HIGHLIGHTS OF PHARMACOLOGY IN LATIN AMERICA[1]

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Many factors have retarded the development of modern pharmacological research in Latin America. Of these, the most important have been the scarcity of full-time research positions in academic institutions; the risks in undertaking long-term projects under conditions of social and political unrest; the almost total lack of private and direct official grant support for research; and the lack of a strong, autochthonous pharmaceutical industry which, elsewhere, is the source of new drugs for pharmacological research and of stimulus for the training of pharmacologists. Notwithstanding these factors, or perhaps because some of them are ceasing to be operant, there has been a substantial increase in the volume of original publications in the field during the last few years. This is best illustrated by the following yearly breakdown of the distribution of the 490 papers which constituted the preliminary selection for this review: 1952, *22* articles; 1953, *27*; 1954, *28*; 1955, *36*; 1956, *48*; 1957, *69*; 1958, *82*; 1959, *142*; 1960, *36* (the figure for 1960 represents publications through February of that year). The first selection was made with no bias in favor of publications from the later part of the period. It is as yet a very modest contribution from a large geographical area with a traditional interest in the action of drugs of the type represented by the sixteenth century, monumental contribution of Francisco Hernández, whose complete works are currently being edited by the Universidad Nacional de México (30).

Certain fields of active pharmacological research will not be discussed, inasmuch as recent reviews by the investigators principally involved are available. In 1956, Braun-Menéndez (6) reviewed the pharmacology of renin and hypertensin. It is of interest that the two groups of workers most actively engaged in this field have agreed to use the term "angiotensin," instead of hypertensin or angiotonin, to refer to the vasoactive polypeptide which results from the action of renin [Braun-Menéndez & Page (*7*)]. Rocha e Silva (60) has recently reviewed his and his collaborator's contributions to the pharmacology of bradykinin. Finally, reference should be made to three reviews by Caldeyro-Barcia and co-workers (9, 10, 11) which summarize the contribution of the Uruguayan workers to the study of the actions of oxytocin and other substances on the pregnant human uterus.

Interest in problems related to theoretical and quantitative pharmacology

[1] The survey of literature pertaining to this review was concluded in February, 1960.

has been apparent. Croxatto & Huidobro (19) have made a general presentation of their theory regarding the dependence of pressor or depressor effects of sympathomimetic amines on the "surface complementarity" between the drugs and two hypothetical types of receptor sites for which they offer shadow models of configuration. Rocha e Silva & Rothschild (63) have proposed an ingenious and relatively simple procedure for assaying materials which induce tachyphylaxis. The decrease in response attributable to repeated administration is confounded with the order of administration in a standard Latin square design using four similar test objects. More recently, Rocha e Silva (61) proposed an indirect method for calculating pAx based on the ratios between the slopes of reciprocal dose-effect regressions obtained in presence and absence of the antagonist. The same investigator (59), referring to the kinetics of recovery from inhibition by antihistaminics, atropine, and antispasmodics, suggests that the process of recovery is of an autocatalytic nature and not to be explained on the basis of the type of breakdown of the drug-receptor complex which can be predicted from mass-action considerations.

Pardo & Magaña (51) and Pardo (49) have suggested the possibility that, of the phenomena loosely grouped under the heading of tachyphylaxis, the classical type seen, for example, after the repeated administration of sympathomimetic amines may be thought of as depending on the lack of correspondence between the fraction of receptors occupied by a drug and the fraction of receptors participating in the process of activation. This disparity would arise from the brevity of the disturbance created by receptor occupation in comparison with the relatively long life of the drug-receptor combination. Autoinhibition of this type would be expected even in the case of the normal mediators. In relation to this possibility, Pardo, Magaña & Vargas (53) have presented evidence that tachyphylaxis of the type mentioned above may constitute a normal mechanism for the regulation of responses to catecholamines. In order to handle quantitative data from systems in which autoinhibition is important, Pardo & Magaña (50) have analyzed the general problem of dose-response relations and have proposed a general formula for use both in the case of responses of an all-or-none type and for responses of variable magnitude. The proposal implies that all biological responses can be thought of as being of a quantal nature, that the sensitivity of effector units referred to the number of receptors needed to be activated for response is distributed normally, and that the classical hyperbolic relation between the concentration of the drug and the fraction of receptors occupied is tenable. The same investigators (52) have offered experimental data in partial adequation of their hypothesis. Indirect evidence for the distributive nature of effector sensitivity has also been derived from the study of the pattern of action of several sympathomimetic amines on the vascular responses to catecholamines [Magaña & Pardo (35)].

