Ann. Rev. Pharmacol. Toxicol. 1981. 21:605–13

REVIEW OF REVIEWS

◆6809

E. Leong Way

Department of Pharmacology, School of Medicine, University of California, San Francisco, California 94143

Like it or not more and more original discoveries are being published first in symposium proceedings without passing rigid review. Unquestionably, the endorsement by a prestigious journal lends credibility to one's report but interminable delays in publication time and an invitation to speak are compelling forces to skip this time-honored route for reporting innovative findings. The desire to be seen and heard coupled with paid travel to a lovely resort are temptations difficult to overcome. Uninvited investigators not in the "in" group find it difficult to compete; hence the tendency is to ignore proceeding reports (unless the report is your own) and cite only published papers in refereed journals. My personal feeling is that priority for discovery must stand on the merits of the data presented no matter where it appears. To pretend that reports appearing in symposium proceedings do not exist reflects an ultraconservative and self-deluding point of view. Sometimes I wish that there were fewer symposium proceedings, but they must create an interest and serve a purpose in a meaningful way or the publishers would hardly bother with them. In any event, I occasionally call attention to symposium proceedings because they keep one better abreast of the current state of interest if not the art than refereed journals. Besides I edited one recently (1).

NEUROPEPTIDES IN THE BRAIN

Neuropeptide research continues to accelerate at a dizzying pace and several competing symposia on the subject are now held annually. The number of peptides that are being found in the central nervous system continues to grow. At least 30 neuropeptides have been identified and likely there will be many more. The list includes those heretofore believed to be present only

0362-1642/81/0415-0605$01.00

in the gastrointestinal tract and endocrine glands such as vasoactive intestinal peptide (VIP), cholecystokinin, gastrin, angiotensin, somatostatin, adrenocorticotropin, melanocyte-stimulating hormone, and many others. Any one neuropeptide may have properties of tremendous or inconsequential significance. The implications await the enormous task of characterizing their specific neurons, mapping their pathways, and delineating their specific functions. Considerable headway has been made, the acquisition of this knowledge being greatly facilitated by the application of immunofluorescence, radioautographic, and radioimmunoassay techniques. Some of the neuropeptides may function as neurotransmitters or neuromodulators and coexist in the same neurons containing the alkaloidal neurotransmitters. They are found localized at nerve endings of specific neurons and can be released from these terminals by a calcium-dependent process.

The role of the neuropeptides may be more global than that attributed to the classic alkaloidal types such as acetylcholine, norepinephrine, epinephrine, serotonin, and histamine. There is evidence suggesting that the peptides may be related to homeostatic processes concerned with electrolyte balance, blood pressure regulation, sexual behavior, pain and reward mechanisms, and temperature regulation. Therapeutic application of the peptides awaits elucidation of their functions; the development of drugs with selective effects requires knowledge about the biosynthesis and inactivation of the peptide. Many of these considerations are covered in the proceedings of a symposium on neuropeptides edited by Costa & Trabucchi with special emphasis on substance P, enkephalins, endorphins, and certain peripheral peptides (2). The topic has also been reviewed by Snyder (3), and Iversen (4) brings together the many aspects of the subject in his highly readable and fascinating account of the chemistry of the brain.

THE ENKEPHALINS AND THE ENDORPHINS

The neuropeptides that have created the most intense interest have been those possessing opiate-like activity, namely, the enkephalins and endorphins. The discovery of these endogenous peptides in the brain and pituitary has given an exciting new dimension to the research on brain function and has resulted in an unprecedented number of publications within a very short period. I reiterate the prophecy made in my previous "Review of Reviews" that the discoverers have a free trip to Stockholm waiting for them.

The enthusiasm over the enkephalins and endorphins does not necessarily mean that these are the most important peptides but only that they are the most convenient to study. Many investigators have jumped on the opioid peptide bandwagon because it is the path of least resistance. The simple reason is that more tools are available for examining the role of these

peptides than for other neuropeptides. Opiate researchers have provided sensitive and selective in vitro tests, specific antagonists, stereoactive, and inactive alkaloidal agonists as well as simple in vivo tests that facilitate the characterization of enkephalins and endorphins. The progress has been truly phenomenal and the salient points are considered in the most recent reviews and monographs (1–4).

At least two general neuronal systems have been reported to exist. The enkephalins are found in smaller cells generally with shorter processes and are localized in many cell groups throughout the brain stem and the dorsal chain of the spinal cord. Their distribution correlates fairly well with opiate receptor binding sites. The second opioid peptide system containing β-endorphin and β-lipotropin consists of single cell group located in the arcuate area of the hypothalamus with long axons projecting throughout the brain stem to a number of limbic structures including the septal area, the medial thalamus, and the midbrain central gray area. The release of the opioid peptides has been shown to be calcium dependent.

