Four of the articles in the present issue of Pain Research & Management discuss preclinical issues relevant to understanding the changes that occur to the analgesic efficacy of opiates over an extended interval of delivery (pages 25 to 57). The articles reflect the extended and interesting discussions that transpired at the Canadian Pain Society meeting held in St John’s, Newfoundland, May 14 to 16, 1999.

The role of changes in opiate responsiveness in long term opiate exposure in clinical pain states is controversial. While few argue that opiate dosing does not rise over time, it is evident that, with chronic exposure, many patients show a very stable dosing requirement. When the dosing necessary to sustain pain relief rises, the rise may occur by several mechanisms, including the appearance of more intense pain and the evolution of opiate-insensitive pain states. Yaksh reviews some of these issues in his contribution (pages 33-39). Nevertheless, clinical and preclinical studies aimed at defining specific dose requirements have emphasized that, of the several mechanisms, pharmacodynamic plasticity can contribute to the ongoing changes in dose requirements. Several of the articles in this issue focus on this component of the process, with an emphasis on the potential importance of changes in receptor coupling and function. An emerging concept is the role of glutamate, and the several ionotropic and metabotropic receptors on which it works. Importantly, such observations are in agreement with the review by Jhamandas and colleagues (pages 25-32) of the potential contributions of a variety of spinal transmitters and second messengers in the development of a reduced response to the chronically delivered opiate. Fundytus (pages 40-48) considers the potential contribution of several neurotransmitter systems and emphasizes the potential role of metabotropic receptors. She draws parallels between the mechanisms of neuropathic pain states and opioid tolerance. Yaksh discusses the role of spinal glutamate receptors in spinal tolerance to opioid and alpha,-adrenergic agonists, and the contribution of phosphorylation to spinal tolerance. Cahill and Coderre (pages 49-57) discuss the interactions of nerve growth factor and the expression of cholecystokinin in the opiate insensitivity noted in some neuropathic states. The reviews, thus, strongly focus on the local neuronal network and the cell type on which the opiate receptor is found. Rather than repetitiously detailing the conclusions of each article, I will consider some of the implications of the opinions of the author(s) of each paper regarding the mechanisms responsible for a rise in opiate dosing. I hope that my interpretations will be viewed forgivingly by each contributor in the possible event that I erred in my reading of their interpretation.

SOME RAMIFICATIONS OF THE MECHANISMS PROPOSED FOR OPIATE TOLERANCE

The mechanism by which opiate tolerance occurs has not been clearly identified. Nevertheless, several consequences of the mechanisms that have been proposed may be considered to offer an opportunity to be ‘hoisted by our own petard’. As with any hypothesis, the more counterintuitive the predictions are, the better.

‘As required’ medication and glutamate release

Because tolerance seems to be, in part, a function of dose and time of agonist receptor exposure, it seems intuitive that removal of the opiate should at least slow the process by which the tolerance mechanisms are driven. On the other hand, one observation that appears clear is that opiate withdrawal leads to the release of glutamate. As reviewed by Fundytus, Jhamandas...
Yaksh

mandas and Yaksh, activation of glutamate receptors (metabotropic or ionotropic) appears to lead to processes that exacerbate tolerance. In that regard, the data reviewed by Jhamandas and Yaksh are clear in that, during withdrawal in different systems, glutamate release is enhanced. It is reasonable then to hypothesize that loss of effect should be less profound with continuous exposure than after bolus opiate exposure. This leads to the speculation that ‘as required’ medication is less desirable than establishing a continued level of opiate dosing. To the degree that there is a ‘half-life’ of tolerance, it may be speculated that if the pain state requires dosing at intervals less than the half-life of tolerance, continued dosing is preferable to ‘as required’ dosing. In other words, continued receptor occupation is preferable to periodic activation and deactivation of the receptor population (see below). This leads to the paradoxical notion that it is not the duration and exposure dose that define the magnitude of loss of effect, but the acute periodicity of exposure, eg, in this case, less exposure leads paradoxically to more tolerance.

