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Editorial Views

Cyclopropane Anesthesia and Plasma Norepinephrine Levels

IT IS GENERALLY AGREED that sympathetic neuronal activity leads to increased release of the neurotransmitter, norepinephrine (NE), from adrenergic nerves. This relationship holds true whether sympathetic-nerve activity reflects operation of homeostatic reflex mechanisms or results from drug action. Once released, NE may: a) be degraded by enzymic activity; b) be taken back into nerve endings by the uptake mechanism of the nerve membrane; or c), diffuse from the tissue into blood. Whether or not plasma levels of NE increase depends upon many factors, including the ability of the first two processes mentioned above to cope with the released amine. It is apparent, therefore, that an increased plasma amine level *per se* cannot be taken as evidence for sympathetic nerve activation unless it can also be shown that neither enzymatic degradation nor re-uptake of NE is affected by the drug or condition thought to cause such stimulation.

In this issue of the Journal, Ngai and his colleagues turn their attention to these considerations in relation to cyclopropane-induced elevation of plasma NE. The most important route for functional inactivation of neuronally-released NE is re-uptake followed by binding of the amine at intraneuronal sites. These pathways frequently are studied by means of tracer doses of radioactive NE. Ngai, Diaz and Ozer report that uptake and retention of intravenously administered tritium-labeled NE ($NE\text{-}^3H$) by rat heart were unaffected by cyclopropane anesthesia. Such treatment also failed to affect cardiac endogenous NE, providing some evidence that the anesthetic did not release amine. Offered as more direct evidence of this conclusion are experiments where intracoronary administration of $NE\text{-}^3H$ in dogs was used to label cardiac NE storage sites. In such preparations, the difference between coronary sinus and arterial tritium levels was assumed to reflect release of NE. Only when cyclopropane lowered blood pressure significantly, and presumably activated arterial baroreceptors, hence promoted reflex sympathetic stimulation, was there any increase in release of tritium. In contrast, halothane, which consistently lowered blood pressure, did not increase release of myocardial NE. If it is assumed that total tritium levels in blood, as measured in this study, reflect only NE (and not its metabolites), or that the proportion of $NE\text{-}^3H$ to tritiated metabolites in both venous and arterial blood is constant, these data suggest that elevated plasma NE during cyclopropane anesthesia results from increased sympathetic activity rather than from a primary peripheral action of the anesthetic. However, since NE released from adrenergic nerves in the heart can be converted to the physiologically-inactive normetanephrine by enzymatic

action, an increased arteriovenous tritium difference could also reflect a larger proportion of this metabolite.

Another possibility is that cyclopropane raises plasma NE by increasing biosynthesis of the amine. Ngai, Neff and Costa examined this supposition by studying the synthesis of NE in hearts and brains of rats exposed to either cyclopropane or halothane. To measure synthesis of NE *in vivo* they used a technique in which an intravenous infusion of the NE precursor, tyrosine-^{14}C, is administered during inhalation of the anesthetic. Infusion of tyrosine at a constant rate permits observation of the manner in which its specific activity in blood increases with time. Costa and Neff [1] previously suggested that the increase in tyrosine specific activity between 20 and 60 minutes was a linear function of time. In the present paper, similar data (see fig. 3) are fitted to a curvilinear function. However, both methods are designed to take into account the dynamic state of precursor as well as NE levels in tissues. After infusion, the specific activity of plasma tyrosine and that of both heart and brain NE are estimated. These data permit calculation of fractional rate constants for plasma tyrosine and tissue NE, which then are used to estimate NE synthesis rates and turnover times (*i.e.*, time for complete biosynthetic replacement of NE in a given tissue). The mathematical basis for these calculations differs slightly from that reported previously.[1] However, fundamental to both mathematical analyses are the assumptions that tissue NE exists in a single open (*i.e.*, nonrestricted influx and efflux) compartment, and that its steady-state level is maintained by balanced rates of synthesis and loss. It is also necessary to assume that synthesis supplies virtually all of the NE found in tissues. In the case of brain, where the blood–barrier restricts access of amine from the circulation, this assumption may well be valid; in heart, however, as much as 20 per cent of the amine can be derived from the circulation by tissue uptake.[2] Thus, while synthesis rates may be accurate, estimates of NE turnover rate in heart, calculated by this method, can be erroneously high. Another important assumption is that plasma tyrosine is in rapid equilibrium with intraneuronal tyrosine, or more specifically, that pool of intraneuronal tyrosine required for synthesis of NE. Despite the necessity for making these assumptions, control NE synthesis rates determined with the technique of precursor administration, show good agreement with those of methods based upon different principles and assumptions.[1]

