tors and triggered pain through local endothelin-A (ET_A) nociceptors. ET_B receptor activation has been shown to induce the release of β-endorphin from keratinocytes, in which the colocalization of ET_B receptors with β-endorphin has been confirmed in rat plantar hind paw epidermis adjacent to nociceptive sensory terminals, and to result in the activation of GIRK channels linked to opioid receptors on nociceptors [65]. μ- and δ-opioid receptors have been shown using GIRK2 knockout mice to significantly contribute to attenuation of ET-1-induced pain, and activation of channels with GIRK2 subunit was shown to be crucial to ET-1-mediated analgesia [65]. The results of this study indicated the existence of an intrinsic feedback mechanism that controls peripheral pain through the action of β-endorphin secreted in the skin [66] and highlighted the possibility that peripheral GIRK channels and ET_B receptors may be important and useful targets for the treatment of pain.

4.4 OTHER PERIPHERAL POTASSIUM CHANNEL TARGETS FOR ANALGESIA

4.4.1 K_{ir} Channels

To date, many studies have suggested the involvement of other K_{ir} channel subunits in addition to GIRK subunits in analgesia or pain. $K_{ir}6.x$ (K_{ATP}) channels, among the K_{ir} channels, have been suggested to be important channel targets for central and peripheral analgesia, although K_{ATP} channels in pancreatic β-cells are well known to link glucose metabolism to insulin release [67]. Functional K_{ATP} channels are composed of four $K_{ir}6$ subunits and four sulfonylurea receptors (SUR1, SUR2A, or SUR2B, depending on the tissue) that regulate the opening and closing of $K_{ir}6$ channels [67]. The four $K_{ir}6$ subunits form a channel pore that is surrounded by four sulfonylurea receptors. The activity of K_{ATP} channels is regulated not only by intracellular adenosine triphosphate (ATP) concentration but also by G protein βγ-subunits through activation of several G protein-coupled receptors (GPCRs), such as α_2-adrenergic, somatostatin, adenosine, and opioid receptors [68]. Accordingly, activation of these receptors by their agonists is antagonized by K_{ATP} channel blockers in tests of analgesia.

Ocaña and Baeyens showed that intracerebroventricular (i.c.v.) pretreatment with the K_{ATP} channel blockers gliquidone, glipizide, glibenclamide, and tolbutamide (antidiabetic sulfonylureas) antagonized morphine-induced analgesia in the tail-flick test in mice, whereas these blockers did not antagonize the analgesic effect induced by U-50,488H (trans-[±]-3,4-dichloro-*N*-methyl-*N*-[2(1-pirrolidynyl)cyclohexyl]benzeneacetamide methanesulfonate salt), a κ-opioid receptor agonist [69]. The spinally mediated analgesic effect of intrathecally (i.t.) injected morphine is also antagonized by i.t. glibenclamide administration in different rat models of pain [70]. Moreover, the analgesia induced by epidural administration of morphine in a tail-flick test in rats was potentiated by epidural administration of the K_{ATP} channel openers nicorandil

and levcromakalim, and this potentiation was abolished by glibenclamide [71]. Rodrigues and Duarte have shown that glibenclamide and tolbutamide injected subcutaneously (s.c.) into the rat hind paw antagonized the peripheral antinociception induced by morphine administered s.c. into the hind paw of hyperalgesic rats [72]. These results suggest that K_{ATP} channels are involved in morphine-induced analgesia through μ- and δ-opioid receptors, possibly at supraspinal, spinal, and peripheral levels.

K_{ATP} channels have been shown to be involved in analgesia induced by other GPCR agonists. For example, i.c.v. or i.t. glibenclamide administration antagonized the antinociception induced by the α_2-adrenoceptor agonists clonidine (i.c.v. and i.t.) and tizanidine (i.c.v.) [73,74], suggesting that K_{ATP} channel blockers antagonize both supraspinal and spinal antinociception induced by α_2-adrenoceptor agonists. Similarly, the antinociception induced by i.c.v. administration of the adenosine A_1 receptor agonist R-PIA ([-]-N6-[2-phenylisopropyl]-adenosine), the muscarinic receptor agonist pilocarpine, and several 5-HT_{1A} receptor agonists was antagonized by gliquidone in the tail-flick and hot-plate tests in mice [73,75,76].

Furthermore, several studies have suggested the involvement of K_{ATP} channels in the analgesic effects induced by nonsteroidal anti-inflammatory drugs (NSAIDs) [77], activation of the nitric oxide (NO)/cyclic guanosine monophosphate (cGMP) pathway by sodium nitroprusside or dibutyryl cGMP [78], tricyclic antidepressants such as amitriptyline and clomipramine [79], H_1-antihistamines [80], and the antiepileptic gabapentin [81].

In addition, the involvement of $K_{ir}4.1$ in pain was suggested in a recent study in which specific silencing of Kir4.1 using RNA interference in the rat trigeminal ganglion led to spontaneous and evoked facial painlike behavior in freely moving rats [82].

In summary, K_{ATP} channels may be involved in analgesic effects induced not only by the mediation of GPCRs but also by many other drugs at supraspinal, spinal, and even peripheral levels [77,78].

