

CURRENT LITERATURE

Pharmacological Studies on the Renal Juxtaglomerular Apparatus by B. S. Garber, F. W. McCoy, E. R. Hayes and B. H. Marks (1959) : *Arch. int. Pharmacodyn.*, **121**, 275.

These investigations were undertaken to determine if there was any correlation between the degree of granulation of the renal juxtaglomerular apparatus (JGA) cells and changes in systematic blood pressure induced by hypotensive drugs. The hypotensive agents studied included dibenamine, chlorisondamine, alkavervir and hydralazine. Each dose was studied on a group of six albino rats or rabbits and the animals were sacrificed two hours after intravenous drug administration. The granulations of JGA responded to changes in blood pressure produced by these agents and various experimental procedures. The changes could be detected 30 minutes after the lowering of the blood pressure had begun. Many of the results obtained could be explained by the direct action of corticotrophin (ACTH) upon the kidney. It has been suggested that JGA may be the site of renin production.

B. N. DHAWAN

Effects of Probenecid, Sodium Salicylate, 2-4 Dinitrophenol and Pyrazinamide on Renal Secretion of Uric acid in Chickens, by B. R. Nechay and L. Nechay (1959) : *J. Pharmacol. Exper. Therap.* **126**, 291.

Uric acid is filtered at the renal glomeruli and reabsorbed but not secreted by the renal tubules in man. But in the chicken, it is excreted mainly by renal tubular secretion. Hence this study was carried out in chickens. Probenecid was found to diminish renal tubular secretion of uric acid and to raise markedly plasma urate concentrations. Sodium salicylate and 2-4 dinitrophenol also reduced uric acid excretion but were less effective. The 2-4 dinitrophenol effect suggests that the tubular transport of uric acid may be dependent on energy supplied by oxidative phosphorylation. As probenecid and sodium salicylate are known to inhibit reabsorption of uric acid in mammals, it is possible that there is a common factor in the transport mechanism for reabsorption and secretion of this substance. Pyrazinamide had no effect on uric acid clearance in this species.

G. P. GUPTA

The action of Morphine and Morphine like Analgesics applied on Intraluminally Peristaltic Reflex of the Isolated Guinea Pig Ileum by *M. Medacovic (1959)*: **J. Pharm. Pharmacol**, **11**, 43.

The action of morphine and related drugs upon peristalsis of isolated guinea pig ileum has been studied when introduced into the lumen of the gut. The peristalsis was inhibited by all these agents and the effects were parallel to their relative analgesic potencies. The stimulation of peristalsis by 5-HT and nicotine was not inhibited by morphine. The author concludes that probably the inhibitory action of morphine like drugs involves the afferent part of peristaltic reflex. The inhibition of peristalsis by intraluminal morphine could however be abolished by intraluminal application of 5-HT. It is suggested that the inhibitory action of the intraluminal morphine upon the peristalsis may be partly caused by its antagonism towards intrinsic 5-HT. The possibility of two drugs acting on the same mucosal receptors is discussed.

B. N. DHAWAN

Mechanism of Sympathomimetic Action of Aldehydes, by *N. R. Eade (1959)*: **J. Pharmacol. Exper. Therap.**, **127**, 29.

Acetaldehyde, propionaldehyde and butyraldehyde (10–20 mg/kg) when given intravenously in spinal cats in which both adrenal veins were ligated produced a typical elevation of blood pressure and contraction of nictitating membrane. These responses were not abolished by hexamethonium although the action of nicotine was. In cats treated with reserpine to deplete their catecholamines, made spinal and with both adrenal veins ligated, these aldehydes produced a fall in blood pressure and no contraction of nictitating membrane. Hence a part of their sympathomimetic action is mediated by release of catecholamines from tissue stores, other than adrenal medulla. The releasing action of the aldehydes appears to differ from that of tyramine and phenylethylamine. Cocaine potentiates the aldehyde sympathomimetic responses but depresses the responses to tyramine and phenylethylamine. Further, infusions of epinephrine and norepinephrine in reserpine treated animals will restore the pressor response and the nictitating membrane stimulant action of tyramine and phenylethylamine while the response to aldehydes after such infusion is unchanged.

G. P. GUPTA

The Secondary Conditioned Response of Rats and the Effects of some Psychopharmacological Agents by *G. Maffi* (1959): **J. Pharm. Pharmacol.**, 11, 129.

