

CURRENT LITERATURE

Observation on the Mechanism of Blood Pressure Changes following Chlorpromazine Administration in the Cat by *S. Feldman and M. Eliakim.* (1958) : **Arch. int. Pharmacodyn.**, 116, 340.

There is no agreement as to the mechanism of hypotensive action of chlorpromazine. In this investigation, an attempt has been made to work out the mechanism in the cat. Intra-aortic and intracarotid administration of chlorpromazine causes a lesser hypotensive response than the same dose given intravenously while the injection into the vertebral artery has almost no effect. Injection into the cisterna magna also causes hypotension. The carotid sinus reflex is suppressed after intravenous or intracisternal administration. From the experiments in which the nervous connections or the arterial supply to the brain have been completely severed, it is concluded that the acute drop in blood pressure is not due to the central effect of the drug. The hypotensive response after the intravenous injection is due to direct effect of chlorpromazine on the heart muscle and on the arterial wall while the drop in blood pressure after the intra-aortic injection is due to the latter effect only. Pretreatment with noradrenaline, serpasil, ergotamine, pitressin, atropine, acetylcholine and novocaine does not influence the hypotensive response of chlorpromazine while Regitine and bezodioxane slightly suppress it probably because of a competitive adrenolytic activity of these drugs with chlorpromazine.

G. P. GUPTA

Mechanism of Hypotensive Action of Reserpine by *B. Horwitz, S. Kuskin and S.C. Wang.* (1959) : **Arch. int. Pharmacodyn.**, 120, 229.

There has been a controversy regarding mechanism of hypotensive action of reserpine. One group of workers has held the activation of some central inhibitory mechanism by reserpine as the cause of hypotension while the other group has demonstrated that reserpine exerts a depressing rather than an

activating effect on the central vasomotor structures. This study has been undertaken to solve this controversy. The effects of reserpine on the central vasomotor mechanism have been studied in the vagotomized cats under pentobarbital or Dial anesthesia. Reserpine has been found to depress both the pressor and depressor vasomotor responses elicited by stereotaxic stimulation of the hypothalamic and medullary vasomotor areas.

In both anesthetized and decerebrate cat, reserpine has been found to lower the blood pressure and to decrease the pressor response following carotid artery occlusion. However, these vasomotor events are not closely and quantitatively correlated.

These findings indicate that reserpine exerts a general depressive effect on the central vasomotor mechanism and the suggestion that the drug action is an indirect one, that is, to excite an inhibitory mechanism is not substantiated.

G. P. GUPTA

Effects of Drugs Which Depress the Peripheral Nervous System on the Reticular Activating System of the Cat by *K. A. Exley, M.C. Fleming and A.D. Espelien. (1958): Brit. J. Pharmacol., 13, 485.*

The authors have examined some depressants of peripheral nervous system for possible depressant actions on the reticular activating system of the cat. Large doses of nicotine, dihydro- β -erythroidine and mecamlamine were without effect. Antimuscarinic agents atropine and hyoscine readily depressed it, the later being more potent. Their effects could be antagonised by physostigmine. The depression by pentobarbitone is not antagonised by physostigmine. The weak depressant effect of lignocaine on the reticular activating system may be due to its central anti-muscarinic effect. Adrenergic blocking agents do not depress the reticular system. The significance of all these findings is discussed. The authors conclude that the hypothetical cholinergic transmitter, acting somewhere within the reticular activating system, displayed actions analogous to the muscarinic actions of acetylcholine.

B. N. DHAWAN

Analysis of the Common Carotid Occlusion Pressor Reflex in the Anesthetized Dog by *H.F. Harman, W.M. Baird, D.B. Suits, and B.K.B. Lum (1959)*: *Am. J. Physiol.*, **196**, 445.