4.4.2 K_V Channels

Several studies have demonstrated the involvement of K_V channels in central or peripheral analgesia. Galeotti et al. showed that i.c.v. administration of an antisense oligodeoxyribonucleotide (aODN) for the $K_V1.1$ gene inhibited the antinociceptive effects of morphine, the gamma-aminobutyric acid B ($GABA_B$) receptor agonist baclofen, clonidine, and the α_2-adrenoceptor agonist guanabenz in the mouse hot-plate test [83,84], suggesting the involvement of the $K_V1.1$ subunits in central analgesia mediated by opioid, $GABA_B$, and α_2-adrenergic receptors. The involvement of the $K_V1.1$ subunits in central opioid analgesia has been further corroborated by evidence indicating that morphine-induced antinociception in $K_V1.1$ null mutant mice is blunted [85]. Additionally, i.c.v. injection of the aODN for the $K_V1.1$ subunits dose-dependently inhibited clomipramine- and amitriptyline-induced antinociception in the mouse hot-plate test, suggesting the involvement of the $K_V1.1$ subunits in tricyclic

antidepressant-induced analgesia [83,86]. In addition to the $K_V1.1$ subunits, Finnegan et al. examined the effect of μ-opioid receptor stimulation on the inhibitory and excitatory synaptic inputs to basolateral amygdala (BLA) neurons that are projected to the central nucleus of the amygdala (CeA) and considered to be important for opioid analgesia. These researchers found that two K_V channel blockers of dendrotoxin-K ($K_V1.1$) and tityustoxin-Kα ($K_V1.2$) attenuated the inhibitory effect of the μ-opioid receptor agonist D-Ala^2,*N*-Me-Phe^4,Gly^5-ol-enkephalin (DAMGO) on miniature inhibitory postsynaptic currents (mIPSCs) [87].

With regard to K_V channel subunits other than K_V1, forms of pain hypersensitivity that are dependent on extracellular signal-regulated kinases (ERKs, which mediate central sensitization during inflammatory pain in spinal cord dorsal horn neurons) were absent in $K_V4.2$ knockout mice compared with wild-type littermates [88]. This result suggests that the $K_V4.2$ channel subunit is a downstream target of ERK in the spinal cord and plays a crucial role in pain plasticity. Furthermore, the neuronal K_V7 channel opener retigabine ($K_V7.2$–7.5, also known as KCNQ2-5 subunits) significantly attenuated mechanical hypersensitivity in response to pinprick stimulation of an injured hind paw in the rat chronic constriction injury model and spared nerve models of neuropathic pain [89]. Retigabine also inhibited carrageenan-induced hyperalgesia in a rat model of chronic pain, an effect that was reversed by the KCNQ channel blocker XE991 (10,10-bis[4-pyridinylmethyl]-9[10H]-anthracenone) [90]. These two studies indicated that K_V7 channels may play a key role in nociceptive sensory systems. In addition, retigabine suppressed capsaicin-induced licking as an index of visceral pain behavior and prolonged the latency to first lick in mice [91], providing evidence that activation of K_V7 channels also plays an inhibitory role in the visceral pain pathway.

In summary, $K_V1.1$, $K_V1.2$, $K_V4.2$, and K_V7 ($K_V7.2$–7.5) channel subunits have been shown to be involved in antinociception in several pain models and could be potential analgesic targets.

4.4.3 K_{Ca} Channels

K_{Ca} channels have also been shown to be involved in analgesia. The SK channel blocker apamin (i.t.) completely blocked [2-D-penicillamine, 5-D-penicillamine]-enkephalin (DPDPE)-induced antinociception in mouse tail-flick tests, suggesting the involvement of the SK channel in the analgesia mediated by the δ-opioid receptor [92]. Apamin (i.t.) also antagonized the antinociception induced by i.t. administration of the cannabinoids Δ^9-THC (tetrahydrocannabinol), Δ^8-THC, and CP 55,940 ([−]-cis-3-[2-hydroxy-4(1,1-dimethylheptyl)phenyl]-trans-4-[3-hydroxypropyl]cyclohexanol) in mouse tail-flick tests, although apamin (i.c.v.) failed to block the antinociceptive effects of these cannabinoids (i.c.v.), suggesting the involvement of the SK channel in the analgesia mediated by cannabinoid receptors at the spinal level but not at the supraspinal level [93]. Furthermore, several reports have suggested the involvement of SK channels in the analgesic effects induced by the

administration of i.c.v. tricyclic antidepressants [79], i.c.v. H_1-antihistamines (e.g., pyrilamine, diphenhydramine, and promethazine) [80], and i.t. gabapentin [81].

Yamazumi et al. demonstrated that antinociception induced by i.t. clonidine or bethanechol, a muscarinic receptor agonist, in rat tail-flick tests was partially antagonized by i.t. administration of the BK channel blocker charybdotoxin [74], suggesting the involvement of the BK channel in analgesia mediated by the α_2-adrenoceptor and muscarinic receptor. Additionally, the involvement of BK channels in the analgesic effects induced by i.t. gabapentin has also been demonstrated [81].

Although little is known about the involvement of IK channels in analgesia or pain, the IK ($K_{Ca}3.1$) channel inhibitor clotrimazole prevented the antinociceptive effects of the peroxisome proliferator-activated receptor-α (PPAR-α) agonists GW7647 (2-[4-(2-[1-cyclohexanebutyl-3-cyclohexylureido]ethyl) phenylthio]-2-methylpropionic acid) and palmitoylethanolamide (PEA) in the formalin test in mice, suggesting that IK channels mediate PPAR-α antinociception [94].

