PHARMACOLOGICAL RESEARCH IN INDIA

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INTRODUCTION

An exhaustive review entitled "Highlights of Pharmacology Research in India" was written by Mukerji and associates in the 1963 issue of *Annual Review of Pharmacology* (1). Subsequently "Trends in Pharmacology Research in India" by Dandiya & Bapna (2) and "CNS Active Drugs from Plants Indigenous to India," by Dandiya & Chopra (3) have been published. A comprehensive review on *Ayurvedic Medicine—Past and Present* has been recently written by Sharma (4). In the present article an attempt has been made to summarize the research work done in India during the past decade, including research on the active materials isolated from plants indigenous to India, which has received considerable attention during the last twelve years.

Pharmacology research in India has been traditionally sponsored by the medical colleges. Several factors have provided impetus to the trend. The growth and expansion of medical education was very rapid generally after 1950 and particularly during the 1960s. New institutions were fortunate in having on their staffs a number of Indian pharmacologists trained abroad under the auspices of various international agencies, some trained under eminent pharmacologists in western countries. Besides, pharmacological research, like research in other medical sciences, was promoted and supported with substantial financial assistance by the Indian Council of Medical Research (ICMR). In 1962 an independent committee was constituted by the ICMR to encourage research on indigenous drugs. A year later ICMR appointed a separate expert group to evaluate research proposals on pharmacology, and thus separated the responsibility that had hitherto been undertaken by the combined committee for physiology and pharmacology. The research projects on indigenous drugs have now been assigned to the Central Council of Research on Indian Medicine and Homoeopathy. For some years this Council has been running composite research units of indigenous drugs comprising subunits of chemistry, pharmacology, pharmacognosy, and clinical trials, the last being housed mostly in the hospitals of indigenous systems of medicine.

The Central Drug Research Institute (CDRI) at Lucknow, functioning under the control of the Council of Scientific and Industrial Research, has been another promoter of drug research in India. Significant work has been done in the last few years in this Institute. Private enterprise in pharmacology research is yet in its infancy in India, the solitary exception being CIBA research center. Lately, the Hoechst Pharmaceuticals have also made a beginning in this direction. These developments have contributed to the advancement of pharmacological research in the country from 1960 onwards. The rate of growth and the quality of work could have been higher but for the following reasons: (*a*) the opening of too many new medical colleges in the 1960s led to the migration of the professional talent from the few institutions then existing to a large number of teaching colleges. Some of the departments left with skeleton manpower that could barely manage the teaching load were unable to indulge in the luxury of research; (*b*) due to stress of expansion of medical education, government funds were directed more and more towards undergraduate teaching while grants for purchasing equipment for postgraduate training and advanced research gradually shrank. The paucity of foreign exchange was another limiting factor in the procurement of sophisticated equipment; (*c*) a good number of pharmacologists who had received training abroad returned to the western countries where superior research facilities were available. This was particularly so in the case of nonmedical pharmacologists who were not easily accepted on the faculties of medical colleges in India. Further, the progress of biochemistry in India was slow and this adversely influenced the growth of pharmacological research; (*d*) the facilities for clinical research were not available to the pharmacologists of this country, the sole exception being the pharmacology department of the Seth G.S. Medical College in Bombay, where a clinical research unit has existed under the leadership of Dr. U. K. Sheth for quite a few years.

CENTRAL NERVOUS SYSTEM

Natural Substances

The sanskrit word "Gandha" means smell and since time immemorial sarpa-gandha (snake smelling) i.e. *Rauwolfia serpentina;* ugra-gandha (strong smelling) i.e. *Acorus calamus;* and ashwa-gandha (horse smelling) i.e. *Withania somnifera,* were the main herbs employed for mental ailments in India. The isolation of reserpine from *Rauwolfia serpentina,* which possessed marked CNS depressant and antihypertensive actions, led to the investigation of the other two herbs.