In their work, Ngai *et al.* failed to find any change in NE synthesis rates, turnover times or steady-state levels in heart or brain after cyclopropane or halothane administration. It is worth emphasizing that techniques similar to those used by these authors allowed observation [1] of altered NE turnover rates produced by drugs or environmental change. Therefore the negative results they report can be assumed to reflect the absence of anesthetic action on NE biosynthesis in heart or brain. Confirmation of these findings by a different technique is not yet at hand. As the authors also point out, studies of NE synthesis in the dog specifically would seem necessary to exclude such an effect of the anesthetic in this species. Studies of this sort seem particularly desirable since it was in the dog that plasma NE was found to be raised by cyclopropane.

These two papers support earlier observations that cyclopropane does not affect uptake of NE,[3, 4] and rule out, in the rat, increased biosynthesis of the amine as an effect of cyclopropane. Since the anesthetic would not be expected to inhibit 0-methylation of NE under the conditions of these experiments,[5] elevated blood NE levels accompanying cyclopropane anesthesia cannot be related to reduced enzymatic destruction of released amine.

If one neglects consideration of possible species differences in response to cyclopropane and concludes, as have Ngai and his colleagues, that the anesthetic apparently does not affect biosynthesis or degradation of NE, what then might be its mechanism of action on the cardiovascular system? The inference drawn by Ngai and his colleagues, that cyclopropane acts at a site distal to the adrenergic neuron and possibly on receptor sensitivity, then seems entirely reasonable. In addition, it should be considered that halothane, which is recognized as depressing cardiovascular function, also failed to affect any of the pa-

rameters of "NE status" measured by these authors. This may well offer some support, admittedly obtuse, for the contention that altered biochemistry of peripheral adrenergic neurons is unlikely to be involved in the much-less-pronounced cardiovascular alterations produced by cyclopropane.

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Clinical Pharmacology of the Neuromuscular Junction

PRESENT KNOWLEDGE of the physiology and pharmacology of the neuromuscular junction shows that transmission between motor neuron and muscle fiber is carried out in a series of complicated steps. Operation of the prejunctional elements includes the synthesis, storage and release of acetylcholine. The initiation of the chain of postjunctional events begins with the arrival of neurally-released acetylcholine, which reacts with postjunctional membrane receptive sites. At the postjunctional membrane, permeability-controlling elements are thereby activated, causing impedance to fall. This change allows an increase in transmembrane ionic flux to occur, producing a depolarization of the postsynaptic membrane (the endplate potential). If these local changes in membrane potential are sufficiently great, a muscle-fiber action potential is initiated and is propagated along the length of the muscle fiber. In the wake of the propagated action potential, excitation–contraction coupling occurs, and thereafter the muscle tension rises.

The complex train of events involved in neuromuscular transmission can be facilitated or depressed in many ways and by many factors. Among the various modifying influences are the ionic composition of the extracellular fluid, the rate at which the neuromuscular junction is activated, and the presence of pharmacologically-active substances, such as anesthetic agents, quaternary ammonium compounds, anticholinesterase drugs, etc. In setting up various procedures designed to produce alterations in the neuromuscular transmission of a patient, and also in interpreting clinical data, the anesthesiologist relies both on basic principles and on empirical observations. The former are derived from laboratory experimentation carried out on whole animals or tissue preparations, the latter obtained from clinical practice. When he makes plans and sets procedures for practical application and when he interprets clinical data obtained from the patient, the anesthesiologist often wonders to what extent the results of laboratory experiments are applicable to patients. His questions and doubts generally do not represent a complete scepticism of the value of basic research in clinical practice; rather, they stem from the realization that it is difficult to assess neuromuscular block in a patient where one must contend with a large number of uncontrollable factors. Frequently, the action of a drug at the human neuromuscular junction must be surmised from indirect clinical ob-