Rats trained with repeated exposures to a noxious stimulus soon exhibit a conditioned avoidance response (I). With further training rats take up the position to avoid the unconditioned stimulus before the presentation of the conditioned stimulus (II). The activity of 17 psychopharmacological agents has been tested on II developed on a stable basis after suitable training. The specificity of the deconditioning effect of a drug may be shown by the loss of II only, the loss of II and I or the loss of II, I and the unconditioned response (III), usually the result of a marked impairment of motor function. Meprobamate, hydroxyzine, azacyclonol, phenaglycadol, mescaline and iproniazid abolish only II; chlorpromazine, promazine, reserpine and morphine block I and II at same dose levels while with barbitone, glutethidimide, L1458 and mephenesin all responses are blocked. On the basis of these findings a new classification of tranquilising agents is proposed.

B. N. DHAWAN

A Comparative Study of the Effects of Drugs on the Arousal System of the Brain, by *P. B. Bradley, and B. J. Key*. (1959): **Brit. J. Pharmacol.**, 14, 340.

The effects of 12 drugs have been studied in relation to thresholds for arousal produced by direct stimulation of the brain stem reticular formation or by afferent nerve stimulation in encephale isole preparations in cats. The drugs can be classified into four groups: (i) Those producing a slight rise in thresholds for brain stem stimulation and blocking sensory-induced arousal e.g. chlorpromazine, promazine, acepromazine and hydroxyzine, (ii) those increasing arousal thresholds but producing a dissociation between behaviour and electrical activity e.g. benactyzine, imipramine, and hyoscine, (iii) those having no effects on thresholds for brain stem stimulation and only slight effect on afferent nerve induced arousal but changing the electrocorticogram towards the activation pattern in high doses e.g. reserpine, rescinnamine and deserpidine, (iv) Those having no effects on arousal responses at all e.g. meprobamate and azacyclonol.

G. P. GUPTA

Differential Effects on Various conditioned Responses in Cats Caused by Intraventricular and Intramuscular Injections of Reserpine and other Substances by E. R. John, B. M. Wenzel and R. D. Tshirgi (1958) : *J. Pharmacol. Exper. Therap.*, 123, 193.

The effects of intraventricular and systematic administration of various substances, singly and in combination, on conditioned responses has been studied in a group of 8 adult female cats. Cats were trained to avoid shock on the presentation of either an auditory or a visual cue, to perform pattern discriminations for food, and to obtain visible food on an elevated runway. Reserpine depressed avoidance responses while approach responses were relatively unaffected. The visually cued responses were blocked earlier than the auditory ones. The interactions of serotonin, iproniazid, epinephrine, norepinephrine, atropine and methamphetamine with reserpine were also studied. Methamphetamine consistently completely reversed the effects of reserpine. The drug was more effective when injected peripherally. Epinephrine also attenuated the effects of reserpine on conditioned behaviour. The autonomic effects of reserpine were also antagonised by the two drugs. Some of the other agents tested could only alter the autonomic effects of reserpine. The implications of these findings have been discussed.

B. N. DHAWAN

The Histamine—Heparin Complex by R. K. Sanyal and G. B. West (1959) : *J. Pharm. Pharmacol.*, 11, 548.

Histamine forms a complex in vitro with heparin. The morphological characters and staining properties of the complex resemble those of natural mast cell granules. Its formation appears to be specific as noradrenaline, adrenaline and 5-HT fail to combine with heparin under similar experimental conditions. More histamine is contained in the complex when precipitation is carried out in acid medium in presence of adenosine triphosphate. It is possible that natural mast cell granules use ATP in this manner. However, it is not possible to release most of the histamine from the synthetic granules by substances like lysine and compound 48/80.

G. P. GUPTA

Mechanism of Action of Oral Antidiabetic Drugs by R. Aiman and N. Chaudhry, (1959) : **Brit. J. Pharmacol.**, **14**, 377.

In rabbits made severely diabetic with alloxan, carbutamide (BZ55) when given 24 hours after the maintenance dose of insulin produced a significantly greater fall in blood sugar ($28.0\% \pm 2.9$ s. e.) than the same drug given 72 hours ($6.8\% \pm 2.0$) or distilled water given 24 hours ($7.7\% \pm 1.3$) after the last dose of insulin. It is postulated that the drug acts by liberating bound insulin from plasma.

