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REVIEW OF REVIEWS

E. Leong Way

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

NEW SERIES

Supply and demand are the cornerstone of a free economy and, although I am an advocate of the system, I sometimes am bewildered by its economics. This past year a number of new book series have emerged, so publishers must believe that their ventures are likely to reap a profit. However, at the prices some of these new publications cost, will they?

Libraries, let alone individuals, would strain to pay eight hundred dollars a year for twelve issues of a volume (1) whose list of authors and titles offers no greater enticements than existing series. Granted that it is produced by a non-profit organization, what a bargain the Annual Reviews volume is and, in contrast, what a profit some private publishers seek. Of course, some series are being offered at prices more reasonable than eight hundred dollars, but they still are not inexpensive.

Grahame-Smith, Hippius & Winokur tackle a highly ambitious undertaking in their two-volume biennial critical survey of the international literature in psychopharmacology (2). Part 1 of this work discusses the preclinical and Part 2 the clinical aspects of the topic. The first volume covers the basic pharmacology of agents used to treat the psychiatric states as well as the pharmacology of abused drugs. In general, the discussion attempts to relate drug affinity, binding sites, and neuroamine disposition to pathological states and drug action. Conceding that most of the drugs in use have been discovered serendipitously, the authors offer some arguments about why deeper insight into mental illness can come only from an understanding of the basic processes involved. However, they also have caveats. Even though excellent correlations can be drawn between the disposition of an endogenous substance and the beneficial effect of a drug, this does not necessarily mean that the relationship is primary. For example, the impressive correlation between the ability of the phe-

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nothiazines to block the action of dopamine in the brain and their antipsychotic potency implied a disturbance in dopaminergic neuronal function that led to the dopamine hypothesis of schizophrenia. However, the possibility that drug effects are mediated at a secondary level can easily lead to erroneous conclusions. It has not been established that dopamine is a primary etiological factor in schizophrenia, and in fact such evidence is meager, if not missing. By analogy, albeit a foolish one, we can make a case for a cholinergic hypothesis based on curare's ability to prevent physical violence during a schizophrenic paranoid delusion.

Part 2 of their survey of psychopharmacological literature, edited by Hippius & Winokur, deals with the clinical aspects of psychopharmacology, but the initial chapters seem to differ little from some of those in Part 1. The meat of the volume is the chapters updating the clinical pharmacology of the conventional psychotropic drugs (neuroleptics, antidepressants, tranquilizers, stimulants, and lithium). Also considered as a cause of mental disorder are hormones, peptides, and miscellaneous agents. Pharmacologists can be educated about the clinical application of certain agents whose rationale is not clear (e.g. lithium in cluster headaches, tricylic antidepressants in chronic pain, and imipramine in enuresis). The book also contains interesting chapters on drugs for the treatment of social, sexual, and childhood disorders, and a fairly comprehensive chapter on alcoholism. Both volumes are informative and useful but, with so many authors, the editors will have quite a task updating the volumes on a biennial basis.

Parnham & Bruinvels edit a new series, *Discoveries in Pharmacology* (3), to compete with *Chronicles of Drug Discovery,* which I reviewed here two years ago (4). The first volume of the present series emphasizes psycho- and neuropharmacology. Bonta's introduction mixes story telling with smatterings of history and science; the author unabashedly admits this but writes a chapter that is fun to read. The main thesis of the presentation by Kramer & Merlin on the ancient use of psychoactive drugs is that such use was practiced widely in the Old World and was a key element in shaping North African, Asiatic, and European cultures. Microfossil evidence is cited to show that Neanderthal man, a subspecies of *Homo sapiens,* was buried with plants used locally even in modern times.

Moving into more current aspects of the subject, Bacq provides an intimate account of the controversy over the theory of the chemical transmission of nerve impulses. Sharp discussions ventilate without acrimony the arguments of the two opposing schools, led by Dale (pro) and Eccles (con). This great debate is a model of how scientific discussion can be conducted with friendly feeling and mutual respect. Bowman's style is monographic in his chronological account of the development of our knowledge of peripherally acting muscle relaxants. The chapter on the use of drugs for testing psychotic behavior is

divided into several subsections, and some of the authors of these subsections played a part in the introduction of drugs for this purpose. Their discoveries, emanating largely from the clinic rather than the laboratory, were not always well received. Initially the therapeutic application of chlorpromazine, lithium, tricyclic antidepressants, and monoamine oxidase inhibitors was opposed vigorously by many experts in the field.