In summary, K_{Ca} channels, especially SK and BK channels, appear to play a role in the analgesic effects mediated by some GPCRs at the spinal level, as well as those mediated by several types of drugs at the supraspinal or spinal levels.

4.4.4 K_{2P} Channels

Only a limited number of studies have investigated the involvement of K_{2P} channels in analgesia, although these channels are widely expressed in central and peripheral tissues, including dorsal root ganglia [95]. Interestingly, K_{2P} channels are sensitive to some types of volatile general anesthetics. TRESK ($K_{2P}18.1$) is activated by clinical concentrations of isoflurane, halothane, sevoflurane, and desflurane [96]. TREK-1 ($K_{2P}2.1$) and TREK-2 ($K_{2P}10.1$) are also opened by chloroform, diethyl ether, halothane, and isoflurane [97,98]. TASK-1 ($K_{2P}3.1$) is activated by halothane and isoflurane, and TASK-2 ($K_{2P}5.1$) is activated by halothane, isoflurane, and chloroform [97]. Indeed, TASK-1 and TASK-3 ($K_{2P}9.1$) knockout mice are less sensitive to the anesthetic effects of halothane and isoflurane than their wild-type littermates [99,100], and TASK-1 knockout mice display increased sensitivity to thermal nociception and reduced analgesic effects of s.c. administration of the cannabinoid agonist WIN55212-2 in the hot-plate test [99]. TREK-1 ($K_{2P}2.1$) knockout mice are resistant to anesthesia induced by volatile anesthetics and more sensitive to painful heat sensations near the threshold between anoxious warmth and painful heat [101,102]. TRAAK ($K_{2P}4.1$) is structurally and functionally similar to TREK and is insensitive to volatile anesthetics. In contrast, halothane inhibits TWIK, THIK, and TALK [97]. These studies indicate that activation of some K_{2P} channels by inhalational anesthetics might be involved in some of the mechanisms of general anesthesia and pain relief. Although further studies will be

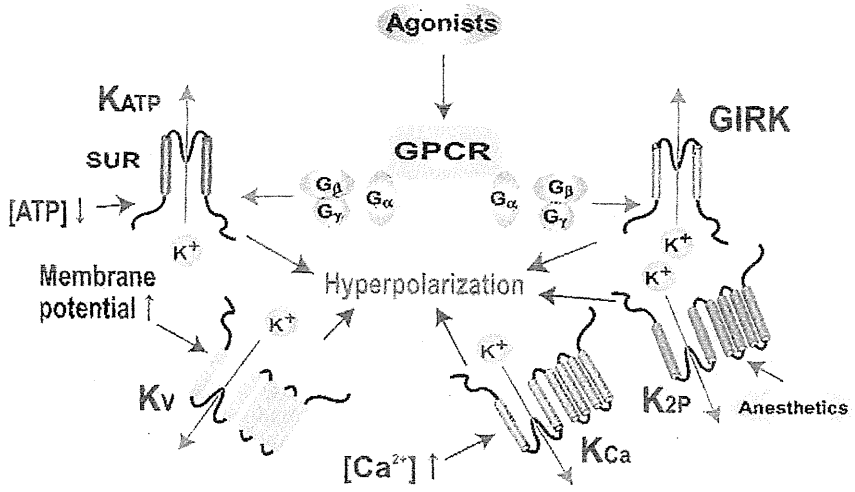

FIGURE 4.3. Schematic illustration of peripheral endogenous analgesia, focusing on major potassium channels, induced by hyperpolarization of membrane potential in the nerve terminus of the peripheral sensory neuron. GPCR, G protein-coupled receptor; SUR, sulfonylurea receptor. See color insert.

needed, K_{2P} channel activators may also be candidates as potent therapeutic analgesics.

4.5 CONCLUDING REMARKS

Figure 4.3 shows a schematic illustration of the peripheral endogenous analgesia mediated by the major potassium channels. GIRK channels and K_{ATP} channels appear to play the most important role in central and peripheral analgesia. However, increasing evidence suggests the involvement of other subunits in analgesia or pain. Far more potassium channel subunits may contribute to the mechanisms of analgesia or pain transduction than the currently known channels. The development of therapeutic drugs targeting such potassium channels may lead to effective pain treatment in the future.

REFERENCES

1. Papazian, D.M., Schwarz, T.L., Tempel, B.L., Jan, Y.N., Jan, L.Y. (1987). Cloning of genomic and complementary DNA from Shaker, a putative potassium channel gene from *Drosophila*. *Science* 237:749–753.