Referring to the pharmacology of catechol amines and of drugs that modify their effects, García Ramos (28) reported that epinephrine greatly

increased the oxygen consumption of isolated strips of intestine and suggested that the smooth muscle relaxation produced by this agent is related to the acceleration of lactic acid production. Rocha e Silva, Corrado & Ramos (62) found that reserpine and sympatholytic agents prolong the vasodilator action of bradykinin. Pardo, Magaña & Villarreal (54) have reported that the nictitating membrane of reserpinized cats, though more sensitive than that of nonreserpinized animals to small doses of injected epinephrine, is none the less much more susceptible to transmission fatigue when stimulated at moderate frequencies through its nerve supply. They suggest that this effect may constitute the basis for the antiadrenergic actions of reserpine on structures in which tonic activity is normally maintained through repetitive stimulation.

Of the cholinergic structures, attention has been given to the secretory glands of the gastrointestinal tract. Vidrio (66, 67) described a useful semicontinuous method for measuring gastric secretory activity and has applied it in order to re-evaluate the effects on secretion of a group of blocking agents and a variety of cholinergic agents. Junqueira, Rothschild & Vugman (34) have suggested that the main action of atropine on the pancreatic exocrine secretion elicited by parasympathetic stimulation is to block the extrusion of zymogen granules. They were unable to find any interference with the synthesis of zymogen granules or with the rate of amylase resynthesis.

Work has been done on the general question of possible selectivity of action of ganglionic blocking agents on sympathetic and parasympathetic structures. Cato, Vélez & Nájera (12) have shown that selectivity for parasympathetic ganglia of the type initially reported for ethyl-methyl-isooctenyl amine, a tertiary amine [Pardo *et al.* (55)], could also be demonstrated for several classical ganglionic blocking agents when their effectiveness in blocking the heart-rate responses to vagus stimulation and the pressor responses to carotid clamping was compared. The probable inadequacy of using effector response as a criterion for ganglionic action led Alonso-deFlorida *et al.* (3) to compare the actions of several blocking agents on the postganglionic action potentials at the superior cervical ganglion and at the ciliary ganglion. They found that the sensitivity of the two structures to the different substances was very similar, and that the only difference was a greater tendency for the ganglionic blocking agents to produce facilitation at the ciliary ganglion at very low dose levels. In a later communication, Alonso-deFlorida *et al.* (4) have reported that an analysis of the effect of tetraethylammonium on synaptic transmission indicates a greater subliminal fringe after maximal preganglionic stimulation in the case of the ciliary ganglion as compared to the superior cervical ganglion.

Additional information regarding the ganglionic effects of drugs is found in the report by Corrado (16) of ganglionic blockade by large doses of streptomycin, in the study of Prado & Carlini (58) on the influence of ganglionic blockade on the actions of hypertensin, and in the report by Magaña,

Ugalde & Pardo (36) of ganglionic blocking activity for several sympathomimetic amines. Mention should be made of the older communication by Middleton *et al.* (43) on stimulation by acetylcholine in the apparently ganglion-free atropinized heart papillary muscle preparation.

In the field of neuromuscular transmission, Chagas (14) has recently reviewed his and his collaborators' work which led to the isolation from electric organs and mammalian tissues of acid mucopolysaccharides which may be identified with the macromolecular substance supposedly responsible for curare fixation in the intact structures. Using radioactive curares and curare-like agents, Braun-Cantilo *et al.* (5) have observed that the organs retaining most of the injected drug are those which have the highest content of mucopolysaccharides. Also in this area, neuromuscular blocking properties have been reported for streptomycin by Vital-Brazil & Corrado (69) and for neomycin by Corrado, Ramos & deEscobar (17). Reference should also be made to the careful analysis of the action of scorpion venom on the neuromuscular system carried out by del Pozo and collaborators some years ago and recently reviewed by him (22).

Contributions dealing with different aspects of the pharmacology, release, and blockade of histamine have appeared recently. Naranjo & Banda de Naranjo (47) have reported that the pressor effect of histamine in the rabbit may not be related to epinephrine release, since adrenalectomy, adrenergic blockade, and ganglionic blocking agents do not modify this response. Mota (44) has shown that histamine depletion produced by the chronic administration of compound 48/80 protects animals from anaphylactic shock. Moussatché & Provoust-Danon, working with guinea-pig lung slices, have observed that succinate favors and malonate interferes with antigen-induced histamine release (45) and that neither substance significantly alters histamine release induced by compound 48/80 (46).

