

This Week's Citation Classic®

Sawynok J, Pinsky C & LaBella F S. Minireview on the specificity of naloxone as an opiate antagonist. *Life Sci.* 25:1621-32, 1979.
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The administration of the narcotic antagonist naloxone has been used commonly as the criterion for implicating endogenous opiates in physiological, pharmacological, and pathological responses. This review points out that (a) naloxone may exert opiate-agonist activity or actions that are not mediated by opiate receptors, and (b) other types of evidence are required to support a role for the endorphins. [The *SCI*® indicates that this paper has been cited in over 470 publications.]

A Probe for Endorphins in Amoeba and Man

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J.J. Jacob showed in 1974 that the injection of the opiate antagonist naloxone aggravated the distress of rats placed on a hot plate.¹ This was one of the first studies hinting at the existence of and a physiological role for endogenous opiates. About the same time, O. Gigliotti and C. Pinsky² found that rodents subjected to the mild noxious stimulus of just-threshold footshock showed little or no change in behavior unless challenged with naloxone, whereupon the animals exhibited marked distress. They concluded that overt behavioral consequences of antagonism by naloxone become manifest only under circumstances that mobilize endogenous opiates. Soon after the recognition that certain peptides constitute the endogenous equivalent of the opiate drugs, a flood of reports described the effects of naloxone in animals under a variety of physiological, pharmacological, and pathological conditions, including greater pain intensity associated with wisdom tooth extraction in humans,³ enhancement of memory consolidation, modification of nutrient selection, and reversal of pupillary constriction associated with running in man. Neurotransmitters and chemical messengers in humans have been characterized in primitive life forms such as the slug, tetrahymena, euglena, and planaria. Thus, it should not be surprising that naloxone modifies the behavior of simple organisms.

Because of the widespread reliance upon naloxone to define endorphinergic systems, we felt that interpretations of experiments with the antagonist should be tempered by certain considerations. For example, is drug action exerted through occupation of membrane receptors for endorphins, as opposed to effects mediated in other ways? Hans Kosterlitz insisted that for a given pharmacological response one compare isomeric pairs of opiate antagonists to define stereospecificity, or lack thereof, as one means of assessing the contribution of nonspecific drug action. He stressed, also, that reversal of opiate effects by naloxone should not exceed the use of an established, generally effective dose of the antagonist—1 mg kg⁻¹ was his favored dose.

The utility of narcotic antagonists extends to potential therapy in clinical states where excessive elaboration or secretion of endorphins may be detrimental.⁴ Salutary effects of naloxone in man have been claimed in shock caused by hypovolemia, sepsis, anaphylaxis, and hepatic failure. In addition, naloxone is claimed to have led to improved clinical status in respiratory depression, including that from drug overdose, and in a variety of disease states. Naloxone is of reported benefit, also, in experimental spinal injury and stroke. Clearly, a number of issues remain to be clarified and confirmed, including whether or not the observed effects result, in fact, from an interaction of naloxone with opiate receptors.

The rapidly accumulated catalogue of physiological, pharmacological, and pathological processes modified by the administration of naloxone argued, at first glance, for the ascendancy of the endorphinergic system in neurotransmission. With the availability of peptide antagonists, and in view of results of central administration of peptide antisera, the catalogue of central circuits in which each of many other putative transmitters are implicated is approaching the magnitude of that tabulated for the endorphins. Indeed, the older scientific literature is replete with accounts of interference by anticholinergics, for example, in the repertoire of centrally mediated processes, including temperature regulation, appetite, locomotion, conditioning, and cardiovascular function, to mention only a few. In view of the numbers of neurons estimated to synapse with any single neuron, and with the recognition of multiple transmitter substances coresiding in neurons, it seems unlikely that any single substance constitutes the predominant neurotransmitter for any given neuron, let alone neuronal circuit. One could reasonably argue, now, that the specific neuronal network subserving any given physiological function is modulated by contributions of most if not all central neurotransmitters and, furthermore, that the profound pharmacological impact resulting from antagonism of any one member of the neurotransmitter ensemble reflects the balanced participation of multiple chemical mediators both in series and in parallel.

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2. Gigliotti O & Pinsky C. Naloxone antagonism of accommodation to unpleasant stimuli. (Abstract.) *RODA abstracts*. Ottawa, Canada: Health and Welfare Canada, 1974. p. 91.
3. Levine J D, Gordon N C, Jones R T & Fields H L. The narcotic antagonist naloxone enhances clinical pain. *Nature* 272:826-7, 1978. (Cited 135 times.)
4. Milne B & Jhamandas K. Naloxone: new therapeutic roles. *Can. Anaesth. Soc. J.* 31:272-8, 1984. (Cited 5 times.)