The enkephalins appear to have inhibitory functions and may regulate sensory input. They have been demonstrated to depress or inhibit firing of neurons in several brain regions including the cortex, striatum, thalamus, dorsal medulla, caudate nucleus, and the periaqueductal gray matter. Enkephalins and other opioids can suppress the release of substance P from sensory fibers. It is possible therefore that the enkephalins may control the input of pain stimuli.

β-Endorphin, on the other hand, appears to be more closely associated with endocrine function. By far the highest concentration of β-endorphin is found in the pars intermedia and pars distalis, whereas only traces of the enkephalins are present. Although the concentrations of β-endorphin in the brain are at least three orders of magnitude lower than those in the pituitary, the distribution is selective with high levels being found in the hypothalamus. This may bear a relationship to pituitary function since release of prolactin and growth hormone is stimulated by β-endorphin.

β-Endorphin and pituitary adrenocorticotropin are apparently synthesized together in the common precursor, pro-opiocortin, and are released concomitantly in response to stress.

The selective distribution of opiate receptors (recognition sites) and their ligands offer logical explanations for the action of morphine and its surrogates. The peptide neurons in the dorsal horn of the spinal cord can account for analgetic responses, those in the brainstem for respiratory effects, and those in the limbic systems for the production of euphoria. At least two types of opiate receptors have been identified, the μ receptor, which exhibits a selective affinity for alkaloidal opioids, and the δ receptor for enkephalin opioids. Although enkephalin can be acted on by a variety of peptidases,

the possibility that a specific inactivating mechanism may exist is evidenced by the finding of membrane-associated enkephalinases which cleave enkephalin between glycine and phenylalanine or between its two glycines.

Other active opioid peptides have been isolated. β-Neoendorphin from porcine hypothalamus containing 15 amino acids has a primary structure identical with that of leu-enkephalin that is followed by a characteristic triad of arginine-lysine-arginine. Assays on the guinea pig ileum reveal it to be even more potent than β-endorphin but it is less with respect to analgesia. Also, active precursor opioid peptides have been found in the adrenal medulla. High molecular weight proteins from the chromaffin granules can be cleaved with trypsin to yield peptides with opioid activity. Several small peptides have also been isolated that are active in their native forms and others yield active tryptic fragments.

TETRODOTOXIN AND SAXITOXIN

Ritchie provides an illuminating and entertaining article on two toxins, tetrodotoxin (TTX), produced by some forms of the puffer and sun fish, and saxitoxin (STX), produced by some dinoflagellates (5). Ritchie traces outbreaks of poisoning by these agents to antiquity. The earliest written record of the puffer fish is depicted from hieroglyphics of Egyptian tombs more than four thousand years ago. He opines that the biblical account of Egyptian water turning to blood may be the earliest published record of a toxic dinoflagellate proliferation. "Shellfish" poisoning still results today from ingestion of clams and mussels that feed on these dinoflagellates; outbreaks are likely to occur when the red tide is in full bloom. The oldest recorded experiment with puffer poison was reported toward the end of the sixteenth century by Fukushima who tested its toxicity by feeding the flesh and entrails to prisoners.

TTX and STX produce similar clinical toxic signs and symptoms which start with tingling to numbness of lips, gum, tongue, and cheeks with gradual progression to the neck and extremities. In terminal stages, motor weakness and paralysis occur and death is due to respiratory failure within 6 to 24 hr. Both agents have become powerful research tools. Both act specifically to block the sodium channels of electrically excitable tissue. They are active when applied to the outer surface but not when injected into the axon. Ritchie suggests that derivatives of these substances have the potential for becoming useful long-acting local anesthetics.

SUBSTANCE P

Henry provides a concise review on substance P (6). The importance of substance P in synaptic transmission has taken more than forty years to gain

acceptance, but the recent advent of the enkephalins and the endorphins has stimulated more research in substance P. Of its various postulated functions, the most well established appears to be its involvement in gating the transfer of pain information through the spinal cord. Henry cites evidence that nociceptive afferents release substance P in the spinal cord. He challenges the claims that substance P is analgetic and cites experiments to the contrary. His arguments are persuasive, and indeed more recent evidence indicated that the enkephalins may antagonize the nociceptive effects of substance P by preventing its release.

PRESYNAPTIC RECEPTORS

Langer succinctly reviews presynaptic receptors (7). Evidence of their existence appears to be clear, especially those that modulate catecholamine release. These presynaptic receptors are involved in the modulation of calcium-dependent stimulation–evoked release of norepinephrine in both the peripheral and central nervous systems. Langer speculates that changes in the number or sensitivity of the presynaptic receptors may be involved in hypertension, schizophrenia, and depression. Examples of drugs that may act at presynaptic sites include clonidine, α-methyldopa, apomorphine, μ-blockers, and the tricyclic antidepressants.