G. P. GUPTA

Antagonism between Alkylated and Norcompounds of the Morphine Group injected Intracisternally into Mice by M. Horlington and M. F. Lockett (1959) : **J. Pharm. Pharmacol.**, **11**, 415.

The mechanism of the analgesic effect of the morphine group of drugs is not completely understood. The object of this paper is to study whether alkylated compounds of the morphine group can produce analgesia by direct combination with receptor without preliminary dealkylation. Animals used were male white mice; normorphine, morphine, pethidine and norpethidine were administered intracisternally and pain threshold were measured with the help of a low resistance microammeter. The results obtained did not agree with the hypothesis of dealkylation put forward by Beckett *et al.* However, it was conceivable that concentration of normorphine injected was sufficient to inhibit the proposed dealkylating system: and if this explanation was accepted, then rate of dealkylation must be governed in C.N.S. by the concentration of the dealkylated compound and there might exist another pathway for the removal of morphine from the sites of analgesic action.

D. P. PHUKKAN

Effects of some Central Depressants on two simple Reflexes in the Mouse, by L. B. Witkin, P. Spitaletta and A. J. Plummer (1959) : **J. Pharmacol. Exper. Therap.** **126**, 330.

It has been suggested that muscle relaxants of the mephenesin type may be distinguished by their ability to block pinna reflex before the corneal reflex. To investigate this, the effects of a variety of central depressants have been

studied on these two reflexes in mice. Reserpine, chlorpromazine, triflupromazine and thiopropazate block the pinna reflex and leave the corneal reflex intact even in lethal doses. With the ethanol and mephenesin, the ratio between the ED 50 values for blocking corneal reflex and pinna reflex respectively is greater than 1 while with phenaglycodol and chloral hydrate this is close to but less than unity. All of the hypnotics studied including meprobamate and zoxazolamine block the corneal reflex first and at doses lower than those blocking the pinna reflex. The implications of these findings are discussed.

G. P. GUPTA

Influence of Adenosine 3'-5'-monophosphate on Corticoid Production by Rat Adrenal Glands, by C. Haynes, J. R. Seymour, B. Koritz and G. Peron, (1959): *J. Biol. Chem.*, **234**, 1421.

Adenosine 3'-5'-monophosphate elicits response in corticosteroid production equal to or greater than that produced by adrenocorticotrophic hormone by incubated rat adrenal sections which are able to respond to A.C.T.H. The results show that 3'-5'-AMP is an intermediate agent in the chain of events leading to corticosteroid production. It has been found that A.C.T.H. causes selectively an increased output of 3'-5' AMP in adrenal tissue which leads ultimately to the high concentration of corticosteroid, supporting the hypothesis suggested by Haynes and Berthet for the mode of action of adrenocorticotrophic hormone.

S. K. SRIVASTAVA

Potentiating the Diabetogenic Effect of Alloxan by N-Sulphonyl N-Butyl Urea (BZ 55) by B. Mostinger and T. Braun. *Experientia* (1959): **15**, 317.

Observations have been made in rats on the increased diabetogenic effect of alloxan by oral administration of BZ 55. A time analysis has been worked out to see the influence of time of BZ 55 administration in acute and chronic experiments. The maximum and most significant potentiation was found when alloxan was injected during 2nd and 6th hour after the administration of BZ 55. Even in cases where BZ 55 was given for 3 weeks, the blood sugar values were significantly higher than in the control animals.

Regarding the mechanism, it has been suggested that BZ 55 causes a state of functional hypoactivity of β -cells either due to its direct effect or secondary to the decrease of the blood sugar, or even both. No signs of protection of the β -cells have been detected as BZ55 may be expected to exert a favourable metabolic effect to increase their functional activity. The hypoglycemic action of BZ55 is not because of the stimulation of β -cells to release more insulin, although insulin is liberated in some unknown (more or less passive) manner. But as confirmed by certain histological studies, the β -cells undergo a quiescent stage after the administration of BZ55, similar to that during fasting or after the administration of exogenous insulin, where the β -cells are less active due to degranulation, showing that the toxicity of alloxan depends mainly on the functional state of B-cells.

R. L. SINGHAL

A Hypothesis concerning the Effect of Cocaine on the action of Sympathomimetic Amines by *W. H. Macmillan (1959)*: *Brit. J. Pharmacol.*, **14**, 385.