The active principles from the roots and rhizomes of *A. calamus* were isolated and identified as α-asarone (asarone) and β-asarone i.e. *trans-* and *cis*-2,4,5-trimethoxy-1-propenylbenzene respectively (5). Asarone was found to have a marked CNS depressant effect in mice, rats, and monkeys. It decreased spontaneous locomotor activity in mice (6) and rats (7) and produced a calming effect in monkeys which lasted for 24 hr (8). The onset of action of asarone was quicker than reserpine and it counteracted the stimulant effect of *d*-amphetamine, LSD, methylphenidate, and

mescaline but only partially antagonized the effect of imipramine in rats and mice (8). It also offered complete protection to aggregated mice treated with toxic doses of *d*-amphetamine, where it was found to be more effective than chlorpromazine (9). It prolonged the hypnosis induced by pentobarbital, hexobarbital, and ethanol, an effect which could not be prevented by LSD or iproniazid (10). It caused hypothermia in mice (10) and counteracted LSD-induced hyperpyrexia (8). It prevented pentylenetetrazol-induced convulsions and electroshock seizures, but facilitated picrotoxin-induced convulsions in rats (10, 11). It potentiated the effect of reserpine on electroconvulsions (12), blocked conditioned avoidance response of trained rats, and potentiated the effect of reserpine on this response. It also antagonized fighting behavior due to foot shock and increased the number of shocks accepted by experimental animals in conflict neurosis (13).

The work done on its mechanism of action revealed that unlike reserpine it did not deplete the brain contents of 5-HT (12) or norepinephrine (NE) (6). It caused sedation in mice treated with iproiazid similar to that of chlorpromazine (6, 8). Because the chemical structure of asarone resembled a part of the reserpine molecule, an attempt was made to find out if both these agents acted on a common receptor site. α-Methyltyrosine pretreatment, which lowered brain NE by about 65%, enhanced the sedative action of both asarone and reserpine (14, 15). However, unlike tetrabenazine, asarone did not block the sedative action of reserpine, suggesting a different site of action (6).

Asarone elicited a mild hypotensive effect in anesthetized dogs and exhibited a varying degree of antiacetylcholine, antihistamine, and antiserotonin activity on isolated muscle preparations (9, 16). It prevented the depletion of adrenal ascorbic acid in rats subjected to cold stress.

In search for more useful and less toxic asarone analogs a number of trimethoxybenzene derivatives: i.e. phenylalkyl derivatives (17, 18), benzamides (17, 19–25), phenylesters, anilides, tetrazoles (22, 26), piperazines (27), azlactones (26, 28, 29), styrenes and cinnamic acids (17, 30, 31), and hydantoins and 2-thiohydantoins (32, 33) were synthesized by Dandiya and co-workers and interesting structure activity relationships were established (34).

The work done on ashwagandha (*W. Somnifera*) revealed that its total alkaloid fraction, ashwagandholine and two saponins becoside A and B, possessed mild CNS depressant activity (35, 36).

Besides these, a few other CNS active principles were obtained from plants. A glycoside saponin principle "hersaponin" isolated from *Herpestis monniera,* which is used in the Ayurvedic system of medicine in insanity, epilepsy, and hysteria, has been shown to produce a sedative effect in rats and guinea pigs. It potentiated hexobarbitone induced sleep in mice, caused hypothermia (37), and was reported to deplete brain NE and 5-HT content in rats (38). Bhide (39) has reported the presence of a tranquilizing principle in the husk of millet from *Paspalum scrobiculatum.* A sesquiterpene Jatamansone, syn. velaranone, having a weak tranquilizing, hypotensive (40, 41), and antihyperkinetic activity (42), has been isolated from *Nardostachys jatamansi.*

Stereotyped Behavior

A successful attempt has been made to analyze the influence of hallucinogens (LSD, mescaline), CNS stimulants (amphetamine, methylphenidate, caffeine), and antidepressants (imipramine, iproniazid, pargyline) on the open field performance in rats (43, 44). Two distinct behavioral actions, namely the horizontal activity (ambulation) and vertical activity (rearing), were observed when rats were subjected to the open field test. The horizontal activity, a function of increasing doses of hallucinogens like LSD and mescaline, was considered as simple stereotypy, while the vertical activity was taken as complex stereotypy, which was found to be a characteristic behavioral pattern of amphetamine and methylphenidate (44–47). The antidepressants, however, failed to modify the behavioral actions in rats in the open field test. Lately, with the aid of enzyme inhibitors and precursors the possible role of brain biogenic amines in the stereotyped behavior was analyzed (48) and it was found that complex stereotypy was mediated by brain dopaminergic mechamism while the simple stereotypy was a function of brain NE (49).