RADIOIMMUNOASSAY

Nobel laureate Rosalyn Yalow provides a brief critical review on radioimmunoassay (RIA) for the nonexpert but even cognoscenti should benefit from this authoritative commentary (8). RIA is an exquisitely sensitive technique and is now widely used for the detection of chemical agents in biologic fluids at concentrations sometimes as low as 10^{-14} M. However, Yalow points out that erroneous or misleading data can result without appropriate controls. A variety of factors can inhibit the antigen-antibody reaction in a nonspecific fashion or destroy the reactants. The dissociation of the antigen-antibody complexes can be affected by pH, proteins, buffer salts, anticoagulants, bacteriostatic agents, enzyme inhibitors, etc. If, for example, the labeled antigen is immunologically altered during incubation, its failure to bind to antibody may be interpreted to be due to the presence of antigen. The assay of peptide hormones is further complicated by the fact that related peptides may react identically with the antiserum. The popularity of RIA procedures has resulted in the development of kits containing all the necessary reagents for an assay, but unfortunately different commercially available kits may yield discrepant values. She ends with the caveat that even though the technique is a powerful tool, the perspicacious user should appreciate the problems and pitfalls involved.

MALE CONTRACEPTIVES

Wong provides the current state of the art with respect to the pharmacology of male contraception (9). After reviewing the available types of agents he concludes that no effective safe "pill" for men has emerged and he is not overly optimistic about any being on the immediate horizon. He points out that the progress in this area is hampered by the lack of basic knowledge of the male reproductive system especially with respect to the mechanisms involved in gonadotropin regulation of spermatogenesis and in sperm maturation in the epididymis. Germane to the latter consideration, he cites work from his own laboratory indicating a specific protein isolated from the epididymal secretion of rats or seminal plasma of bulls that stimulates forward motility of the immature epididymal sperm. He is hopeful that the knowledge of the role of this protein will provide an approach toward developing an agent that would be viable but incapable of fertilizing the female egg.

DRUG DEPENDENCE

Of the continuing National Institute on Drug Abuse series, NIDA Research Monograph No. 27, edited by Harris, is of especial interest to pharmacologists (10). The volume contains the proceedings of the 41st annual meeting of the Committee on Problems of Drug Dependence. The contents cross disciplinary lines and include basic, clinical, and sociologic contributions by active workers in the field.

Monograph No. 30, Theories on Drug Abuse, contains much talk, little substance, and has limited value for pharmacologists (11). More than 30 pet notions for drug abuse are advanced. But not all are bad. Some of the more substantial views include those by Wikler (conditioning), Dole & Nyswander (metabolic), Jonas & Jonas (bioanthropologic), and Robins (natural history).

Monograph No. 31, edited by Petersen includes reviews by experts on the current status of research on marijuana up through 1979 (12). Marijuana now appears to be used at an earlier age and more frequently than a decade ago. "Street" marijuana is increasing in potency; the tetrahydrocannabinol content now reaches 5% whereas confiscated materials in 1975 rarely exceed 1%. Additional data have confirmed the acute effects of marijuana on altering short-term memory. There is increasing evidence indicating that long-term usage impairs pulmonary function to a greater degree than tobacco smoking and may also alter reproduction functions. Its possible effects on the immune systems remain controversial. No definitive evidence

has been obtained indicating that marijuana decreases bodily defense to disease. Marijuana and THC have shown definite promise in treating nausea and vomiting which often accompanies cancer chemotherapy whereas varying success has been obtained in the treatment of glaucoma. This volume is one of the more useful ones in the series for pharmacologists that is published by NIDA, and it is hoped that progress in this area will continue to be reviewed periodically.

GENERAL PHARMACOLOGY

The sixth edition of Goodman & Gilman's classic pharmacology textbook has appeared with a new senior author joining and bearing the same names of the original twosome (13). There are also many new authors but fortunately they and the editors had the wisdom to merely update the original material so that readability and ease of comprehension have been essentially preserved. However, many chapters have undergone extensive revision, such as the one on agents acting on the heart. A long overdue treatment of toxicology is included. Also some topics have been accorded more emphasis throughout, particularly principles and mechanism of drug action. I note with pleasure that the treatment of general principles has now been expanded into three chapters, the first discussing drug disposition, the second, dose-response considerations and mechanisms of drug action, the third, principles of therapeutics.

The order of presentation of the topics has been somewhat improved. Drugs acting on the peripheral nervous system are now introduced before those acting centrally. This is only logical since the subject matter is less complex and more basic advances have been made with models taken from the peripheral nervous system. The chapter on therapeutic gases, which used to appear as an appendage in previous editions, is now incorporated into the section on drugs acting on the central nervous system. Personally, I prefer the organizational approach used by my great teacher, Chauncey Leake, who discussed in order, the pharmacology of chemical agents for the prevention, diagnosis, and treatment of diseases. The last topic was divided into drugs for the cure of disease and followed by those for the alleviation of signs and symptoms. This all makes good pedagogic sense and, furthermore, reserves for final presentation material in which pharmacologists have been traditionally interested and have made major research contributions.