Chronic pain and clinical versus preclinical opiate tolerance

As indicated by all of the authors, there is little doubt that, in animal models, there is a rapid decrement in drug effect during a defined drug exposure, ie, tolerance, whether the drug is delivered as a bolus or continuously, or systemically or neuraxially. In contrast, as reviewed by Yaksh, tolerance in pain patients is less clear and is typically less acute. This difference poses some theoretical embarrassment for those who promulgate mechanisms based on the preclinical models. Why do humans not show the same rapid and continued incrementation as seen in animal models? One argument is that the preclinical models often involve systems in which continuous exposure leads to a parallel loss of effect over a five- to seven-day interval. Thus, all drugs show an ongoing loss of effect with continued exposure. Nevertheless, measuring the right shift of the probe a bolus after completion of the infusion reveals that the magnitude of tolerance, as measured by the right shift of the probe dose-response curve, was least for DAMGO and sufentanil.

Parallels between injuries leading to hyperalgesia and to opiate tolerance

All of the contributors to this issue are quite taken with the similarities between mechanisms that lead to tolerance and those that are related to the loss of opiate reactivity. During opiate withdrawal, animals display glutamate release and hyperalgesia that is diminished by N-methyl-D-aspartate antagonism. Fundytus emphasizes that the lack of opiate sensitivity in neuropathic pain may be related to the role played by group I metabotropic glutamate receptors. She notes that blockade of these receptors returns the sensitivity of animals to opiates and prevents tolerance. Cahill and Coderre note that nerve injury leads to an increase in nerve growth factor levels that may serve to downregulate the spinal expression of cholecystokinin, which itself serves to downregulate opiate sensitivity. The question of interest is whether the relationships are corollary or causal. As considered above, chronic pain states should enhance glutamate release and initiate the cascade leading to tolerance. Is this what leads a neuropathic state to be opiate resistant? One can imagine that chronic pain states may lead to a ‘tolerance cascade’ and, by an independent mechanism, produce a pain state that is not regulated by opiates. Thus, as reviewed, nerve injury models, such as the Chung tactile allodynia model, are relatively resistant to the spinal effects of opiates. This may be due to the fact that the phenomenon is mediated by large afferent input that is not regulated by spinal opiate receptors.

If the chronic pain state is responsible for opiate tolerance, it may produce tolerance to the opiate in models that are sensitive to spinal opiates, eg, thermal escape. There are few data to suggest that the thermal escape in Chung animals is not blocked by opiates. Indeed, the thermal hyperalgesia in the Bennett chronic compression model is clearly opiate in nature. An additional implication of this thinking relates to other agents that have a spinal action through G-coupled proteins. On example is the alpha, receptor. As reviewed by Yaksh, this system produces a potent antinociception after spinal delivery and shows tolerance with continued delivery. This tolerance is attenuated by intrathecal N-methyl-D-aspartate antagonism. Yet, unlike opiates, intrathecal alpha, agonists are active in models of nerve injury-evoked allodynia. This suggests that there is at least one dissociation between the neuropathic state and spinal G protein-mediated receptor tolerance.

TOLERANCE AND DRUG CHARACTERISTICS

Previous studies have shown that continuous intrathecal infusion of DAMGO (a mu opioid peptide), sufentanil or morphine in doses that initially produce equal analgesic effects leads to a parallel loss of effect over a five- to seven-day interval. Thus, all drugs show an ongoing loss of effect with continued exposure. Nevertheless, measuring the right shift of the dose-effect curve for the respective toleragen given as a bolus after completion of the infusion reveals that the magnitude of tolerance, as measured by the right shift of the probe dose-response curve, was least for DAMGO and sufentanil.
and greatest for morphine (1). Moreover, when the degree of cross-tolerance was defined, the rank ordering of the magnitude of the dose-response curve shift was as follows: morphine/morphine greater than morphine/sufentanil greater than sufentanil/morphine greater than sufentanil/sufentanil (where the first drug is the toleragen and second is the probe drug). This suggests an asymmetry in the cross-tolerance.

While it has been only minimally investigated in human conditions, instances of asymmetric cross-tolerance have been reported in opiate-tolerant patients (2). These observations thus raise the intriguing possibility that tolerance produced by different opiates may be distinguishable. Because the agents are given by continuous infusion, the issue of local kinetics is probably not relevant. Several possibilities may be relevant; two are considered – receptor internalization and agonist efficacy.

