news and views

Narcotic action at the molecular level

OPIUM and its derivatives have been used for centuries to ease the pain of injury and illness, and to blur the mental anguish of society's less fortunate. Morphine, the primary active ingredient of opium, has long been the standard analgetic. Morphine's medical usage, however, is constrained by the body's tolerance to opiates. Ever increasing dosage is required to maintain the analgetic effect. With chronic usage the body becomes dependent on the presence of opiate, and withdrawal causes agony.

For several decades scientists have sought a morphine analogue which would produce analgesia without tolerance (see Eddy and May's review in *Science*, **181**, 407; 1973). Attempts to elucidate the mechanism of opiate action have been spurred on by the epidemic of heroin (diacetylmorphine) abuse which has became a socio-medical problem of staggering proportions in most western cities.

Last spring Pert and Snyder announced their biochemical demonstration of a receptor in nervous tissue which binds opiates with stereospecific selectivity and with affinity paralleling pharmacological potency (*Science*, **179**, 1011; 1973). In the ensuing months a stream of reports from Snyder's laboratory has demonstrated the utility of their assay, both for studying the basic pharmacology of opiate action and for rapid screening of narcotics with medical potential.

In *Nature* on October 26, Kuhar, Pert and Snyder (**245**, 447; 1973) described detailed mapping of the concentration of opiate binding sites in both human and monkey brains. They discovered striking regional variation in binding, with receptor concentrations varying more than thirty-fold between the highest and the lowest areas. Interestingly, the regions high in opiate binding all lie within the limbic system. Binding is greatest within the anterior amygdala, uniformly high throughout the hypothalamus, and high in medial but not in lateral thalamus. Frontal cortex areas show moderate binding of opiate, but little is found elsewhere in the cerebrum. This distribution leads to intriguing speculation about how the analgetic and euphoric effects of opiates might be related to limbic involvement in perception and expression of emotion and in the direction of motivated behaviour.

How well does the density of opiate binding sites correspond to the locations at which externally administered narcotics affect the brain? Previous workers have inserted morphine into various brain regions of living animals and tested for analgetic response; the distributions of opiate binding and of pharmacological effect seem well correlated.

There has been considerable controversy over whether opiate action is associated with some particular neurotransmitter. From the evidence various proponents have presented, one may conclude that the target of opiates is serotoninergic, or noradrenergic, or perhaps cholinergic. In this study, Snyder's group asked whether opiate binding could be correlated with distributions of acetylcholine, catecholamines, GABA or serotonin. Disappointingly, although there were some similarities, there was no clear-cut parallel in any case. Furthermore, lesions of well known nerve tracts specific for acetylcholine, noradrenaline, or serotonin produced no change in opiate binding in the affected areas.

Much narcotic research has centred on searches for the basis of the contrasting actions of opiate agonists and opiate antagonists. Many modifications of the morphine chemical structure have been studied in search of an analogue with a more amenable spectrum of pharmacological activity. In the process of searching, there were discovered certain analogues which block completely the action of opiate agonists (structures with morphine-like action). These 'antagonists' do not cause dependency, and in fact dramatically precipitate withdrawal in morphine-dependent animals. Safe, long lasting opiate antagonists are avidly being sought, with the idea of 'treating' addicts by thwarting the effect of heroin consumption.

Pert and Snyder have recently shown that the various opiate agonists and antagonists have a wide range of binding affinities for nervous tissue, and that there is a high correlation between affinity and pharmacological efficacy of these drugs *in vivo* (*Proc. natn. Acad. Sci., U.S.A.*, **70**, 2243; 1973). Agonists and antagonists apparently compete for the same receptors, and because there is complete overlap in the range of affinities of the two classes of opiate, it would seem that the difference in their pharmacological effect must lie in some difference in cellular response ('intrinsic action') due to contrasting structure. Pert, Pasternak and Snyder have now discovered a difference in the way agonists and antagonists are bound by brain tissue, and that this differential effect can be used to discriminate *in vitro* between the two classes of opiate (*Science*, **182**, 1359; 1973). They first found that injection of mice with either opiate agonists or antagonists produced within minutes a significant increase in the number of opiate binding sites. The narcotic antagonists were 10 to 1,000 times more potent than structurally related agonists in enhancing receptor binding, which corresponds well to the fact that antagonists affect the body at much lower concentrations than do agonists.

In the light of the far greater pharmacological potency of narcotic antagonists, it seemed puzzling that agonists, such as morphine, oxymorphine and levorphanol, showed *in vitro* binding affinities quite similar to those of the structurally corresponding antagonist derivatives nalorphine, naloxone and levallorphan (respectively). This puzzle was resolved by the propitious discovery that adding sodium to the assay medium (in concentrations corresponding to those found in the body) considerably increased antagonist binding, while lowering that of agonists. Interestingly, the increase in binding is caused not by a change in receptor affinity but by an increase in the number of receptor sites available.

The discovery of this differential ionic effect on binding offers the prospect of a simple biochemical test for discriminating the agonist and antagonist activities of drugs which might be used for treatment of heroin addiction or which might provide analgesia without physical dependency. The authors examined the ability of a series of known opiate agonists and antagonists to inhibit the binding of tritium-labelled naloxone (an antagonist), both in conditions of low sodium and of high sodium. High sodium did not alter the binding of antagonists, but drastically lowered the ability of agonists to compete for receptor sites. Pentazocine, which has a mixture of agonist and antagonist properties, showed an intermediate loss of binding. Such mixed action drugs are clinically important because they offer the possibility of 'non-addicting' analgesia. It is theorised that the ability to block pain is a function of agonist affinity, and that addiction is prevented when agonist and antagonist actions are present simultaneously.

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