In a carefully instrumented study of the effects of K-strophanthoside and lanatoside C on atrial muscle, Méndez & Méndez (40) found that the glycosides, at therapeutic levels, reduced atrial excitability and slowed conduction velocity. A discussion of the significance of this and previous studies of the physiological actions of cardiac glycosides has been published [Méndez & Méndez (41)]. More recently, Aceves, Méndez & Méndez (1) and Méndez, Aceves & Méndez (38) have reported that digitoxin and acetyldigitoxin antagonize the increase in heart rate following epinephrine injection or stimulation of the adrenergic nerves. In a separate paper, Méndez, Aceves & Méndez (39) reported that the digitalis increase in the refractory period of the A-V node is mediated, in part, through peripheral inhibition of the effects of adrenergic tone. Recently, Méndez & Rodríguez (42) have focussed new interest on the antifibrillatory actions of spartein. Since then, Fuentes published papers on the antagonism between spartein and veratrine (26) and on the antiaccelerator effects of spartein (27). Esperanza (23) has successfully used the the intra-auricular injection of very high doses of

this alkaloid in the treatment of ventricular fibrillation in anesthetized patients undergoing cardiac surgery.

Among other contributions in the area of cardiovascular pharmacology, the following should be mentioned. Folle (25) has reported that the hypotensive effects of quinidine are principally attributable to the adrenergic blocking actions of the alkaloid. Cesarman (13) and Cossio (18) have published reports on the former's original observation regarding the possible usefulness of iproniazid in the treatment of angina pectoris. Villarreal, Magaña & Pardo (68) have reported that animals treated chronically with iproniazid are more susceptible to ephedrine tachyphylaxis than animals not so treated. They interpret their results as signifying occupation of adrenergic receptors by iproniazid. Comesaña *et al.* (15) and Nava *et al.* (48) have reported on the antihypercholesterolemic effects of nicotinic acid in dogs and in humans.

Croxatto, Rosas & Barnafi (20) have reported an increase in the renal excretion of water, sodium, and choride induced by purified oxytocin both in normal and hydrated rats. This response was abolished by hypophysectomy and restored by administration of sodium chloride and DCA [Croxatto & Zamorano (21)]. Cafruny & Vargas (8) have shown that a variety of vasodilator agents depressed mercurial diuresis. The same authors [Vargus & Cafruny (65)] have observed that *p*-chloromercuribenzoate, a nondiuretic organic mercurial, was capable of producing salt and water diuresis when kidney blood flow was kept at a constant rate. Pines has studied some cardiac actions of acetazolamide (56) and of chlorothiazide (57). He reports that the latter drug protects against arrhythmias induced by prednisolone and strophanthin.

In another area, Werner (70) and Timo-Iaria & Werner (64) have presented data which they interpret as signifying that some analeptic drugs facilitate impulse transmission in the reticular formation. Fernández & Roldán (24) have reported that atropine is capable of blocking the spread of convulsive activity elicited by cortical stimulation. Gutiérrez-Noriega & Zapata-Ortiz (29) have observed that cocaine produces marked inhibition of multisynaptic and moderate inhibition of monosynaptic reflexes, effects which are antagonized by short-acting barbiturates. Zapata-Ortíz, Castro & Campos (71) have reported that bemegride antagonizes the central nervous system action of barbiturates, urethane, and ethyl alcohol and that it may produce convulsions at low dose levels in animals treated with large doses of morphine. Matallana & Borison (37) have described a method for producing cough in unanesthetized decerebrate cats which has proved useful for the evaluation of central-acting antitussive agents. Alcocer, Eckhaus & Villaseñor (2) have found that epinephrine and norepinephrine prolong the slow negative potential resulting from physiological stimulation of the frog's olfactory epithelium.

Several contributions regarding the mechanism of action and the use of

hypoglycemic sulfonylureas have been published. Houssay & Penhos (31) and Houssay *et al.* (32) found that the presence of pancreatic tissue was necessary to obtain the hypoglycemic effect of these compounds and that adrenalectomized animals were very sensitive to this effect. In a separate paper, Houssay *et al.* (33) reported that sulfonylureas reinforced the hypoglycemic action of insulin both in depancreatized and in eviscerated animals and that, in the absence of insulin, no hypoglycemia could be elicited in these preparations. Zubirán, Domenge & Escobar (72) have studied the general human pharmacology of sulfonylureas and report evidence suggesting that these drugs act through the release or protection of endogenous insulin, or both.

Numerous contributions which refer to the clinical use of the sulfonylureas will not be reviewed, nor will mention be made of the rather abundant publications referring to the biological effects of other hormones. Papers reporting clinical investigations, on the chemotherapy of the infectious and parasitic diseases prevalent in the area have been considered to be outside the scope of the present review. Finally, research on potentially active products of natural origin has been sporadic, and no transcendental contribution can be commented upon.

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