO. Papaverine induced relaxation also remain unaltered by basal NO. Thus basal NO deferentially modulates the interaction of pinacidil and levecromakalim with the K^-\text{ATP} channels in goat coronary artery through a cGMP-dependent pathway. NO mediated attenuation of the reactive oxygen species (ROS) dependent norepinephrine-induced contraction of the aortic rings has also been reported. The effect was not observed in the endothelium denuded preparations, suggesting that NO interact with ROS in the endothelium during contraction. Similar attenuation in the acetylcholine induced NO release and augmentation in the endogenous ROS generation plays an important role in the modulation of vasoreactivity in the ren hypertensive rats. Thus both NO and ROS considerably influence vasoreactivity in the normotensive as well as in hypertensive rats. Methylene blue attenuated the acetylcholine (ACh) induced relaxation in the endothelial intact monkey aortic strips; therefore it appears that in these strips ACh increases the intracellular cGMP levels. However, ACh induced contractions in the endothelial denuded rings were further augmented.

Polymorphonuclear leukocyte (PMNL), the cohabit of platelets in blood, release several factors that alter platelet response. Following thrombosis circulating PMNLs release more NO and less free radicals and this could be a defence mechanism of the body. A factor was found to be present in the PMNLs cell suspension, which inhibits ADP, arachidonic acid and calcium ionophore induced platelet aggregation. Nonsteroidal anti-inflammatory drug, aspirin when taken along with nifedipine, a calcium channel antagonist and anti-hypertensive drug exhibited a synergistic inhibitory effect on collagen, ADP and epinephrine induced platelet aggregation.

Free radical scavengers, PAF-antagonists, cyclo-oxygenase inhibitors and NO releasing compounds have been found to be effective in preventing paralysis/death due to intravenous collagen and adrenaline injection in mice and rats. These findings suggested that free radicals could be involved in the genesis of thrombosis. Therefore role of free radical generating and scavenging enzymes in this pathological state had been investigated. Involvement of free radicals and neutrophils in thrombosis has been suggested.

The oxidative burst of PMNLs is primarily meant for the killing of ingested micro-organisms. However, research on these cells has shown that they also play an important role in ischaemia reperfusion, inflammation and thrombosis. PMNLs release both NO and ROS. Investigation on the interaction of NO with superoxide radicals suggested towards the possibility of NO regulating the generation of ROS. NO donors like sodium nitroprusside (SNP) and diethylamino-nitric oxide (DEA-NO) as well as NO precursor, L-arginine inhibited formyl-methionine-leucylphenylalanine (FMLP, a chemotactic peptide), arachidonic acid (AA, NADPH-oxidase activator), phorbol ester (PMA, protein kinase C activator) or opsonized zymosan (OZ, a phagocytic ligand) induced luminol-dependent chemiluminescence (LCL), hydroxyl radical generation, oxygen consumption and NADPH-oxidase activity in the PMNLs. Both exogenous and endogenous NO inhibited the NADPH-oxidase activity. Thus superoxide radical generation was inhibited and NO also scavenged the free radicals released/generated from PMNLs. NOS inhibitors and their D-enantiomers attenuated the LCL response, which was not due to non-availability of NO. Therefore, effect of L-arginine analogues, and their D-enantiomers was also investigated on NADPH-oxidase activity and oxygen consumption of the rat PMNLs. It was seen that NO mediated attenuation of LCL response was due to the inhibition of NADPH-oxidase activity and oxygen consumption. Nevertheless, NOS inhibitors and their antipodes inhibited LCL response without inhibiting NADPH-oxidase activity and oxygen consumption. The results obtained thus warrant caution in using NOS inhibitors (arginine analogues) to analyse the role of NO in PMNLs LCL response, as they themselves seem to scavenge free radicals.

In an interesting study on the free radical generation from PMNLs in control and in smokers (cigarette, bidi, hookah and mixed products), a significant increase in the superoxide radical generation was observed. Role of PMNLs and free radicals has been suggested in the chronic obstructive pulmonary disease. NO production in the 26 patients of systemic lupus erythematosus was increased in comparison to the control, as evident by an increase in the serum nitrite and citrulline levels.