2. Eyre, T.A, Ducluzeau, F., Sneddon, T.P., Povey, S., Bruford, E.A., Lush, M.J. (2006). The HUGO Gene Nomenclature Database, 2006 updates. *Nucleic Acids Res* 34(Database issue):D319–D321.
3. Catterall, W.A., Chandy, K.G., Clapham, D.E., Gutman, G.A., Hofmann, F., Harmar, A.J., Abernethy, D.R., Spedding, M. (2003). International Union of Pharmacology: approaches to the nomenclature of voltage-gated ion channels. *Pharmacol Rev* 55:573–574.
4. Tamnra, K., Dudley, J., Nei, M., Kumar, S. (2007). MEGA4: Molecular Evolntionary Genetics Analysis (MEGA) software version 4.0. *Mol Biol Evol* 24:1596–1599.
5. Anderson, P.A, Greenberg, R.M. (2001). Phylogeny of ion channels: clues to structure and function. *Comp Biochem Physiol B Biochem Mol Biol* 129:17–28.
6. Gntman, G.A., Chandy, K.G., Grissmer, S., Lazdunski, M., McKinnon, D., Pardo, L.A., Robertson, G.A., Rudy, B., Sanguinetti, M.C., Stühmer, W., Wang, X. (2005). International Union of Pharmacology. LIII. Nomenclature and molecular relationships of voltage-gated potassium channels. *Pharmacol Rev* 57:473–508.
7. Yellen, G. (2002). The voltage-gated potassium channels and their relatives. *Nature* 419:35–42.
8. Kubo, Y., Reuveny, E., Slesinger, P.A., Jan, Y.N., Jan, L.Y. (1993). Primary structure and functional expression of a rat G-protein-coupled muscarinic potassium channel. *Nature* 364:802–806.
9. Reimann, F., Ashcroft, F.M. (1999). Inwardly rectifying potassium channels. *Curr Opin Cell Biol* 11:503–508.
10. Ho, K., Nichols, C.G., Lederer, W.J., Lytton, J., Vassilev, P.M., Kanazirska, M.V., Hebert, S.C. (1993). Cloning and expression of an inwardly rectifying ATP-regulated potassium channel. *Nature* 362:31–38.
11. Alexander, S.P.H., Mathie, A., Peters, J.A. (2008). Guide to Receptors and Channels (GRAC), 3rd edition. *Br J Pharmacol* 153(Suppl. 2):S1–S209.
12. Kubo, Y., Adelman, J.P., Clapham, D.E., Jan, L.Y., Karschin, A., Kurachi, Y., Lazdunski, M., Nichols, C.G., Seino, S., Vandenberg, C.A. (2005). International Union of Pharmacology. LIV. Nomenclature and molecular relationships of inwardly rectifying potassium channels. *Pharmacol Rev* 57:509–526.
13. Vergara, C., Latorre, R., Marrion, N.V., Adelman, J.P. (1998). Calcium-activated potassium channels. *Curr Opin Neurobiol* 8:321–329.
14. Roosild, T.P., Lê, K.T., Choe, S. (2004). Cytoplasmic gatekeepers of K^+-channel flux: a structural perspective. *Trends Biochem Sci* 29:39–45.
15. Ocaña, M., Cendán, C.M., Cobos, E.J., Entrena, J.M., Baeyens, J.M. (2004). Potassium channels and pain: present realities and future opportunities. *Eur J Pharmacol* 500:203–219.
16. Wei, A.D., Gutman, G.A., Aldrich, R., Chandy, K.G., Grissmer, S., Wulff, H. (2005). International Union of Pharmacology. LII. Nomenclature and molecular relationships of calcium-activated potassium channels. *Pharmacol Rev* 57:463–472.
17. Goldstein, S.A., Bayliss, D.A., Kim, D., Lesage, F., Plant, L.D., Rajan, S. (2005). International Union of Pharmacology. LV. Nomenclature and molecular relationships of two-P potassium channels. *Pharmacol Rev* 57:527–540.
18. Vaughn, J., Wolford, J.K., Prochazka, M., Permana, P.A. (2000). Genomic structure and expression of human *KCNJ9* (*Kir3.3IGIRK3*). *Biochem Biophys Res Commun* 274:302–309.

