The Importance of Sensory Nerve Endings as Sites of Drug Action***

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Received September 6, 1974/Accepted January 23, 1975

Summary. The role that sensory nerve endings can play in drug action and the strategy used for its experimental analysis and proof is first exemplified by three effects of nicotine which are seen when the lowest effective doses of the drug are given intravenously in the cat: (1) a vasopressor effect due to arterial chemoreceptor stimulation; (2) a triad of bradycardia, hypotension and apnea, and (3) a depressant effect upon somatic motor activity, both of which are traced to vagal afferent endings in the pulmonary circulation. While receptors in the lung are responsible at least for the initial phase of the reflex responses listed in (2) and (3), sensory endings in heart, aorta, and carotid sinus region may be recruited into action as the drug reaches them. Several of these reflex effects can also be elicited by other sensory stimulant agents such as phenylbiguanide, 5-hydroxytryptamine, and veratrum alkaloids.

In the second part, a general outline is given of what may be classified as 'afferent Pharmacology', dealing with drug action upon sensory receptors and with the resulting remote drug effects. The action upon sensory receptors can either be a direct one ('primary' drug effect) consisting of stimulation, sensitization, desensitization, depression or combinations thereof, or an indirect ('secondary') effect brought about by a variety of drug-induced changes in the tissues surrounding the receptors. Depending on the nature of the primary or secondary action, the remote drug effect can be either an initiation, modification or impairment of those reflexes which have their origin in the sensory endings acted upon. Indeed, the grossly observable pharmacological actions of 'afferent drugs' are generally those relating to the reflex response. To avoid blurring of the boundaries of afferent pharmacology, drugs acting on central synapses of reflex pathways, or on the elaborate efferent control system of afferent input, are not included. A discussion follows of the topics of investigation, the influence of experimental conditions and anesthesia, various approaches and methods, the physiological and pharmacological importance of inquiry in this area, and some of the therapeutic aspects. Finally, brief mention is made of certain features and problems which appear to be characteristic of afferent pharmacology.

Key words: Afferent Pharmacology — Sensory Nerve Endings — Autonomic and Viscerosomatic Reflexes — Nicotinic Agents — Veratrum Alkaloids.

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* This report is based on a lecture presented at the Pharmacology Meeting Graz '74, September 2—5, 1974.

** Part of this work was supported by USPHS Grants NB 01143 and NS 10004.
Two brilliant feats mark the beginnings of experimental pharmacology: one was Bezold and Hirt’s demonstration in 1867 that veratrine decreases heart rate and blood pressure by a vagovagal reflex, the other Claude Bernard’s ingenious analysis of the action of curare (1856). The latter fell on more fertile ground, and ever since the greatest advances in pharmacodynamic research have been made in the realm of efferent systems, somatic as well as autonomic. Drug action upon sensory nerve endings and the variety of potential reflex responses thus activated, i.e., an area of pharmacology that could be classified as ‘afferent pharmacology’, has attracted less attention despite significant studies, to which numerous reviews attest (Konzett and Rothlin, 1953; Dawes and Comroe, 1954; Heymans, 1955; Heymans and Neil, 1958; Krayer, 1961; Bevan, 1962; Anichkov and Belen’kii, 1963; Painatal, 1963, 1964, 1971, 1972, 1973; Smith, 1963, 1967, 1973; Keele and Armstrong, 1964; Trendelenburg, 1965; Zipf, 1966; Benforado, 1967; Coleridge and Coleridge, 1972).

A decisive factor for the preference that efferent nervous function and its modification by drugs has received over the years was, no doubt, the early discovery of neurohumoral transmission, while proof of a chemical principle in the initiation of electrical activity at sensory receptors has, so far, eluded the keenest efforts (see Painatal, 1964, 1971). Another quite different influence, possibly contributing to our preoccupation with efferent systems, may have been the “Zeitgeist” which focused upon man as the doer and mover, the conquerer and controller of nature.

Today, as a new awareness and sensitivity begins to stir, it is finally realized that the external environment is not just the passive recipient of our unchecked efferent violence but also the constant source and provider—and it better be allowed to be a good one—of all the innumerable stimuli which impinge upon the living organism and supply it, via efferent inputs, not only with specific information but indeed with the basic energies upon which efferent activity lastly depends.

In approaching this lecture I cannot help but fall back upon nicotine as perhaps the most suitable candidate for illustrating the important role of sensory endings in drug action, on one hand, and the neglect of it, on the other. Indeed, Comroe (1960), discussing the cardiovascular effects of nicotine, criticized the widespread ignorance about the drug’s stimulant action on sensory systems which are at best considered “a pharmacological curiosity”. I would like to begin with experimental examples mostly from my own work of recent years, and then proceed to a more general appraisal of the state of the art in this area of pharmacology. Within the available space, the treatment of the subject will of necessity by sketchy, highlighting some points while shortcutting or omitting many others.

Fig. 1 shows three different responses to nicotine: a blood pressure rise, a blood pressure fall and a skeletal motor paralysis in a cat made.