Effect of Pasteurella multocida on hydrogen peroxide (H_2O_2) and NO generation from isolated PMNLs

\[ \text{Effect of Pasteurella multocida on hydrogen peroxide (H}_2\text{O}_2) \text{ and NO generation from isolated PMNLs} \]
was studied in control and in vaccinated buffaloes against haemorrhagic septicemia. Lipopolysaccharide (LPS) of *P. multocida* and live *P. multocida* both potentiated the release of H$_2$O$_2$ and NO from the control and the vaccinated animal cells in comparison to the non-activated cells. However, PMNLs isolated from vaccinated animals exhibit a significant increase in H$_2$O$_2$ and NO release in comparison to control. Thus results obtained indicate an up regulation in oxidant defence system in presence of an antiphagocytic bacterium, in the PMNLs. Septilin, an Ayurvedic formulation, showed significant protection in *E. coli* induced abdominal sepsis in normal mice and *Staphylococcus aureus* induced sepsis in neutropenic mice. It also stimulated the phagocytic function of neutrophils and reticuloendothelial system in mice. In normal rats, Septilin enhanced anti- sheeph RBC agglutination antibody titer by 6 folds and showed significant protection against cyclophosphamide - induced humoral suppression. Involvement of NO in the hypoglycemic activity of tolbutamide is suggested.

Calcium modulating agents such as EGTA, nifedipine, TMB-8 and calmodulin antagonist W$_7$ inhibited the Cisplatin (CP, a potent chemotherapeutic drug) induced tumoricidal activity of peritoneal macrophages by decreasing the release of tumor necrosis factor-α (TNFα) and interleukin-1 (IL-1) in the supernatant. CP and LPS pretreatment of murine peritoneal macrophages showed an enhanced production of NO and a tumoricidal activity against P815 mastocytoma cells. L-Nitro mono methyl arginine (L-NMMA) a specific NOS inhibitor, blocked this response. Protein kinase C (PKC) inhibitor, H$_2$, and chelerythrine chloride and tyrosine kinase inhibitor genistein and levendustin A, inhibited the CP induced IL-1 and TNFα secretion and tumoricidal activity of macrophages, thus suggesting the involvement of PKC and tyrosine kinase in activation of peritoneal macrophages with CP. Expression and secretion of Oncostatin M, a novel cytokine that regulates growth of a single dose.

Indole, triazine, benzopyran derivatives and substituted quinazolines were evaluated for anti-inflammatory activity in rats. A crude extract from the roots of *Gmelina asiatica* exhibited anti-inflammatory activity against carrageenan induced rat paw edema and cotton pellet granuloma models in the rat. Anti-proliferative, anti-oxidant and lysosomal membrane stabilisation activity of the drug possibly mediated the inhibitory effect. 4',5,6-trihydroxy-3', 7-dimethoxy flavone-from *Vicoa Indica DC* showed consistent anti-inflammatory and analgesic activity in various models. Methanolic and aqueous extract of *Curculigo orchioides* exhibited significant anti-inflammatory activity in comparison to ibuprofen and indomethacin. Effect of triterpenes from *Crataeva nurvala* stem bark has been investigated on adjuvant induced arthritis in the rats. The water-soluble extract of the alcoholic extract of *A. indica* leaves exerted significant anti-inflammatory activity in cotton pellet granuloma assay in the rat. Synthetic analogues of liposomes prepared from non-ionic surfactants known as niosomes have been used to prepare the trapped diclofenac sodium. Formulations of diclofenac prepared by 1:1 combination of Tween 85 and poloxamer F-108 exhibited better and consistent anti-inflammatory activity for more than 72 hr after administration of a single dose.
Combination of the non-steroidal anti-inflammatory drugs diclofenac, piroxofene and fenpiverinium might have antispasmodic activity as they inhibited the ACh induced contractions in the rat colon. Effect of ATP, adenosine or caffeine was investigated on Brewer's yeast induced peripheral inflammation and nociception after their icv administration. The results indicated that central purinergic system exerted anti-inflammatory effect. Further study showed that centrally administered PGF$_{2\alpha}$ exerts anti-inflammatory while PGE$_2$ exerts pronociceptive effects on Brewer's yeast induced peripheral inflammation and pain.