Sourkes & Gaulthier trace the discovery of levodopa and dopamine agonists in the treatment of Parkinson's disease. In this instance, the application of these agents resulted from information on dopamine generated in the laboratory using histochemical, metabolic, and pathological techniques. Hulzer & Lembeck's account of our developing understanding of pain makes rather dull reading because their recitation is telegraphic, but Livingston compensates in part with an account on the development of anesthesia. Garretta and I provide a history of the narcotic antagonists, pointing out that the conceptualization and development of narcotic antagonists were a significant achievement because so much practical knowledge has grown out of their discovery, prime examples being the development of potent analgetics with low-addiction potential, the isolation of opiopeptins (or endorphins), and the characterization of opiate receptors. There are also chapters on hypnotics by Koppanyi, antiepileptics by Meijer, Meinardi, & Binnie, benzodiazepines by Halfly, and neuropeptides by de Wied. In general, the *Discoveries in Pharmacology* is of greater reading interest than its older competitor. We will have to wait and see whether both volumes can survive.

CAFFEINE

Dew has edited a monograph on caffeine, important mainly for its timely analysis of the possible long-range effects of the substance (5); activist groups questioning the innocuousness of beverages containing caffeine have pressed the regulatory agencies of several countries to reevaluate the consequences to society of caffeine intake. First, one chapter covers thoroughly the bioavailability of caffeine, including its measurement in body fluids, absorption, distribution, metabolism, and excretion, followed by an interspecies comparison of these aspects of the subject. Epidemiological studies of the intake of coffee, tea, cocoa, and soft drinks provide a measure of the range of consumption, including the maximum amount of caffeine likely to be ingested. The discussion then centers on the cardiovascular, behavioral, and neuroendocrine effects of caffeine and their dose-response relationships. Finally, mutagenic, carcinogenic, and genotoxic potential of caffeine is critically analyzed. The reviewers do not question that high doses of caffeine can produce serious pharmacological and toxicological effects. However, the experts overwhelmingly agreed that the amount of caffeine in the daily diet does not

constitute a health hazard. Nonetheless, it would not surprise me if in a few years another isolated study reporting adverse toxic effects of high doses of caffeine will result in another inquiry.

NEW CARDIOVASCULAR AGENTS

Scriabine edits a review of thirteen cardiovascular drugs recently approved for use or under clinical investigation (6). The calcium channel blockers receive considerable attention, although under this category are various types of drugs that may act preferentially at different sites to find selective, sometimes overlapping, applications. Four antihypertensives are discussed, including an angiotensin converting-enzyme inhibitor (enalapril), a β-receptor antagonist (celiprolol), a calcium channel inhibitor (nitrendipine), and a loop diuretic (muzolimine). Under the rubric of antiarrhythmics, another calcium channel blocker (verapamil) and a prolongator of action potential duration (clofilium) are considered. Four antianginal agents are covered, including two more calcium entry inhibitors (dilitiazem and bepridil), a vascular smooth muscle relaxant (molidomine), and a new type of agent that acts to slow the heart by an effect on the pacemaker cells of the cardiac sinus node (alinidine). Prenalterol, a selective β-adrenoreceptor agonist, is listed as a cardiac stimulant, and yet another calcium entry blocker is listed as a cerebral antihypoxic agent for treating migraine (flunarizine).

RECEPTOLOGY

Kenakin provides a thorough critical analysis of the theory and methods used to classify drug and drug receptors in isolated tissues (9). The reader cannot help but be impressed by the scope and depth of his coverage as well as by his scholarly, authoritative treatment of the subject matter. Kenakin points out, for instance, that if two agonists under comparison have large differences in receptor reserve, selective desensitization or the selective irreversible inhibition of responses by an alkylating agent can yield misleading information. Thus, if one agonist has a 90% receptor reserve and another a 40% receptor reserve, then the responses to the latter agonist will be more sensitive to the removal of portions of the receptor pool either by desensitization or by alkylation. In addition, the application of theoretical considerations can be useful in the screening of new drugs. Thus, the most potent agonist may not be the most useful if its potency is related mainly to a high efficacy rather than to a high affinity, because drugs of high affinity but low efficacy are more susceptible to the efficiency of receptor coupling than are drugs of high efficacy. Moreover, the concept that a screening program can stress high selectivity presupposes the existence of a unique receptor or mechanism, but two activities in one molecule

may be critical to the selectivity or overall activity of that molecule in vivo. The presentation is invaluable for the graduate student and the post-doctoral fellow.

OPIOIDS

Duggan & North provide a comprehensive review of the electrophysiology of opioids, implicating calcium in opioid action (7). The coverage includes in vitro as well as in vivo systems and an analysis of the methods used for opioid administration. Considerable evidence is cited to support the notion that calcium is more basic to the acute action of opioids than adenosine 3'-5'-cyclic monophosphate (cAMP). Although the inhibition of adenylate cyclase has been popular as the suggested mechanism by which opioids produce their effects on neurons, electrophysiological studies do not to support this hypothesis; manipulations designed to elevate cellular cAMP by administering dibutyryl cAMP or a phosphodiesterase inhibitor (isobutylmethylxanthine) failed to alter neuronal firing in systems known to be highly sensitive to opioids.

