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Commentary

The central questions in pain perception may be peripheral

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Pain and its control are still a daunting problem. Although drugs such as morphine have been around since ancient times and recent years have seen the introduction of a number of additional painkillers, many gaps remain in our ability to control the suffering of pain. Pain is an emotional response that is triggered by nociceptive inputs from the periphery that are transmitted centrally to the spinal cord and then ascend through the paleospinothalamic tracts to limbic structures. The complexity of pain perception reflects the presence of both nociceptive and antinociceptive systems that modulate nociceptive input at many levels of the neuraxis (1). Descending brainstem systems influence nociceptive stimuli spinally while other systems modulate nociceptive input supraspinally. The opioid peptides and their receptors comprise the most efficacious antinociceptive systems, effectively relieving the suffering component of pain without interfering with basic sensation (2). They comprise a complex collection of many discrete, but interacting, receptor systems. All the various classes of opioid receptors and the numerous opioid peptides have been implicated in pain modulation.

In contrast, blocking nociceptive pathways pharmacologically has proven more difficult. Substance P has long been considered an important peptide in the transmission of nociceptive input, working at the level of the dorsal horn of the spinal cord (3). Contained within small diameter fibers of peripheral nerves, substance P is released by noxious stimuli such as capsaicin, an action that can be blocked by opioids (3). However, the role of substance P in pain perception remains somewhat unclear. Substance P antagonists typically have not been very effective as analgesics (4). Disruption of the neurokinin-1 (NK-1) receptor gene that mediates substance P actions gives mixed results (5). The knockout mice did not display the intensity encoding in the electromyographic activity associated with nociceptive stimuli seen in the wild-type controls and knockout animals did not show any "wind up," a potentiation of nociceptive responses with repeated treatments. These results are consistent with earlier studies implicating a role for substance P in these actions. There also was a modest reduction in the second phase of the formalin test, implying that substance P likely influences nociceptive transmission of this type of pain. However, the loss of the NK-1 receptor had no effect on nociceptive thresholds using several other thermal and nonthermal stimuli, and morphine analgesia was unaffected. One problem with knockout mice is the potential of compensatory changes during development. An alternative approach is the recently reported selective ablation of neurons containing substance P receptors in rats by a targeted cytotoxin (6). Loss of neurons containing substance P receptors decreases the hyperalgesic actions of capsaicin. Yet, nociceptive thresholds to heat stimuli in these animals remain intact, results consistent with those seen in the knockouts.

The paper in this issue of the *Proceedings* by Inoue *et al*. (7) presents novel insights into the actions of substance P and the recently described peptide orphanin FQ/nociceptin (OFQ/N; Fig. 1) (8, 9), the endogenous ligand for the cloned orphan opioid receptor (ORL_1) (10–12). Using an innovative paradigm exploring peripheral drug actions, they find that intraplantar OFQ/N is profoundly nociceptive at doses far lower than any other described peptide. Antisense approaches confirmed that these OFQ/N actions are mediated through the ORL_1 receptor, which induces the release of peripheral substance P. Intraplantar tachykinin antagonists block the OFQ/N responses, and the responses are not seen in mice with a targeted mutation of the tachykinin gene that renders them unable to produce either substance P or substance K. Finally, they present evidence implicating a role for phospholipase C and IP_3 as intermediaries in these actions.

Uncovering these mechanisms offers a number of new approaches toward the development of pain therapies that can be exploited. The potential of OFQ/N antagonists is obvious, as are other agents that can interfere with this pathway. Equally important, this work also offers a number of insights into the basic physiology of sensory processing. The ability of OFQ/N to induce the release of substance P and activate the nociceptive cascade extends our knowledge of these systems. Conceptually, however, the site of these actions is even more intriguing. Central OFQ/N and substance P actions have been extensively studied and their importance clearly established. Yet Inoue *et al*. (7) suggest a far greater role for peripheral processing than previously appreciated. Peripheral actions in nociceptive processing have been well established pharmacologically. For example, peripheral opioid actions interact synergistically with central opioid mechanisms to relieve pain (13). However, carrying out these studies has been technically difficult and the molecular mechanisms underlying these effects remain poorly understood. Inoue *et al*. demonstrate that OFQ/N acts peripherally to release substance P (Fig. 2), which is then responsible for transmitting nociceptive stimuli. The evidence for this model seems quite strong, although additional studies are needed to extend and confirm these initial observations.