19. Corey, S., Clapham, D.E. (1998). Identification of native atrial G-protein-regulated inwardly rectifying K^+ (GIRK4) channel homomultimers. *J Biol Chem* 273:27499–27504.
20. Marker, C.L., Stoffel, M., Wickman, K. (2004). Spinal G-protein-gated K^+ channels formed by GIRK1 and GIRK2 subunits modulate thermal nociception and contribute to morphine analgesia. *J Neurosci* 24:2806–2812.
21. Marker, C.L., Lujan, R., Loh, H.H., Wickman, K. (2005). Spinal G-protein-gated potassium channels contribute in a dose-dependent manner to the analgesic effect of μ- and δ- but not κ-opioids. *J Neurosci* 25:3551–3559.
22. Jelacic, T.M., Kennedy, M.E., Wickman, K., Clapham, D.E. (2000). Functional and biochemical evidence for G-protein-gated inwardly rectifying K^+ (GIRK) channels composed of GIRK2 and GIRK3. *J Biol Chem* 275:36211–36216.
23. Kobayashi, T., Ikeda, K., Ichikawa, T., Abe, S., Togashi, S., Kumanishi, T. (1995). Molecular cloning of a mouse G-protein-activated K^+ channel (mGIRK1) and distinct distributions of three GIRK (GIRK1, 2 and 3) mRNAs in mouse brain. *Biochem Biophys Res Commun* 208:1166–1173.
24. Wickman, K., Karschin, C., Karschin, A., Picciotto, M.R., Clapham, D.E. (2000). Brain localization and behavioral impact of the G-protein-gated K^+ channel subunit GIRK4. *J Neurosci* 20:5608–5615.
25. Kofuji, P., Davidson, N., Lester, H.A. (1995). Evidence that neuronal G-protein-gated inwardly rectifying K^+ channels are activated by $G\beta\gamma$ subunits and function as heteromultimers. *Proc Natl Acad Sci U S A* 92:6542–6546.
26. Feruandez-Fernandez, J.M., Wanaverbecq, N., Halley, P., Caulfield, M.P., Brown, D.A. (1999). Selective activation of heterologously expressed G protein-gated K^+ channels by M_2 muscarinic receptors in rat sympathetic neurones. *J Physiol* 515(Pt 3):631–637.
27. Pillai, G., Brown, N.A., McAllister, G., Milligan, G., Seabrook, G.R. (1998). Human D_2 and D_3 dopamine receptors couple through $\beta\gamma$ G-protein subunits to inwardly rectifying K^+ channels (GIRK1) in a *Xenopus* oocyte expression system: selective antagonism by L-741,626 and L-745,870 respectively. *Neuropharmacology* 37:983–987.
28. Bünemann, M., Bücheler, M.M., Philipp, M., Lohse, M.J., Hein, L. (2001). Activation and deactivation kinetics of α_{2A}- and α_{2C}-adrenergic receptor-activated G protein-activated inwardly rectifying K^+ channel currents. *J Biol Chem* 276:47512–47517.
29. Saugstad, J.A., Segerson, T.P., Westbrook, G.L. (1996). Metabotropic glutamate receptors activate G-protein-coupled inwardly rectifying potassium channels in *Xenopus* oocytes. *J Neurosci* 16:5979–5985.
30. Kreienkamp, H.J., Hönck, H.H., Richter, D. (1997). Coupling of rat somatostatin receptor subtypes to a G-protein gated inwardly rectifying potassium channel (GIRK1). *FEBS Lett* 419:92–94.
31. Ho, B.Y., Uezono, Y., Takada, S., Takase, I., Izumi, F. (1999). Coupling of the expressed cannabinoid CB1 and CB2 receptors to phospholipase C and G protein-coupled inwardly rectifying K^+ channels. *Receptors Channels* 6:363–374.
32. McAllister, S.D., Griffin, G., Satin, L.S., Abood, M.E. (1999). Cannabinoid receptors can activate and inhibit G protein-coupled inwardly rectifying potassium channels in a *Xenopus* oocyte expression system. *J Pharmacol Exp Ther* 291:618–626.

33. Ikeda, K., Kobayashi, K., Kobayashi, T., Ichikawa, T., Kumanishi, T., Kishida, H., Yano, R., Manabe, T. (1997). Functional coupling of the nociceptin/orphanin FQ receptor with the G-protein-activated K^+ (GIRK) channel. *Brain Res Mol Brain Res* 45:117–126.

34. Kobayashi, T., Ikeda, K., Kumanishi, T. (2002). Functional characterization of an endogenous *Xenopus* oocyte adenosine receptor. *Br J Pharmacol* 135:313–322.

35. Ikeda, K., Kobayashi, T., Ichikawa, T., Usui, H., Kumanishi, T. (1995). Functional couplings of the δ- and the κ-opioid receptors with the G-protein-activated K^+ channel. *Biochem Biophys Res Commun* 208:302–308.

36. Ikeda, K., Kobayashi, T., Kumanishi, T., Niki, H., Yano, R. (2000). Involvement of G-protein-activated inwardly rectifying K (GIRK) channels in opioid-induced analgesia. *Neurosci Res* 38:113–116.

37. Ikeda, K., Yoshii, M., Sora, I., Kobayashi, T. (2003). Opioid receptor coupling to GIRK channels: in vitro studies using a *Xenopus* oocyte expression system and in vivo studies on *weaver* mutant mice. *Methods Mol Med* 84:53–64.

38. Patil, N., Cox, D.R., Bhat, D., Faham, M., Myers, R.M., Peterson, A.S. (1995). A potassium channel mutation in weaver mice implicates membrane excitability in granule cell differentiation. *Nat Genet* 11:126–129.

39. Navarro, B., Kennedy, M.E., Velimirovic, B., Bhat, D., Peterson, A.S., Clapham, D.E. (1996). Nonselective and $G_{\beta\gamma}$-insensitive weaver K^+ channels. *Science* 272: 1950–1953.

40. Tong, Y., Wei, J., Zhang, S., Strong, J.A., Dlouhy, S.R., Hodes, M.E., Ghetti, B., Yu, L. (1996). The weaver mutation changes the ion selectivity of the affected inwardly rectifying potassium channel GIRK2. *FEBS Lett* 390:63–68.

41. Rakic, P., Sidman, R.L. (1973). Weaver mutant mouse cerebellum: defective neuronal migration secondary to abnormality of Bergmann glia. *Proc Natl Acad Sci U S A* 70:240–244.

42. Triarhou, L.C., Norton, J., Ghetti, B. (1988). Mesencephalic dopamine cell deficit involves areas A8, A9 and A10 in weaver mutant mice. *Exp Brain Res* 70:256–265.

43. Kobayashi, T., Ikeda, K., Kojima, H., Niki, H., Yano, R., Yoshioka, T., Kumanishi, T. (1999). Ethanol opens G-protein-activated inwardly rectifying K^+ channels. *Nat Neurosci* 2:1091–1097.