The well established concept that the magnitude of the carotid occlusion pressor reflex is dependent upon the pre-existing mean arterial pressure has been quantitatively analysed. The data was obtained from the experiments on the anesthetized dogs in which blood pressure was reduced by spontaneous decay, haemorrhage or administration of a vasodilator drug, sodium nitroprusside. The relationship between mean arterial pressure and the common carotid occlusion pressor response was found to be linear over a blood pressure range of approximately 100-160 mm. Hg. It was found that the slope of the regression line varied considerably for individual dogs and could not be predicted in advance of actual experimentation. A single regression line drawn from pooled data for this reflex has no predictive value in determining the regression line slope for an individual dog because of extensive variation in slope values among dogs. In order to predict the carotid occlusion pressor response at a given mean arterial pressure for a particular dog, one must know the slope of the regression line for the reflex in that dog.

G. P. GUPTA

Comparative Effects of Chlorothiazide and Mersalyl (Mersalyl Sodium and Theophylline) on the Kidney by *W. P. Blackmore (1959)*: *J. Pharmacol. Exper. Therap.*, **125**, 303.

The comparative effects of chlorothiazide and mersalyl have been studied on osmolar clearance, free water clearance, glomerular filtration rate and renal excretion of sodium, potassium and chloride in trained un-anesthetized dogs. It has been found that chlorothiazide has a more rapid onset of action, and is an effective diuretic even in the presence of a significant decrease in glomerular filtration rate, indicating a direct tubular response. In moderately hydrated dogs, it produces no change in "free" water clearance and a moderate increase in osmolar clearance. Mersalyl increases "free" water clearance and greatly increases osmolar clearance. In dogs undergoing maximal water diuresis, both the diuretics produce a significant increase in osmolar clearance and no significant change in "free" water clearance. The possible reasons for the difference observed between maximally and moderately hydrated dogs are discussed.

G. P. GUPTA

The Anti-tremorine Effect of Some Drugs as Determined by Haffner's Method of Testing Analgesia in Mice by *G. Chen (1958)*: **J. Pharmacol. Exper. Therap.**, **124**, 73.

Tremorine has been shown to produce analgesia in mice by Haffner's method. The Tremorine-induced analgesia may be antagonized by hyoscine, atropine and other anti-parkinson drugs. The antagonism appears to be unique in that anti-tremorine activity of a compound does not necessarily parallel its mydriatic potency. Nalorphine, desoxyephedrine, phenobarbital and numerous CNS stimulants and depressants are ineffective at minimal neurotoxic dose levels.

G. P. GUPTA

Effect of Cyanide on Some Chlorpromazine Responses by *J. Leblanc (1959)*: **Proc. Soc. Exp. Biol. Med.**, **100**, 635.

Chlorpromazine has been reported to destroy mast cells in vivo. It has been speculated that some of the effects of chlorpromazine may be explained partly by disruption of mast cells. Cyanide prevents disruption of mast cells caused by histamine liberators. In this investigation the effect of cyanide on hypothermia and mast cell disruption induced by chlorpromazine in rats, has been studied. Cyanide prevents this disruption as well as some of the hypothermic effect of chlorpromazine. This indicates a possible relationship between mast cell disruption and hypothermia caused by chlorpromazine.

G. P. GUPTA

Effects of Chlorpromazine, Promazine, Diethazine, Reserpine, Hydroxyzine and Morphine upon some Mono-and Polysynaptic Motor Reflexes by *B. Silverstrini and G. Maffii (1959)*: **J. Pharm. Pharmacol.**, **11**, 224.

The effects of these drugs have been investigated on some mono-and polysynaptic motor reflexes in intact, spinal and decerebrate cats and rabbits. Chlorpromazine, promazine, reserpine and hydroxyzine selectively depress the monosynaptic reflexes (knee jerk) in the intact animals with only slight

effect on the polycynaptic reflexes (linguo-mandibular and crossed extensor). The inhibitory action of these drugs disappears when the connections of the spinal cord with the brain are severed by sections at different levels. On the other hand, morphine and diethazine depress the polysynaptic reflexes selectively but the monosynaptic ones to a minor degree. Moreover, this action is retained even in spinal animals. These findings have been discussed in relation to other neuropharmacological properties of these compounds.

