PHARMACOLOGICAL REVIEWS
Vol. 29, No. 3

Printed in U.S.A.

Conversations in Pharmacology

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"Opinions that are opposed to mine do not offend or estrange me; they only arouse and exercise my mind."

MICHEL EYQUEN DE MONTAIGNE (1533–1592)
An Essay on Conversation

"It is easier to acquire facts, than to judge what they prove, and how, through the facts we know, to get to those which we want to know."

JOHN STUART MILL
Inaugural Address at Saint Andrews, 1867

This issue of PHARMACOLOGICAL REVIEWS is dedicated to conversation and controversy, twin catalysts for the advancement of scientific thought. It can be said with certainty that earlier generations of scientists have introduced errors, resulting from technical and conceptual limitations, into the fabric of science. It can be said also, and with an equal degree of certainty, that the present generation of scientists will replace those errors with errors of their own. The forward march of science, however, is a self-correcting process and it is to be hoped that errors will be corrected at a rate that is faster than the rate of their initiation. Open vigorous discussion supported by fact and reason and touched with some passion is insurance that this will be so. With this view in mind, two classic problems in pharmacology, both resisting solution, are discussed by Akera and Brody and by Miyamoto.

Digitalis glycosides are known to increase the force of myocardial contraction and to inhibit the enzyme, Na^+,K^+-ATPase. Akera and Brody take the position that the evidence is incontrovertible to support the notion that these actions of digitalis are related causally and that positive inotropism results directly from enzyme inhibition. They point out that dose-response relationships, kinetics of onset and offset of digitalis actions and results obtained with Na^+,K^+-ATPase inhibitors unrelated to the digitalis group of drugs are compatible with their view. Further, they propose that the inhibition of Na^+,K^+-ATPase leads to an inhibition of the sodium pump and a resulting increase in the magnitude of sodium transients. The enhancement in sodium transients in turn increases intracellular calcium transients and the force of contraction. In addition, Akera and Brody attempt to explain discrepant findings, usually on the basis of inadequate experimental design or technical limitations. An explanation of the failure to find an increase in the intracellular sodium concentration in the face of inhibition of Na^+,K^+-ATPase or the sodium pump is provided.

There is opposing opinion. Critics hold that the accumulated evidence is not always consistent with causality. Alternative explanations, *e.g.*, that the binding of digitalis to Na^+,K^+-ATPase alters the properties of a calcium pool within the sarcolemma or is required for the transport of the agent to an unknown intracellular site of action provide equally acceptable models to test. Clearly the debate is joined and the controversy delineated.

The concept that synaptic information is

transferred by the chemical activation of postsynaptic membranes has widespread if not universal acceptance. The evidence that acetylcholine and *d*-tubocurarine, acetylcholine and atropine, norepinephrine and phenoxybenzamine and other pairs of agonists and antagonists act on postsynaptic receptor systems to imitate or block transmission processes has been an essential component of the development of the concept of chemical transmission. Further, there is little dispute about the results showing that these pairs of drugs have powerful effects on presynaptic nerve endings. The adrenergic nerve terminals contain receptors which respond to muscarinic and nicotinic cholinomimetic agents and to *alpha* or *beta* sympathomimetic amines. Sensory nerve endings and, probably, sensory nerve trunks contain receptors for nicotinic agonists and antagonists. One can only wonder if the general acceptability of chemical transmission as a concept to explain the synaptic process would have been retarded if the almost ubiquitous distribution of receptors at pre- and postsynaptic sites had been fully recognized in the decades spanning 1930 to 1960.

Miyamoto writes on a curiously controversial topic, the acetylcholine receptor on the motor nerve terminal. Unlike the presynaptic receptors on adrenergic nerve terminals, those on the motor nerve terminal arouse emotions. Highly charged questions have been raised. Do receptors for acetylcholine exist on the motor nerve terminal? Considerable effort has been made to establish or deny their existence. If such receptors exist, what is their function? Once again, many studies have been carried out with the intention to show that the existence of such receptors requires the reexamination of the concept of chemical transmission or to show that, in fact, such receptors are nonfunctional and, for that reason, have no bearing on concepts of transmission. Of course, attempts have been made to reconcile the presynaptic cholinergic receptors with the common view of transmission by postulating a role for either positive or negative feedback on transmitter release. Miyamoto concludes that receptors for acetylcholine are present on the motor nerve terminal, sufficient acetylcholine is present in the junctional cleft for the activation of the receptors and that the receptors, when activated, may lead to an increase or decrease in transmitter release and, therefore, subserve a modulating function.

Both articles meet the objective of this volume. A systematic review of data in a way that leads to conclusions that serve to stimulate useful conversation and debate.

"Reading maketh a full man; conference a ready man; and writing an exact man."

FRANCIS BACON (1561–1626)
Of Studies