44. Ikeda, K., Kobayashi, T., Kumanishi, T., Yano, R., Sora, I., Niki, H. (2002). Molecular mechanisms of analgesia induced by opioids and ethanol: is the GIRK channel one of the keys? *Neurosci Res* 44:121–131.

45. Blednov, Y.A., Stoffel, M., Alva, H., Harris, R.A. (2003). A pervasive mechanism for analgesia: activation of GIRK2 channels. *Proc Natl Acad Sci U S A* 100:277–282.

46. Marker, C.L., Cintora, S.C., Roman, M.I., Stoffel, M., Wickman, K. (2002). Hyperalgesia and blunted morphine analgesia in G protein-gated potassium channel subunit knockout mice. *Neuroreport* 13:2509–2513.

47. Mitrovic, I., Margeta-Mitrovic, M., Bader, S., Stoffel, M., Jan, L.Y., Basbaum, A.I. (2003). Contribution of GIRK2-mediated postsynaptic signaling to opiate and α_2-adrenergic analgesia and analgesic sex differences. *Proc Natl Acad Sci U S A* 100:271–276.

48. Takahashi, T., Kobayashi, T., Ozaki, M., Takamatsu, Y., Ogai, Y., Ohta, M., Yamamoto, H., Ikeda, K. (2006). G protein-activated inwardly rectifying K^+ channel inhibition and rescue of *weaver* mouse motor functions by antidepressants. *Neurosci Res* 54:104–111.
49. Smith, S.B., Marker, C.L., Perry, C., Liao, G., Sotocinal, S.G., Austin, J.S., Melmed, K., Clark, J.D., Peltz, G., Wickman, K., Mogil, J.S. (2008). Quantitative trait locus and computational mapping identifies *Kcnj9* (GIRK3) as a candidate gene affecting analgesia from multiple drug classes. *Pharmacogenet Genomics* 18:231–241.
50. Kobayashi, T., Ikeda, K. (2006). G protein-activated inwardly rectifying potassium channels as potential therapeutic targets. *Curr Pharm Des* 12:4513–4523.
51. Kobayashi, T., Washiyama, K., Ikeda, K. (2003). Inhibition of G protein-activated inwardly rectifying K^+ channels by fluoxetine (Prozac). *Br J Pharmacol* 138: 1119–1128.
52. Kobayashi, T., Washiyama, K., Ikeda, K. (2004). Inhibition of G protein-activated inwardly rectifying K^+ channels by various antidepressant drugs. *Neuropsychopharmacology* 29:1841–1851.
53. Kobayashi, T., Washiyama, K., Ikeda, K. (2004). Modulators of G protein-activated inwardly rectifying K^+ channels: potentially therapeutic agents for addictive drug users. *Ann N Y Acad Sci* 1025:590–594.
54. Kobayashi, T., Washiyama, K., Ikeda, K. (2006). Inhibition of G protein-activated inwardly rectifying K^+ channels by the antidepressant paroxetine. *J Pharmacol Sci* 102:278–287.
55. Kobayashi, T., Ikeda, K., Kumanishi, T. (1998). Effects of clozapine on the δ- and κ-opioid receptors and the G-protein-activated K^+ (GIRK) channel expressed in *Xenopus* oocytes. *Br J Pharmacol* 123:421–426.
56. Kobayashi, T., Ikeda, K., Kumanishi, T. (2000). Inhibition by various antipsychotic drugs of the G-protein-activated inwardly rectifying K^+ (GIRK) channels expressed in *Xenopus* oocytes. *Br J Pharmacol* 129:1716–1722.
57. Yamakura, T., Lewohl, J.M., Harris, R.A. (2001). Differential effects of general anesthetics on G protein-coupled inwardly rectifying and other potassium channels. *Anesthesiology* 95:144–153.
58. Weigl, L.G., Schreibmayer, W. (2001). G protein-gated inwardly rectifying potassium channels are targets for volatile anesthetics. *Mol Pharmacol* 60:282–289.
59. Zhou, W., Arrabit, C., Choe, S., Slesinger, P.A. (2001). Mechanism underlying bupivacaine inhibition of G protein-gated inwardly rectifying K^+ channels. *Proc Natl Acad Sci U S A* 98:6482–6487.
60. Lewohl, J.M., Wilson, W.R., Mayfield, R.D., Brozowski, S.J., Morrisett, R.A., Harris, R.A. (1999). G-protein-coupled inwardly rectifying potassium channels are targets of alcohol action. *Nat Neurosci* 2:1084–1090.
61. Jakob, R., Krieglstein, J. (1997). Influence of flupirtine on a G-protein coupled inwardly rectifying potassium current in hippocampal neurones. *Br J Pharmacol* 122:1333–1338.
62. Kelly, M.J., Rønnekleiv, O.K., Ibrahim, N., Lagrange, A.H., Wagner, E.J. (2002). Estrogen modulation of K^+ channel activity in hypothalamic neurons involved in the control of the reproductive axis. *Steroids* 67:447–456.
63. Zeidner, G., Sadja, R., Reuveny, E. (2001). Redox-dependent gating of G protein-coupled inwardly rectifying K^+ channels. *J Biol Chem* 276:35564–35570.