G. P. GUPTA

Effect of Reserpine on Thyroid Activity in Rats by R.C. Moon and C.W. Turner (1959) : **Proc. Soc. Exp. Biol. Med.**, 100, 679.

A number of investigations have indicated that reserpine may alter thyroid function but their results are somewhat contradictory. In this study, this problem has been reinvestigated in rats by employing thyroid secretion rate and thyroidal I^{131} release rate as indices of thyroid function. Reserpine at doses of 5, 10, or 50 $\mu\text{g./100 g./day}$ inhibits thyroid activity in rats. Thyroidal I^{131} output is decreased significantly and thyroid secretion rate is reduced approximately 84-90% below control values. It has been suggested that reserpine alters thyroids function through inhibition of thyrotropin secretion.

G. P. GUPTA

Further Evidence for Mediation by Histamine of Estrogenic Stimulation of the Rat Uterus by E. Spaziane and C.M. Szego (1959) : **Endocrinology.**, 64, 713.

Introduction of solutions of histamine dihydrochloride or of a synthetic histamine releasing agent (compound 48/80) in the uterine lumen of adult castrated rat leads to increase in water content and changes in gross vascular appearances of the organ within four hours. The effects are comparable with those produced by intravenous or intraluminal estrogen (estradiol). Administered locally Chlor-trimeton or Benadryl are effective in substantially inhibiting water imbibition due to estrogen (even in adrenalectomised animals).

Intravenously administered cortisol substantially diminishes the hyperaemia and water imbibition produced by Histamine or 48/80.

These data strongly suggest participation of histamine or related substances at a primary stage in the action of estrogen at the target organ. It is proposed that cortisol may antagonise responses to estrogen in the uterus by non-specifically decreasing capillary permeability in that organ.

B. N. DHAWAN

Effect of Short Change of Environmental Temperature and Low Atmospheric Pressure on the Ovulation of Rats by *M.C. Chang and L. Fernandez-Caro* (1959) : **Am. J. Physiol.**, 196, 653.

In order to elucidate the basic external factors that affect the occurrence of ovulation the effect of short exposure to higher or lower environmental temperature and to low atmospheric pressure on ovulation has been studied. Female albino rats were exposed to a higher ($103\pm 1^\circ\text{F}$) or to a lower ($26\pm 1^\circ\text{F}$) temperature or to a lower atmospheric pressure (410 cm. Hg.) for 5 hours a day on two consecutive days and soon after the exposure caged with proven fertile males. It was found that estrus and ovulation was inhibited significantly for two normal estrus but subsequent ovulation, maintenance of pregnancy or development of embryo was not affected. The authors postulate a shift from gonadotropic hormone secretion to ACTH secretion in the anterior pituitary gland in a stressful condition.

B. N. DHAWAN

The Effects of Some Possible Neurohumoral Agents on Spinal Cord Reflexes by *J.W. Kissel and E.F. Domino* (1959) : **J. Pharmacol. Exper. Therap.**, 125, 168.

The effect of some neurohumoral agents has been studied on spinal cord reflexes in cats. Experiments were carried out in acute spinal cats maintained under artificial respiration. Arterial blood pressure stabiliser was used to prevent effects due to vascular phenomena secondary to drug administration. Epinephrine and nor-epinephrine produce phasic inhibition

and a slight facilitation in the patellar reflex. This was interpreted by the authors to be a direct central effect. Acetylcholine produces some spontaneous activity upon elicitation of crossed extension when given after physostigmine and neostigmine. The effect can be blocked by atropine. It is postulated to result from acetylcholine stimulation of cholinergic facilitatory interneurons. Histamine produces an irregular depression of the patellar and crossed extension reflexes. Serotonin causes phasic inhibition and facilitation of the patellar and crossed extension reflexes. The response might be due to a central effect or an action on peripheral receptors. Substance P was without effect on the spinal reflexes studied. None of the agents studied were effective on ipsilateral inhibition of the patellar reflex. The possible cause of this has been discussed.