Inoue *et al*. clearly document that OFQ/N is an extraordinarily potent nociceptive peptides, acting at doses 10,000-fold lower than substance P and 1,000-fold lower than bradykinin. As Inoue *et al*. point out, it remains to be determined whether OFQ/N is released from peripheral nerve terminals or nonneuronal cells. It will be equally important to determine the stimuli leading to the release of OFQ/N. Connecting these peripheral actions to central effects also needs to be explored. Does OFQ/N release substance P both peripherally and centrally? Are other neurotransmitters important in these pathways? Finally, are these OFQ/N and substance P interactions associated with specific nociceptive stimuli or are they a general mechanism in nociceptive processing? These are all important questions that now can be addressed. Overall, the current observations provide a new focus in the study of nociceptive processing.

The companion to this commentary begins on page 10949.

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OFQ/N Phe-Gly-Gly-Phe-Thr-Gly-Ala-***Arg-Lys***-Ser-Ala-***Arg-Lys***-Leu-Ala-Asp-Glu
OFQ/N(1-11) Phe-Gly-Gly-Phe-Thr-Gly-Ala-***Arg-Lys***-Ser-Ala
OFQ/N(1-7) Phe-Gly-Gly-Phe-Thr-Gly-Ala

FIG. 1. Structure of orphanin FQ/nociceptin (OFQ/N). Note the pairs of basic amino acids, denoted in italics. They raise the possibility of additional processing to yield the truncated derivatives OFQ/N(1–11) and OFQ/N(1–7). Although the pharmacology of these fragments differs from OFQ/N, their physiological significance has not yet been established.

Earlier studies indicate that the pharmacology of OFQ/N is quite complex (11, 12). Despite its nociceptive actions (8, 9, 14, 15), higher OFQ/N doses are analgesic, both peripherally and centrally (14, 16–19). Furthermore, these analgesic actions also are mediated through an ORL_1 receptor. These analgesic responses can be blocked by antisense probes specific for this receptor and they are lost in mice in which the ORL_1 gene has been disrupted. Thus, OFQ/N has opposite actions depending on the dose and paradigm. Dose-dependent biphasic responses with their "U"-shaped curves often are associated with multiple receptor classes, and this possibility remains to be explored. ORL_1 receptor splice variants have been reported (20–22), and traditional receptor binding studies also have raised the suggestion of binding site heterogeneity, but their physiological significance has not been established. Alternatively, the differences in OFQ/N actions may reflect the generation of truncated OFQ/N peptides with differing binding selectivities and activities. As indicated by its sequence (Fig. 1), OFQ/N has two pairs of basic amino acids, raising the possibility of additional processing to OFQ/N(1–11) and OFQ/N(1–7). Although OFQ/N(1–11) shares the analgesic actions of OFQ/N, it does not display the prominent hyperalgesia and anti-opioid activity of its parent peptide (14). It will be interesting to see further exploration of these opposing OFQ/N systems.

In conclusion, the work by Inoue *et al*. fundamentally changes the way we will look at the problem of nociception, illustrating the importance of peripheral processing of nociceptive stimuli. The importance of peripheral sites of action with new transmitters opens the possibility of novel approaches to pain management. New drug targets and a peripheral site of action may lead to analgesics lacking many of the side effects seen with systemic drugs.

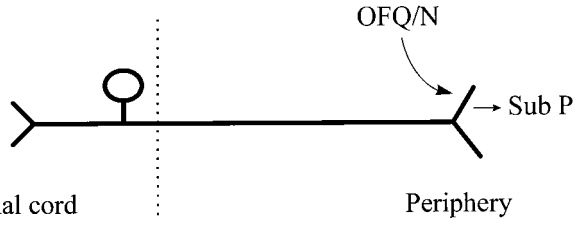

FIG. 2. Schematic of the actions of OFQ/N on the release of substance P. The studies described in the paper by Inoue *et al.* (see ref. 7) imply that OFQ/N acts peripherally to release substance P, which then initiates the nociceptive cascade. The source of OFQ/N remains unknown, as does the site of action of the released substance P.