Sethy et al (50) suggested the use of "amphetamine stereotypy" as a test for CNS stimulant or depressant drugs. It was also shown that small doses of CNS depressants could enhance amphetamine activity when given in combination (51).

Monoamines and CNS Drugs

The role of catecholamines (CA) and 5-HT in the action of psychotropic drugs was studied by Dandiya and associates employing specific enzyme inhibitors that are known to block their synthesis at the rate-limiting step. It was found that α-methyltyrosine, which lowered brain CA, remarkably enhanced the sedative actions of reserpine, chlorpromazine (14, 52), and asarone (6) and antagonized the excitatory actions of mescaline, amphetamine, morphine, and cocaine (53). It was further reported that α-methyltyrosine protected aggregated mice from the toxicity of amphetamine (15), suggesting that CA play an important role in the actions of the above-mentioned drugs. The excitation caused by reserpine in pargyline-treated rats was also suggested to be more closely related to CA than 5-HT (54, 55). These workers have also reported the beneficial influence of a number of monoamine oxidase inhibitors and some other antidepressants on the efficacy of diphenylhydramine in preventing drug-induced parkinson-like signs in rats and mice (56, 57).

Influence of Drugs in Stress

Dandiya et al (58) have investigated the antistress actions of some tranquilizers. Physiological stress caused a varying degree of biochemical alterations in the animals. A fall in adrenal ascorbic acid content, serum cholesterol, and serum sodium levels was reported after subjecting the animals to cold stress (58, 59). Heat stress lowered brain glutathione and acetylcholine contents but increased 5-HT and NE levels (59, 60). Both chlorpromazine and reserpine offered protection to these heat stress-induced changes. Mescaline and LSD produced a lowering of brain glutathione levels and aggravated the heat stress-induced reduction in glutathione level (59). Sharma and associates showed that both reserpine and chlorpromazine prevented the rise in stress-induced cardiac and plasma CA and acetylcholine contents

(61, 62). α-Methyltyrosine was able to prevent the fall in myocardial glycogen and blood glucose in rats (63). Pohujani and co-workers have reported the protective influence of a number of barbiturates, glucocorticoids, and chlorpromazine against the effects of centrifugal stress on rat adrenals (64–66).

Analgesics and Muscle Relaxants

Sheth and his colleagues investigated the mechanism of morphine- and meperidine-induced analgesia. The ED_{50} of meperidine significantly increased in mice pretreated with reserpine or *p*-chlorophenylalanine (PCPA) when tested by tail clip and electroshock method (67, 68). Similarly the ED_{50} of tremorine also increased in mice treated with reserpine, PCPA, or diethyldithiocarbamate when tested for analgesic activity (69). It was suggested that morphine released dopamine in the CNS which in turn excited the central dopaminergic receptors (70).

Sinha et al (71, 72) demonstrated the muscle relaxing property of tricyclic antidepressants and some β-adrenergic blocking agents. On intravenous administration, imipramine, desmethylimipramine, and amitriptyline showed neuromuscular blocking properties, and amitriptyline was found to be the most potent. The nature of blockade appeared to be competitive. Bhargava et al (73) studied the muscle relaxant properties of methaqualone and its derivatives and found that dimethaqualone was more potent than methaqualone and mephenesin as a muscle relaxant.

Emesis

Bhargava & Dixit (74) suggested the presence of histaminergic receptors in the chemoreceptor trigger zone, which were possibly responsible for the mechanism of emesis. They suggested that reserpine may be acting directly on the CT-zone and not by depleting the CA (75). Gupta et al (76) have ruled out the possibility of cholinergic mediation in the central integration of emesis and showed that antidepressants blocked reserpine- and apomorphine-induced emesis (77).

The alcoholic extract of the root of *Cyperus rotundus* has been found to protect dogs against apomorphine-induced emesis (78).