64. Nishizawa, D., Gajya, N., Ikeda, K. (forthcoming). Identification of selective agonists and antagonists to G protein-activated inwardly rectifying potassium channels: candidate medicines for drug dependence and pain. *Ann N Y Acad Sci* (in press).
65. Khodorova, A., Navarro, B., Jouaville, L.S., Murphy, J.E., Rice, F.L., Mazurkiewicz, J.E., Long-Woodward, D., Stoffel, M., Strichartz, G.R., Yukhananov, R., Davar, G. (2003). Endothelin-B receptor activation triggers an endogenous analgesic cascade at sites of peripheral injury. *Nat Med* 9:1055–1061.
66. Zanello, S.B., Jackson, D.M., Holick, M.F. (1999). An immunocytochemical approach to the study of β-endorphin production in human keratinocytes using confocal microscopy. *Ann N Y Acad Sci* 885:85–99.
67. Campbell, J.D., Sansom, M.S., Ashcroft, F.M. (2003). Potassium channel regulation. *EMBO Rep* 4:1038–1042.
68. Wada, Y., Yamashita, T., Imai, K., Miura, R., Takao, K., Nishi, M., Takeshima, H., Asano, T., Morishita, R., Nishizawa, K., Kokubun, S., Nukada, T. (2000). A region of the sulfonylurea receptor critical for a modulation of ATP-sensitive K^+ channels by G-protein βγ-subunits. *EMBO J* 19:4915–4925.
69. Ocaña, M., Baeyens, J.M. (1993). Differential effects of K^+ channel blockers on antinociception induced by α_2-adrenoceptor, $GABA_B$ and κ-opioid receptor agonists. *Br J Pharmacol* 110:1049–1054.
70. Kang, Y., Zhang, C., Qiao, J. (1997). Involvement of endogenous opioids and ATP-sensitive potassium channels in the mediation of carbachol-induced antinociception at the spinal level: a behavioral study in rats. *Brain Res* 761:342–346.
71. Asano, T., Dohi, S., Iida, H. (2000). Antinociceptive action of epidural K^+_{ATP} channel openers via interaction with morphine and an α_2-adrenergic agonist in rats. *Anesth Analg* 90:1146–1151.
72. Rodrigues, A.R., Duarte, I.D. (2000). The peripheral antinociceptive effect induced by morphine is associated with ATP-sensitive K^+ channels. *Br J Pharmacol* 129:110–114.
73. Raffa, R.B., Martinez, R.P. (1995). The "glibenclamide-shift" of centrally-acting antinociceptive agents in mice. *Brain Res* 677:277–282.
74. Yamazumi, I., Okuda, T., Koga, Y. (2001). Involvement of potassium channels in spinal antinociceptions induced by fentanyl, clonidine and bethanechol in rats. *Jpn J Pharmacol* 87:268–276.
75. Ocaña, M., Baeyens, J.M. (1994). Role of ATP-sensitive K^+ channels in antinociception induced by R-PIA, an adenosine A1 receptor agonist. *Naunyn Schmiedebergs Arch Pharmacol* 350:57–62.
76. Robles, L.I., Barrios, M., Del Pozo, E., Dordal, A., Baeyens, J.M. (1996). Effects of K^+ channel blockers and openers on antinociception indueed by agonists of $5\text{-}HT_{1A}$ receptors. *Eur J Pharmacol* 295:181–188.
77. Ortiz, M.I., Torres-López, J.E., Castañeda-Hernández, G., Rosas, R., Vidal-Cantú, G.C., Granados-Soto, V. (2002). Pharmacological evidence for the activation of K^+ channels by diclofenac. *Eur J Pharmacol* 438:85–91.
78. Alves, D.P., Soares, A.C., Francischi, J.N., Castro, M.S., Perez, A.C., Duarte, I.D. (2004). Additive antinociceptive effect of the combination of diazoxide, an activator of ATP-sensitive K^+ channels, and sodium nitroprusside and dibutyryl-cGMP. *Eur J Pharmacol* 489:59–65.

79. Galeotti, N., Ghelardini, C., Bartolini, A. (2001). Involvement of potassium channels in amitriptyline and clomipramine analgesia. *Neuropharmacology* 40:75–84.

80. Galeotti, N., Ghelardini, C., Bartolini, A. (1999). The role of potassium channels in antihistamine analgesia. *Neuropharmacology* 38:1893–1901.

81. Mixcoatl-Zecuatl, T., Medina-Santillán, R., Reyes-García, G., Vidal-Cantú, G.C., Granados-Soto, V. (2004). Effect of K^+ channel modulators on the antiallodynic effect of gabapentin. *Eur J Pharmacol* 484:201–208.

82. Vit, J.P., Ohara, P.T., Bhargava, A., Kelley, K., Jasmin, L. (2008). Silencing the Kir4.1 potassium channel subunit in satellite glial cells of the rat trigeminal ganglion results in pain-like behavior in the absence of nerve injury. *J Neurosci* 28:4161–4171.

83. Galeotti, N., Ghelardini, C., Papucci, L., Capaccioli, S., Quattrone, A., Bartolini, A. (1997). An antisense oligonucleotide on the mouse Shaker-like potassium channel Kv1.1 gene prevents antinociception induced by morphine and baclofen. *J Pharmacol Exp Ther* 281:941–949.

84. Galeotti, N., Ghelardini, C., Vinci, M.C., Bartolini, A. (1999). Role of potassium channels in the antinociception induced by agonists of α_2-adrenoceptors. *Br J Pharmacol* 126:1214–1220.