1. Basbaum, A. I. & Fields, H. L. (1984) *Annu. Rev. Neurosci.* **7,** 309–338.
2. Reisine, T. & Pasternak, G. W. (1996) in *Opioid Analgesics and Antagonists*. eds. Hardman, J. G. & Limbird, L. E. (McGraw-Hill, New York), pp. 521–556.
3. Jessell, T. M. & Iversen, L. L. (1977) *Nature (London)* **268,** 549–551.
4. Giros, B., Jaber, M., Jones, S. R., Wightman, R. M. & Caron, M. G. (1996) *Nature (London)* **379,** 606–612.
5. De Felipe, C., Herrero, J. F., O'Brien, J. A., Palmer, J. A., Doyle, C. A., Smith, A. J. H., Laird, J. M. A., Belmonte, C., Cervero, F. & Hunt, S. P. (1998) *Nature (London)* **392,** 394–397.
6. Mantyh, P. W., Rogers, S. D., Honore, P., Allen, B. J., Ghilardi, J. R., Li, J., Daughters, R. S., Lappi, D. A., Wiley, R. G. & Simone, D. A. (1997) *Science* **278,** 275–279.
7. Inoue, M., Kobayashi, M., Kozaki, S., Zimmer, A. & Ueda, H. (1998) *Proc. Natl. Acad. Sci. USA* **95,** 10949–10953.
8. Meunier, J. C., Mollereau, C., Toll, L., Suaudeau, C., Moisand, C., Alvinerie, P., Butour, J. L., Guillemot, J. C., Ferrara, P., Monsarrat, B., *et al*. (1995) *Nature (London)* **377,** 532–535.
9. Reinscheid, R. K., Nothacker, H. P., Bourson, A., Ardati, A., Henningsen, R. A., Bunzow, J. R., Grandy, D. K., Langen, H., Monsma, F. J. & Civelli, O. (1995) *Science* **270,** 792–794.
10. Uhl, G. R., Childers, S. & Pasternak, G. W. (1994) *Trends Neurosci.* **17,** 89–93.
11. Pasternak, G. W. & Standifer, K. M. (1995) *Trends Pharmacol. Sci.* **16,** 344–350.
12. Henderson, G. & McKnight, A. T. (1997) *Trends Pharmacol. Sci.* **18,** 293–300.
13. Kolesnikov, Y. A., Jain, S., Wilson, R. & Pasternak, G. W. (1996) *J. Pharmacol. Exp. Ther.* **279,** 502–506.
14. Rossi, G., Leventhal, L., Boland, E. & Pasternak, G. W. (1997) *J. Pharmacol. Exp. Ther.* **282,** 858–865.
15. Grisel, J. E., Mogil, J. S., Belknap, J. K. & Grandy, D. K. (1996) *NeuroReport* **7,** 2125–2129.
16. Rossi, G. C., Leventhal, L. & Pasternak, G. W. (1996) *Eur. J. Pharmacol.* **311,** R7–R8.
17. Tian, J. H., Xu, W., Fang, Y., Mogil, J. S., Grisel, J. E., Grandy, D. K. & Han, J. S. (1997) *Br. J. Pharmacol.* **120,** 676–680.
18. King, M. A., Rossi, G. C., Chang, A. H., Williams, L. & Pasternak, G. W. (1997) *Neurosci. Lett.* **223,** 113–116.
19. Xu, X. J., Hao, J. X. & Wiesenfeld-Hallin, Z. (1996) *NeuroReport* **7,** 2092–2094.
20. Wick, M. J., Minnerath, S. R., Roy, S., Ramakrishnan, S. & Loh, H. H. (1995) *Mol. Brain Res.* **32,** 342–347.
21. Halford, W. P., Gebhardt, B. M. & Carr, D. J. J. (1995) *J. Neuroimmunol.* **59,** 91–101.
22. Wang, J. B., Johnson, P. S., Imai, Y., Persico, A. M., Ozenberger, B. A., Eppler, C. M. & Uhl, G. R. (1994) *FEBS Lett.* **348,** 75–79.