Sleep

Haranath and co-workers (79, 80) studied the role of cholinergic mechanism in sleep and REM sleep, using cholinergic agonists and antagonists. By perfusing the cerebral ventricles of anesthetized and unanesthetized dogs with cholinergic agents, these workers demonstrated that the release of acetylcholine diminished before and at the time of sleep but increased during REM sleep (81–83). They further showed that quaternary ammonium compounds, like curare, gallamine, and atropine, and NE passed into cerebrospinal fluid when given intravenously (84–86).

CARDIOVASCULAR SYSTEM

Antiarrhythmics

Antiarrhythmic activity of a number of drugs: i.e. some phenothiazines (87–89), ajmaline and its esters (90), phencarbamide (91), BP-400, cyproheptadine, chlor-

phenoxamine (92), glucagon (93), propranolol (94), INPEA (95), MJ-1999 (96) pronethalol (97), and H66/29 was reported. It was found that β-adrenergic receptor blocking drugs were most effective in blocking experimental cardiac arrhythmias (95, 96, 98). However, Madan et al (98) suggested that this activity was independent of β-receptor antagonism.

Studies on the role of various neurochemical substances like acetylcholine (99–101), CA (102), and 5-HT (103) in the genesis of cardiac arrhythmias indicated that acetylcholine may be involved (100, 104). Madan & Gupta (99) found that acetylcholine and atropine acted synergistically rather than antagonistically on the myocardium. Bhargava et al (102) reported that CA may be responsible in the centrogenic cardiac arrhythmias induced by aconitine, which could be blocked by prior reserpinization, bilateral adrenelactomy, thoracic splanchnic nerve section, or β-receptor blocking drugs. Aconitine also increased the 5-HT content of the heart, which returned to control value when normal rhythm was restored by quinidine (103).

Cardiotonics

Arora et al (105) found that peruvoside, a cardiac glycoside obtained from *Thevetia neriifolia,* produced positive inotropic and chronotropic effects on cat heart. Its toxicity, potency, and clinical efficacy were similar to ouabain. Singh & Rastogi (106, 107) isolated asclepin, a cardenolide from *Asclepias curassavica,* and determined its chemical structure. Its action was similar to digoxin but lasted longer. The extract obtained from *Nerium indicum* was also reported to possess cardiotonic activity (108, 109).

Hypertension

The effects of neurochemical substances like choline (110), histamine (111), 5-HT (112), and CA (113) on the central vasomotor loci have been studied. It was shown that cerebroventricular (ICV) administration of choline caused initial pressor followed by depressor response. These responses were explained on the basis of the peripheral and central release of CA by choline (110). 5-HT produced a depressor response in dogs, which was prevented by pretreatment with dibenzylene or morphine, suggesting the pressence of undifferentiated receptors for 5-HT which could be blocked by M or D types of blockers (112). Phenylephrine or NE caused bradycardia, whereas isoprenaline caused tachycardia, which could be blocked by α- and β-receptor blocking agents respectively (113). The injection of propranolol into the lateral ventricles elicited a biphasic response, i.e. an initial short-lived pressor phase with tachycardia followed by a prolonged depressor effect and bradycardia (114). The role of CA in renal hypertension was studied using 6-hydroxydopamine and it was suggested that the functional sympathetic nervous system was important in the development of renal hypertension in rats (115, 116). Gulati and co-workers studied the mechanism of antihypertensive action of guanethidine and supported the hypothesis of a cholinergic link in sympathetic transmission (117, 118).

Dhar and co-workers isolated a number of alkaloids from *Croton sparsiflorus morong* and reported that N-methylcrotsparine produced a moderate hypotension

in anesthetized dogs. A derivative of this alkaloid, N-methylapocrotsparine, produced a marked hypotension due to its central and peripheral actions (119, 120).

MISCELLANEOUS

Chemotherapy

Berberine-containing plants like *Berberis aristata* have been used in the Indian system of medicine for a long time as a stomachic, bitter tonic, and in the treatment of leprosy, snake bite, and jaundice (121). Dutta & Panse (122) found that the effect of berberine in experimental cholera was comparable to chloramphenicol (123). The alkaloid was also reported to possess antibacterial activity against a wide variety of microorganisms such as fungi, *Vibrio cholerae,* and *Entamoeba histolytica* (124–130). It also protected rabbits from cholerogenic toxins (131). Desai et al (132) have studied the cytotoxic actions of *Abrus precatorius* and reported that the seed extract produced chromosomal aberrations in ciliates (133–135).