Receptor internalization

Opiate receptors undergo internalization. Coupling studies have indicated that this phenomenon is mediated by activation of beta-arrestin and by phosphorylation of the cytosolic tail of the mu receptor (3,4). Interestingly, such internalization is not uniformly performed by all opiates. Thus, in a variety of cell systems transfected with mu receptors, internalization was produced by DAMGO but not by morphine (5-8). Studies with receptor chimeras suggest that this difference depends on the characteristics of the cytosolic tail of the mu opioid receptor. Increasing the ability of the cytosolic tail of the chimeric mu receptor to be phosphorylated subsequently allowed morphine to induce internalization (7).

This dichotomy regarding internalization with two agents that display a similar tolerance indicates either that internalization plays no role or that there are at least two distinct cellular mechanisms. Thus, agents that do not internalize the receptor (eg, morphine) may result in downstream changes that inactivate the receptor. On the other hand, the ability of an agonist to drive internalization of the receptor (eg, DAMGO) may prevent a continuous activation and avoid downstream changes. Both events lead independently to a loss of agonist effect. Internalization may be seen as a local ‘protective’ mechanism preventing the downstream effects that may have profound consequence for cellular function (7).

Agonist efficacy

Previous studies using irreversible spinal mu antagonism have shown that, for a given degree of spinal mu opioid receptor inactivation, the degree of right shift in the intrathecal dose-response curve is as follows: DAMGO equivalent to sufentanil greater than morphine (9). Such an observation is consistent with the interpretation that morphine shows less intrinsic efficacy than either DAMGO or sufentanil, ie, morphine requires a higher fraction of the receptor to be occupied to produce a given effect than the fraction required by either DAMGO or sufentanil. Under these conditions, any degree of receptor inactivation (by either internalization or by some downstream change in receptor coupling) leads to a greater right shift in the probe dose-response curve for morphine than for either sufentanil or DAMGO. Importantly, this observation is consistent with the asymmetric cross-tolerance that was previously noted between morphine and sufentanil.

Jointly, one may speculate that certain agents such as DAMGO and sufentanil may lead to a transient internalization of the receptors over time and that this accounts for their ongoing loss of effect. In contrast, morphine, by not resulting in an internalization, may induce downstream changes that lead to more pronounced changes in receptor function for a given degree of functional activation. In addition, if morphine possesses a receptor occupancy requirement, the degree of right shift produced by any mechanism of receptor/coupling downregulation would lead to a greater right shift than that observed for sufentanil. An additional intriguing possibility is that a variety of conditions may alter the relationship between receptor occupancy and internalization that reflect on the events discussed in the articles in this issue. Thus, consider that the in vitro cell studies cited above suggest that morphine may not internalize the receptor, except where there is an increased opportunity for phosphorylation of the cytosolic tail. Suppose that over time a phosphorylating function is induced. Will this lead to a condition in which morphine develops the ability to induce internalization? Recent work has shown that chronic opiate exposure increases the expression of protein kinase C protein (10). Is there a triggering level of activation at which morphine becomes more comparable to the functionality of DAMGO and begins to induce internalization? As the contributors to this issue have suggested, chronic afferent traffic leads to enhanced phosphorylation. Can one imagine a seemingly paradoxical series of events in which pain leads to enhanced phosphorylation of the mu receptor that turns morphine (and other agonists such as buprenorphine) into an agent that internalizes the receptor rather than producing a hypothesized downstream regulation? Is it possible that a certain level of afferent input activating ionotropic or metabotropic receptors, or the transport of trophic factors, leads to a change in cellular phosphorylating function that results in stabilization (through the mechanism of internalization) in the rate or degree to which the receptor will internalize for any given degree of receptor downregulation? Whatever the case, the above reasoning suggests that the characteristics of the tolerance observed after administration of each of the two classes of mu agonists may have distinct properties. Which one is better remains to be seen.

CONCLUSIONS

The phenomenon of tolerance is complex and dynamic. The comments made by the authors of these articles reflect the exciting discussions held in St John’s.

REFERENCES

2. de Leon-Casasola OA, Parker BM, Lema MJ, Groth RI, Orsini-Fuentes J. Epidural analgesia versus intravenous patient-