Riboflavin supplementation showed increased activity of the glutathione redox cycle enzymes and glutathione content in the selinite induced cataractous rat lenses. Ocimum sanctum exhibits anti-cataract activity in different experimental models, which might be due to the free radical scavenging. Involvement of both H$_1$ and H$_2$ receptors in the production of histamine aerosol induced bronchospasm in the guinea pigs is observed. Sublingual nifedipine exhibited clinical improvement in the moderately symptomatic, non-smoking allergic bronchial asthma patients. Ethanolic extract of the leaves of Vitex negundo Linn inhibited the immunologically induced degranulation of the mast cells. It also inhibited the oedema during active paw anaphylaxis in mice. It appears that this extract has the ability to alter calcium fluxes from the extracellular medium and in the membrane. Furosemide significantly attenuated compound 48/80 and egg albumin induced contractions in the guinea pig tracheal rings by either causing local release of PGE$_2$ or by affecting the mediator release from mast cells. Fluticasone alone and in various formulations effectively reduced histamine induced wheal and flare. Ethanolic extract of Vitex negundo Linn inhibited the 48/80 and antigen induced contractions in the guinea pig trachea. The results suggest that it interferes with histamine and arachidonic acid metabolite mediated responses. 5-Methyl benzoxazoline-2-one inhibited the contractile response to histamine, 5-HT, acetylcholine and barium chloride in the guinea pig ileum but not to the same extent suggesting a non-specific antagonism of the papaverine or sympathomimetic agents. Coleonol, an adenylyl cyclase activator, was shown to exert significant antipassive cutaneous anaphylaxis and mast cell stabilising activity. CDRI compound, 88/765 (4-amino-6-methyl thio-1-(2', 2'-diethoxyethyl) - 1H-pyrazolo [3,4-d]pyrimidine) inhibited the passive cutaneous anaphylaxis in rat and mice and mast cell degranulation of normal and passively sensitised rats induced by 48/80 or egg albumin, the effect was comparable to sodium cromoglycate. Bleomycin, the glycopeptide antibiotics used in the cancer therapy, induced injury was protected by curcumin due to the restoration of the antioxidant status in the rats. Superoxide dismutase alone or in combination with glutathione reduces the clastogenic action of bleomycin. Five analogues of Ala-Asp-Ser-Asp-Gly-Lys (ADSDK) with modification at position 1,2 and 6 have been tested for anti-allergic activity, one of the peptides (compound 94/335) has shown anti-allergic activity in various experimental models of allergy even by the oral route. Development of mast cells from bone marrow precursor cells was performed in cultures using Concanavalin A stimulated splenocyte supernatant.

Prolonged treatment with oestrogen or progesterone led to a down regulation of histamine H$_1$ and H$_2$ receptors in the rat and guinea pig. The possible mechanism appears to be oestrogen and progesterone induced elevation of the histamine levels in the blood. Diflunisal, a salicylic acid derivative produced significant changes in the neural tube development of chick embryo. PGE$_2$, and PGF$_{2\alpha}$ treatment potentiated the effect of diflunisal. It appears that diflunisal induced changes might be mediated at the cellular level. L-NAME pretreatment led to a failure of implantation when administered at 2.5 mg/kg per uterine horn on day 3 of pregnancy. L-NAME mediated effect was reversed by SNP pretreatment, suggesting a role of NO in implantation.