Opioids inhibit neuronal firing in sensitive cells that contain a high density of opiate binding sites. In certain exceptional cases, when excitation is noted, the effect can be considered the result of disinhibition. The inhibition of neuronal firing after the acute administration of opioids is believed to be due to a reduction in the release of excitatory neurotransmitters that is calcium dependent. However, the mode by which calcium may be involved has not been clearly established. The mechanism the authors seem to opt for is that opioids cause cell membrane hyperpolarization that, following a period of repetitive firing, is particularly susceptible to enhancement by opiates. Other possibilities whereby transmitter release can be reduced by opioids can be attributed to hyperpolarization of nerves leading to propagation block, to a block of voltage-dependent calcium currents, or to interference with the ability of intracellular calcium currents to promote release. Based on studies in slices of the *locus caeruleus* and *substantia gelatinosa,* the researchers concluded that hyperpolarization induced by opioids results from an increase in potassium conductance that then could lead to a shunting of the calcium action potential and an inhibition of transmitter release. The mechanism for the increased potassium conductance has not been determined, but the elevation of intracellular calcium as a result of its displacement from sequestered sites has been suggested. This seems reasonable, since the binding of calcium in an enriched nerve ending preparation has been shown to be altered by opiates at the inner synaptic plasma membrane and synaptic vesicles. These findings are contained in our review summarizing the neurochemical evidence for implicating calcium in the acute and chronic actions of opiates (8).

Akil and company review the current knowledge of the biology and function of opiopeptins (endogenous opioids) (10). The various types of opiopeptins,

their biosynthesis, processing, anatomy, and possible function are discussed in an attempt to provide some understanding of a rapidly moving field. To this end, the committee of six have succeeded in authoring a concise summary of the state of knowledge of the three opioid gene families, their distribution in the central nervous system (and the periphery as well), and the multiple receptors through which they interact. Their possible relevance to homeostatic function, which is related to stress, pain, and cardiovascular action, is presented in an interesting and provocative manner. The omission of their relationship with other anterior pituitary hormones is disappointing; nevertheless, this review is recommended for its readability and its expertise.

DRUG DEPENDENCE

In addition to the usual original reports on the chemistry and the basic and clinical pharmacology of substances of abuse, the proceedings of the 45th annual meeting of the Committee on Problems of Drug Dependence, edited by Harris, contains several presentations of general pharmacological interest (11). Isbell eulogizes H. Frank Fraser, who made many notable contributions to psychopharmacology, including the development of a quantitative methodology for the assessment of the behavioral effects of drugs in human subjects. He also carried out extensive studies with the opiates, nalorphine, and the barbiturates on addicts at the Addiction Research Center at the US public health hospital in Lexington. Isbell, the late Abe Wikler, and Fraser were the acknowledged giants in research on drug dependence and made the center internationally renowned.

Nathan B. Eddy award winner Eric Simon summarizes his work on the isolation of the opiate receptor. Of particular interest is his evidence for a physical separation of the κ site from the μ and δ sites. Martin, who developed the multireceptor concept for opiates, offers a steric theory of opioid agonist, antagonist, antagonist-agonist, and partial agonist action. He uses three-dimensional models to explain the diverse effects of these substances and considers a large number of reactive sites that play two roles: their occupancy initiates a pharmacological action and they orient the drug in the receptor. Kornetsky cautions that attempts to relate the endorphins (or opiopeptins) to analgesia may overlook a more general role for these endogenous substances in stress as well as a possible role for them in modulating the attentional component of perception. O'Brien discusses the role of conditioning in drug dependence and describes problems in attempts to apply extinction methodology to the treatment of drug addicts. Kadden, Pomerleau, & Meyer examine a number of clinical and experimental findings that implicate conditioned respondents as a factor in the stimulus control of problem drinking.

Peturrsson & Lader have put together a volume on dependence on tranquilizers (12). The term *tranquilizer* is restricted to the diazepams and I rather like that. I never could reconcile myself to using the terms *major tranquilizers* for antipsychotic drugs and *minor tranquilizers* for anti-anxiety agents. In recent years dependence on diazepams has become an increasingly apparent problem. Duration of intake is the most reliable measure of the likelihood of developing physical dependence, but dosage, of course, is also a major consideration. High dosage intake for four months can lead to physical dependence, and, although a withdrawal syndrome becomes apparent in only 5–10% of misusers after six months of use, the incidence increases to 25–45% after two to four years. Withdrawal signs and symptoms include severe sleep disturbance, irritability, increased tension and anxiety, perceptual hypersensitivity, panic attacks, tremors, sweating, nausea, retching, and weight loss. The direct way to handle this problem is to educate primary-care physicians to detect diazepam dependence and to treat it by graded withdrawal. Most important, however, physicians must learn not to prescribe such agents indiscriminately.

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