Among the antifilarial agents synthesized, 3-ethyl-8-methyl-1,3,8-triazabicyclo(4,4,0)decan-2-one was found to be more effective than diethylcarbamazine in cotton rats (136). Rao & Narasimharao (137) isolated champamycin B from *Streptomyces champavatii,* which protected mice from sublethal doses of *Candida albicans.*

Anti-inflammatory Drugs

Studies on determining the association of histamine, 5-HT (138, 139), and CA (140, 141) with the inflammatory process revealed that only histamine or 5-HT may be involved in it at the exudative and reparative stages of the response (138). Reserpine, which depleted 5-HT, antagonized the inflammatory process (139). Studies carried out on the anti-inflammatory activity of a large number of substances obtained from natural products have shown that triterpenoids, saponins, flavonoids, β-glycyrrhetinic acid, β-amyrin, and turmeric (142–148) possessed moderate antiinflammatory action. Among the flavonoids, taxifolin, isolated from *Madhuca butyracea,* possessed potent anti-inflammatory activity (149).

Antidiabetic Activity

In India a number of herbs have been used in the indigenous system of medicine for the treatment of diabetes mellitus. In the 1960s an extensive effort was made by the Indian pharmacologists to determine their efficacy and the pharmacological basis of their use. It was reported that *Ficus bengalensis* Linn contained three flavonoid compounds, each possessing a hypoglycemic action in fasting rabbits (150–152). The extracts of several other plants such as *Gymnema sylvestre* (153), *Vinca rosea, Cassia auriculata, Eugenia jambolana* (154), and *Momordica charantia* (155) were shown to possess similar properties. The fact that these investigators have practically given up further investigation of these materials indicates the low degree of blood sugar lowering property possessed by them.

Antifertility Agents

Anand and co-workers synthesized a number of furans (156), benzofurans (156–158), arylophenones (159–163), coumarins, chromans, and chromenes (164) and reported antiimplantation activity in many of these. The most effective compound was 3, 4-*trans*-2, 2-dimethyl-3-phenyl-1, 4-(*p*-β-pyrrolidinoethoxyphenyl)-7-methoxychroman (164). A single oral dose administered postcoitum completely prevented conception in mice, rats, dogs, and monkeys (165).

Sympathomimetics

The sympathomimetic action of acetylcholine on nictitating membrane of dog (117) and rat ileum (166) was demonstrated by Gulati and co-workers. This action was blocked by adrenergic neurone blocking agents and regenerated by indirectly acting sympathomimetics (167, 168), tetrodotoxin, and NE (118). These workers also reported the α-adrenergic blocking activity of β-blockers (169) and the excitatory action of tyramine on human umbilical cord (170).

In conclusion, one could state categorically that pharmacology has been developing steadily in India during the last twelve years, and a larger number of pharmacologists than before are tending to specialize in specific fields. More intensive work is being carried out on the CNS than in other fields. Behavioral studies, too, have found their place in Indian pharmacology.

The cost of modern drugs, in terms of the earning capacity of the masses of India, remains high and is rising every year. Intensive efforts made to discover new and potent drugs from a plethora of plant drugs, employed empirically in the Indigenous system of medicines, have so far been unrewarding. This makes the situation desperate. The average man in India is not interested in the discovery of a new drug in a western country, because it will be beyond his means. For example, he is not looking forward to a miracle cure of cancer. Today, he is challenging the Indian pharmacologist to bring out effective drugs that are inexpensive, so that his suffering is alleviated at low cost. The need is so urgent that it will be logical to expect that in the next few years Indian pharmacologists in collaboration with chemists, biochemists, and physicians will take up the search for less expensive, readily available agents having antifertility, antiamoebic, and broad spectrum anthelmintic properties with low side effects, and which could be manufactured from raw materials available indigenously. Whether they will respond to these challenges and train themselves to solve these national problems is a matter of conjecture.

ACKNOWLEDGMENTS

The authors are thankful to Mr. S. K. Kulkarni and Mr. N. K. Gurbani for their valuable support in the preparation of the manuscript.

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