Cauvery 100, an Ayurvedic formulation exhibited a potent anti-ulcer effect against indomethacin induced ulcers in the rat. Effect of verapamil, nifedipine and diltiazem was evaluated on experimental models of ulcers in the rat. Both verapamil and nifedipine offered protection but diltiazem exacerbated the cysteamine-induced ulcers. Sulpiride, a D$_2$ receptor antagonist increased the total carbohydrate content and decreased the protein contents and exhibited anti-ulcer activity. An herbal drug formulation, UL-409, displayed cytoprotective action against ethanol induced ulcers in the rat. Alterations in the lipid peroxides and antioxidants status were reversed by UL-409. Cholinergic involvement and a partial
role of NO in the gastrokinetic effects of exepanol in mice and guinea pig ileum have been demonstrated. It has been recently reported that ulcers in the rat are closely associated with augmented free radical generation. Poly I: Poly C, an inhibitor of interferon inducer was found to inhibit the peptic ulcers in the rat. Endoscopic evaluations of osteoarthritis patients for gastrointestinal problems after treatment with ketorolac and diclofenac sodium suggested that short-term analgesic use of ketorolac is safer. Ketorolac also provides progressively increasing and long lasting pain relief in comparison to nefopam in immediate post-operative period following upper abdominal surgery. Ranitidine, famotidine and omeprazole, potent anti-ulcer drugs, have no significant effect on the hepatic functions and lipid profile when used for a period of 12 weeks in the peptic disease patients. Central adenosine A1 via noradrenergic receptors and GABA-B receptors independently inhibit gastric acid secretion.

4. Conclusion

5-HT is involved in the pathophysiology of depression, anxiety, hypertension etc. All the physiological and pathophysiological effects of 5-HT are due to its interaction with various distinct membrane receptors. Thus basic studies on the 5-HT interaction with the receptor and behavioural changes following administration of monoclonal antibodies might help us in understanding the interaction at the receptor level and its involvement in the modulation of the behaviour. In addition, studies on the metabolism of drugs which modulate the concentration and availability of 5-HT in the brain is also quite useful as the variability in the effect of drugs could be partly explained on this basis also. Studies on the herbal drugs have shown that some of these drugs/active components exert their effect by modulating the 5-HT levels in the brain or periphery. Interestingly changes in the central serotonergic system have been reflected in the platelets of the patients of social phobia and in epilepsy patients in comparison to the controls. In the diabetic patients and in the toxemia associated with pregnancy, levels of 5-HT were elevated in the platelets. 5-HT induced rat aortic ring contractions were blocked by the calcium channel antagonists and nifedipine was found to block the 5-HT induced increase in the paw volume thus suggesting that calcium is involved in the 5-HT induced responses.

Studies on NO and free radicals have shown the importance of these mediators in several physiological and pathological conditions. Role of NO in central regulation of blood pressure in both normotensive and hypertensive animals has been observed. In the experimental models of Parkinson’s disease and in the cerebral ischaemia involvement of free radicals has been observed. In addition, BBB permeability in the infectious conditions appears to be increased by NO, while in the normal situation it does not seem to play an important role.

NO mediated vasorelaxation is not mediated by the K⁺-ATP channels. However, vasorelaxant response of K⁺-ATP channel opener, levcromakalim was potentiated in the absence of basal NO. NE induced vasoconstriction seems to be modulated by the endothelial NO and ROS in the rat aortic rings. In addition ACh induced NO release is attenuated while NE induced ROS generation was potentiated in the rings obtained from hypertensive rats. Methylene blue, a guanylate cyclase inhibitor prevented the ACh induced relaxation in the monkey aortic strips but augmented the ACh induced contraction in the denuded strips.

Studies on PMNLs indicate that NOS inhibitor L-NAME scavenges free radicals. NO also seems to modulate the free radical generation from PMNLs by scavenging as well as by inhibiting the generation of free radicals. In addition, work on NO in relation to Leishmania has also been carried out in India.

Cisplatin was found to induce the microbicidal activity by inducing the release of various inflammatory mediators including NO. During the report period various natural and synthetic compounds were found to exhibit, anti-inflammatory, anti-ulcer and anti-allergic activities.

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