practice patterns can be changed \(^1\) to decrease costs, \(^2\) to try to improve patient outcome, \(^3\) or both. However, changing practice patterns requires more than just education and practice guidelines. Either "negative" barriers limiting undesired practice (e.g., signatures, voice release, or forms), \(^1\) "positive" individualized feedback, \(^3\) or both \(^3\) should be combined with education to change physicians' behavior.

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References


"Exciting" Aspects of Opiate Receptor Signal Transduction

The process that causes a cell to produce a particular response after binding of an agonist to its receptor is called signal transduction. Of particular interest to anesthesiologists is the transmembrane signaling that follows agonist binding to ligand-gated ion channels (e.g., \(\gamma\)-aminobutyric acid \(_A\) receptors) or G protein-coupled receptors (e.g., adrenergic and opiate receptors). In the former case, the receptor and the channel that translocate chloride anions are on the same protein, whereas in the case of the opiate receptors at least three separate proteins participate in the signal transduction; i.e., the receptor, the G protein, and the effector. With that many "moving parts," the opportunity to modulate such a system abounds. When one considers that each family of receptors has many subtypes (e.g., there are nine adrenergic receptor subtypes), which can couple to more than 20 different G proteins and nearly 100 effector mechanisms, it becomes easy to understand how a single species of agonist can give rise to a plethora of diverse biologic responses.

In this issue of Anesthesiology, Gutstein et al. \(^1\) tested the hypothesis that opiate receptors are coupled to mitogen-activated protein kinase cascades, which induce changes in cellular function by phosphorylation of cytoplasmic and nuclear proteins. Until a few years ago, such a notion would have seemed far-fetched because the hyperpolarization effects of opioids in neuronal cells could be easily explained by a well-characterized activation of potassium channel (promoting escape of intracellular cations), inhibition of calcium channels (preventing calcium from entering into the cell), or both. Although these transduction mechanisms can explain the inhibitory effect of opioids on neuronal excitability, they do not provide an answer for the multitude of excitatory effects (e.g., tolerance, dependence/addiction, muscle rigidity) that opioids also exhibit at the cellular level.

The authors have developed cDNAs for each of the rat opiate receptors, which, when spliced into an appropriate vector, can be introduced into cells, which then express "pure" populations of these receptor subtypes. The fidelity of transfection and protein expression en-

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ures that only one species of receptor is present and is a useful technique for defining the transduction pathways used by specific receptor subtypes. In two mammalian cell types they demonstrated that the μ- and δ-receptor subtypes activate extracellular signal-related kinase, one of the three defined mitogen-activated protein kinase species.

These findings have novel implications at the fundamental and clinical levels. At the fundamental level, it will be important to define which are the “downstream” effects of extracellular signal-related kinase activation and to determine if these can explain some of the excitatory effects of opioids. Such information may lead to therapeutic strategies that can interrupt the development of tolerance, dependence, and addiction. In addition, the fact that κ-agonists cannot stimulate extracellular signal-related kinase may provide insights into the different pharmacologic actions exhibited by drugs acting exclusively at the κ-receptor subtype.

I have one final thought: Even though nature is parsimonious in having but two endogenous opiate ligands and three opiate receptor subtypes, it can still introduce remarkable specificity by discriminating which molecular component in transduction pathways can “match” with one other component.

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Why Does Insensitivity to Opioid Narcotics Develop?

OPiATE receptors hold a place of prominence for practitioners of anesthesia. Not only are these targets for several analgesic and anesthetic drugs that are used commonly but the primary structure of each of the opiate receptor subtypes was first reported in 1993 by an anesthesiologist, Dr. Kazuhiro Fukuda working in Professor Kenjiro Morita’s department in Kyoto, Japan. The isolation and cloning of this family of proteins proved particularly difficult because of its relatively low abundance. However, following the example of Fukuda’s pivotal studies, molecular genetic reagents have been developed that have prompted a profusion of cell biology studies that has greatly increased our understanding of opioid action.

Of particular interest to investigators in Dr. Robert Peterfreund’s laboratory at the Massachusetts General Hospital are factors that regulate sensitivity to opioid narcotics. Biochemical changes are induced in chronic pain states, which reduce the analgesic efficacy of opioids. In addition, patients develop tolerance to the analgesic properties of opioids after they are administered continuously. In both settings, a similar cascade of neuroplastic changes are induced, resulting in activation of the NMDA receptor and activation and translocation of protein kinase C.

These investigators have directed their attention to the “downstream” effects of the activation of protein kinase C. In a model cell system derived from humans (SH-SY5Y cell line) that contains the μ-opioid receptor and the entire signaling system responsible for neuroplasticity, the authors directly activated protein kinase C with the phorbol ester. Then they determined

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