The currentness of the text on mechanisms is exemplified by the detailed considerations given to receptor binding in relationship to drug action. In most instances, recognition site might be more appropriate terminology than receptor. It is gratifying that this approach, developed conceptually

and exploited primarily by pharmacologists, has gained widespread respectability in the wake of recent work on acetylcholine, the catecholamines, the opiates etc. The title, *The Pharmacological Basis of Therapeutics,* becomes increasingly meaningful as the number of receptors, together with its subtypes and ligands, becomes isolated, identified, and characterized.

A good example of thorough revision and greater emphasis on basic mechanism is the chapter on digitalis. A sense of authoritativeness prevails in the detailed critical treatment of the mechanism of action of digitalis. The thesis is developed that its positive inotropic effect is due to its ability to inhibit membrane-bound Na^+ K^+ activated adenosine triphosphatase. As a consequence there is an increase in intracellular Na^+ which causes a net influx of Ca^{2+}. The implication of this latter effect is not given but presumably this is essential in excitation-contraction coupling and represents an example of receptor binding leading to sensing of regulatory signals extracellularly with its translation into a physiological or metabolic event.

The scope and depth of the presented material are such that it is difficult for one person to critique the specifics narrated by 55 authors chosen for their expertise, but one can always nitpick. The section on the history of surgical anesthesia is less entertaining because it has been abbreviated excusably to make room for a consideration of preanesthetic medication. Unfortunately, in doing so, a host of drug types including benzodiazepines, phenothiazines, butyrophenones, and opioids are lumped together and described as "tranquilizers," a term deservedly discarded that now has been revived. The antipyretic analgetics have been removed from its CNS categorization and now appears as a separate section, "Drug Therapy on Inflammation." It is difficult to dispute this move but it is still pertinent to point out that even though inhibition of prostaglandin synthesis appears to be the common mode of action of these agents it is not clear why acetaminophen is such a weak anti-inflammatory agent and yet equivalent to aspirin in analgetic potency and efficacy. On the positive side opioid analgetics have been well covered. The chapter is remarkably up-to-date and incorporates recent knowledge on opioid receptor binding and their native ligands as well as a discussion of novel antagonists that are more potent than morphine and equally efficacious.

By and large the new edition and authors appeared to have successfully spanned the generation gap. They have brought a refreshing outlook to the presentation and coverage without materially altering format, style, and readability. The old and new are to be congratulated for maintaining breadth and depth while improving the quality to this popular well-known text.

Literature Cited

1. Way, E. L., ed. 1980. *Endogenous and Exogenous Opiate Agonists and Antagonists.* New York: Pergamon. 570 pp.
2. Costa, E., Trabucchi, M. 1980. *Neural Peptides and Neural Communication. Adv. Biochem. Psychopharmacol.,* Vol. 22. New York: Raven. 651 pp.
3. Snyder, S. H. 1980. Bra n peptides as neurotransmitters. *Science* 209:976–83
4. Iversen, L. L. 1979. The chemistry of the brain. *Sci. Am.* 241:134–39
5. Ritchie, J. M. 1980. Tetrodotoxin and saxitoxin and the sod um channels of excitable tissue. *Trends Pharmacol. Sci.* 1:275–79
6. Henry, J. L. 1980. Substance P and pain: An updating. *Trends Neurosci.* 3:95–97
7. Langer, S. Z. 1980. Presynaptic receptors and modulation of neurotransmission: Pharmacological impl cations and therapeutic relevance. *Trends Neurosci.* 3:110–12
8. Yalow, R. S. 1980. Radioimmunoassay: A major advance but not without problems. *Trends Pharmacol. Sci.* 10:266–68
9. Wong, P. Y. D. 1980. Pharmacology of male contraception. *Trends Pharmacol. Sci.* 10:254–57
10. Harr s, L., ed. 1980. *Problems of Drug Dependence 1979. Proc. 41st Ann. Meet. Comm. on Problems of Drug Dependence. NIDA Res. Monogr. 27:* Washington DC: GPO. 483 pp.
11. Lett er , D. J., Sayers, M., Pearson, H. W. 1980. *Theories on Drug Abuse. NIDA Res. Monogr. 30.* Washington DC: GPO. 225 pp.
12. Petersen, R. C., ed. 1980. *NIDA Res. Monogr. 31.* Washington, DC: GPO. 225 pp.
13. Gilman, A. G., Goodman, L. S., Gilman, A. 1980. *The Pharmacological Basis of Therapeutics.* New York: Macmillan, 1841 pp. 6th ed.