Tissues with sympathetic innervation probably have a store of noradrenaline in chromaffin tissue which can be depleted by reserpine. Sympathomimetic amines like tyramine fail to act after depletion or when cocaine is present, while catecholamines like noradrenaline have a much greater action than usual under such conditions. It has been suggested that cocaine blocks the spontaneous release from the store which is responsible for the normal (low) sensitivity to noradrenaline, the action of noradrenaline is then potentiated because more receptors are free for the injected noradrenaline. Similarly tyramine is ineffective if release from the store is stopped. Results of the experiments carried out on isolated atria of the rabbit heart, perfused rabbit ear and in the heart lung preparation of the dog are in accordance with this view.

K. N. DHAWAN

Diketopiperazines—a new Group of Central Nervous System Depressing Agents, by *D. K. de Jongh and E. G. van Proosdij-Hartzema (1959)*: **J. Pharm. Pharmacol.**, **11**, 393.

By introducing the main features of barbiturate nucleus into the piperazine instead of the pyrimidine nucleus, a series of NN'-substituted 2:6- and 5:4--diketopiperazines was synthesized. In this investigation, the pharmacology of Ph. 481, N (3':4' dimethoxyphenylethyl)—2:6--diketopiperazine HCl, a member of this series has been worked out. The compound augments the effect of barbiturates in mice and of ether in rats. It specifically inhibits the conditioned escape response in rats. It is practically devoid of anticonvulsive, analgesic or antitussive activity and it diminishes the tone of the skeletal muscles without interfering with neuromuscular transmission or polysynaptic spinal reflexes. It has slight antispasmodic activity on smooth muscles.

G. P. GUPTA

Antiemetic Activity of 4-(2 Dimethylaminoethoxy) N-3, 4, 5 Trimethoxybenzoyl Bezymine Hydrochloride, by *W. Schallek, A. Heise F. Keith and C. Bagdon (1959)*: **J. Pharmacol. Exper. Therap.**, **126**, 270-277.

The antiemetic activity and other pharmacological actions of this new compound and chlorpromazine have been compared. Both the drugs prevent apomorphine induced emesis in dogs but have no effect on emesis due to copper sulphate. Chlorpromazine is, however, more effective. The site of antiemetic action is probably chemoreceptor trigger zone as in the case of chlorpromazine. The drug causes speeding up of e. e. g. waves in dogs and cats. Both of them cause fall in B. P. when given by rapid i. v. injection but the fall with this drug is fleeting while it is sustained with chlorpromazine. It differs from chlorpromazine in causing smooth muscle stimulation and in having no effect on duration of pentobarbital induced hypnosis. It is relatively nontoxic.

The evidences indicate that this drug is a safe and effective antiemetic agent of a new type which lacks the sedative properties of chlorpromazine.

S. C. SRIVASTAVA

Biosynthesis and Secretion of Adrenocortical Steroids by J. E.

Grant (1951): *Nature*, 184, (4684) 415.

1. Indirect evidence is available suggesting that human adrenocortex secretes a substance which promotes sodium excretion. A new compound (3β : 16α -dihydroxy- 5α -pregnan-20-one) having a sodium excretory effect in rats has been isolated by Wettstein from the swine adrenals.
2. Symington drew the attention to two important histological features of the adrenals: the musculature of the adrenal veins which may be influencing the synthesis of the hormones by restricting blood flow and the structural difference between the adrenals of ruminants and nonruminants. In the ox adrenals a broad zone of 'compact' cells are found extending from the medulla to the glomerulosa. The glomerulosa layer is prominent and not irregular as in the case of other animals. Ox adrenal therefore is considered a better object for studying the '*in vitro*' synthesis of aldosterone than the human glands.
3. As a result of the studies carried out on fresh human adrenals removed surgically for treatment of breast cancer Symington has suggested that the cells of the fasciculata zone may function as stores of hormone precursor while the cells of the reticularis may actually be the site of the hormone synthesis instead of being the inactive senescent cells that they are supposed to be by some.
4. Studies carry out by Ayres regarding the zonal relation of steroids secretions of the adrenals showed that in the ox 17-hydroxylating enzyme system lies in the deeper zones (i.e. underneath the glomerulosa) while the 18-oxidase system concerned in aldosterone synthesis is found only in the zone glomerulosa.
5. Vogt discussed the nature of the mediators that increase or decrease the activity of hypothalamus for regulating the release of corticotropine. The level of corticosteroids in blood is considered only as a contributory but not the sole factor for controlling the corticotropine secretion during stress.

T.H. RINDANI