B. N. DHAWAN

The Effect of Salicylates on the Thymus Gland of the Immature Rat by *N.R. Stephenson (1959)*: **J. Pharm. Pharmacol.**, **11**, 339.

Salicylates have been used in the treatment of rheumatic disease since 1876. Salicylates probably have a direct corticoid effect on some peripheral tissues and exert their therapeutic effect in this manner. Involution of thymus gland is a well known manifestation of gluco-corticoid activity. The present study was undertaken to study the effect of salicylates and other salicyl derivatives on this "target" organ. Oral or subcutaneous administration of salicylic and acetylsalicylic acids induces thymic atrophy in normal and adrenalectomised immature rats. Hence salicylates act directly on thymus and not via pituitary - adrenal system. No evidence has been found that they potentiate the effects of endogenous adrenal corticoids. A linear relation has been found between log dose of the salicyl derivative and the relative thymus weight and this has been used to compare the relative thymolytic activity of several of these compounds.

B. N. DHAWAN

Comparison of Lysergic Acid Derivatives and Antihistamines as Inhibitors of the Edema Provoked in the Rat's Paw by Serotonin by *W. Doepfner and A. Cerletti (1958)*: **Int. Arch. Allergy.**, **12**, 89.

Local injection of 1 μ g. serotonin in rat's paw produces a more marked edema than is obtained with 200 times larger doses of histamine. The

serotonin edema is blocked by various amide derivatives of Lysergic acid. Methyl-derivatives of ergonovine and of methyl ergonovine are more potent in this respect than LSD. Amongst the anti-histamines tested only those having a phenothiazine or piperidine ring are effective antagonists of serotonin edema. Their potency however is 100 to 1000 times less than that of Lysergic acid derivatives.

B. N. DHAWAN

The Antagonism of Atropine to the EEG Effects of Adrenergic Drugs by R.P. White and E.A. Daigreault (1959): *J. Pharmacol. Exper. Therap.*, 125, 339.

EEG arousal could be produced in rabbits transected at the ponto-mesencephalic junction by epinephrine, methamphetamine and d-amphetamine but not in those transected at midbrain level. The arousal was antagonised by atropine. Atropine also abolished the persistent alert pattern induced by methamphetamine and d-amphetamine in normal rabbits. A similar arousal could be produced by physostigmine in ponto-mesencephalic transected rabbits but not those transected at midbrain. The effects could be antagonised by atropine. Atropine also synchronised a persistent EEG alert pattern produced by transection at the posterior border of the pons. The authors conclude that

(1) Posterior parts of the midbrain are necessary for the effects observed and ;

(2) The same region of brain stem is apparently involved in the EEG arousal produced by cholinergic and adrenergic drugs.

B. N. DHAWAN

The Role of the Hypothalamus in Pituitary Adrenal Activation and Antidiuresis by Morphine, by R. George and E. Leongway (1959): *J. Pharmacol. Exper. Therap.*, 125, 111.

The role of hypothalamus in pituitary adrenal activation and in morphine antidiuresis has been investigated in rats with stereotaxically produced hypothalamic lesions. Lesions of median eminence completely block the adrenal ascorbic acid depletion which normally occurs about an hour after morphine administration. Diabetes insipidus was observed in 9 of the 11 animals in which adrenal cortical response was blocked.

Partial lesions of the anterior median eminence, as well as lesions placed anterior and dorsal to median eminence do not modify this adrenal cortical effect of morphine. Lesions in hypothalamus which produce diabetes insipidus can block only the antidiuretic response of a small dose of morphine. The failure to block the effect of larger doses may be due to the fact that an alteration in renal hemo-dynamics as well as ADH discharge contributes towards the water retention effects of morphine. The authors have further demonstrated that ADH and ACTH release can be independently influenced by pharmacological agents. They conclude that ACTH release does not necessarily have to be accompanied by parallel increase in ADH release.

B. N. DHAWAN