85. Clark, J.D., Tempel, B.L. (1998). Hyperalgesia in mice lacking the Kv1.1 potassium channel gene. *Neurosci Lett* 251:121–124.

86. Galeotti, N., Ghelardini, C., Capaccioli, S., Quattrone, A., Nicolin, A., Bartolini, A. (1997). Blockade of clomipramine and amitriptyline analgesia by an antisense oligonucleotide to mKv1.1, a mouse Shaker-like K^+ channel. *Eur J Pharmacol* 330:15–25.

87. Finnegan, T.F., Chen, S.R., Pan, H.L. (2006). μ Opioid receptor activation inhibits GABAergic inputs to basolateral amygdala neurons through Kv1.1/1.2 channels. *J Neurophysiol* 95:2032–2041.

88. Hu, H.J., Carrasquillo, Y., Karim, F., Jung, W.E., Nerbonne, J.M., Schwarz, T.L., Gereau, R.W., 4th. (2006). The Kv4.2 potassium channel subunit is required for pain plasticity. *Neuron* 50:89–100.

89. Blackburn-Munro, G., Jensen, B.S. (2003). The anticonvulsant retigabine attenuates nociceptive behaviours in rat models of persistent and neuropathic pain. *Eur J Pharmacol* 460:109–116.

90. Passmore, G.M., Selyanko, A.A., Mistry, M., Al-Qatari, M., Marsh, S.J., Matthews, E.A., Dickenson, A.H., Brown, T.A., Burbidge, S.A., Main, M., Brown, D.A. (2003). KCNQ/M currents in sensory neurons: significance for pain therapy. *J Neurosci* 23:7227–7236.

91. Hirano, K., Kuratani, K., Fujiyoshi, M., Tashiro, N., Hayashi, E., Kinoshita, M. (2007). Kv7.2-7.5 voltage-gated potassium channel (KCNQ2-5) opener, retigabine, reduces capsaicin-induced visceral pain in mice. *Neurosci Lett* 413:159–162.

92. Welch, S.P., Dunlow, L.D. (1993). Antinociceptive activity of intrathecally administered potassium channel openers and opioid agonists: a common mechanism of action? *J Pharmacol Exp Ther* 267:390–399.

93. Welch, S.P., Thomas, C., Patrick, G.S. (1995). Modulation of cannabinoid-induced antinociception after intracerebroventricular versus intrathecal administration to

mice: possible mechanisms for interaction with morphine. *J Pharmacol Exp Ther* 272:310–321.

94. LoVerme, J., Russo, R., La Rana, G., Fu, J., Farthing, J., Mattace-Raso, G., Meli, R., Hohmann, A., Calignano, A., Piomelli, D. (2006). Rapid broad-spectrum analgesia through activation of peroxisome proliferator-activated receptor-α. *J Pharmacol Exp Ther* 319:1051–1061.
95. Medhurst, A.D., Rennie, G., Chapman, C.G., Meadows, H., Duckworth, M.D., Kelsell, R.E., Gloger, I.I., Pangalos, M.N. (2001). Distribution analysis of human two pore domain potassium channels in tissues of the central nervous system and periphery. *Mol Brain Res* 86:101–114.
96. Liu, C., Au, J.D., Zou, H.L., Cotton, J.F., Yost, C.S. (2004). Potent activation of the human tandem pore domain K channel TRESK with clinical concentrations of volatile anesthetics. *Anesth Analg* 99:1715–1722.
97. Patel, A.J., Honoré, E. (2001). Properties and modulation of mammalian 2P domain K^+ channels. *Trends Neurosci* 24:339–346.
98. Patel, A.J., Honoré, E., Lesage, F., Fink, M., Romey, G., Lazdunski, M. (1999). Inhalatioual anesthetics activate two-pore-domain background K^+ channels. *Nat Neurosci* 2:422–426.
99. Linden, A.M., Aller, M.I., Leppä, E., Vekovischeva, O., Aitta-Aho, T., Veale, E.L., Mathie, A., Rosenberg, P., Wisdeu, W., Korpi, E.R. (2006). The in vivo contributions of TASK-1-containing channels to the actions of inhalation anesthetics, the α_2 adrenergic sedative dexmedetomidine, aud cannabinoid agonists. *J Pharmacol Exp Ther* 317:615–626.
100. Linden, A.M., Sandu, C., Aller, M.I., Vekovischeva, O.Y., Rosenberg, P.H., Wisden, W., Korpi, E.R. (2007). TASK-3 knockout mice exhibit exaggerated nocturnal activity, impairments in cognitive functions, and reduced sensitivity to inhalation anesthetics. *J Pharmacol Exp Ther* 323:924–934.
101. Alloui, A., Zimmermaun, K., Mamet, J., Duprat, F., Noël, J., Chemin, J., Guy, N., Blondeau, N., Voilley, N., Rubat-Coudert, C., Borsotto, M., Romey, G., Heurteaux, C., Reeh, P., Eschalier, A., Lazdunski, M. (2006). TREK-1, a K^+ channel involved in polymodal paiu perception. *EMBO J* 25:2368–2376.
102. Honoré, E. (2007). The neuronal background K_{2P} channels: focus on TREK1. *Nat Rev Neurosci* 8:251–261.

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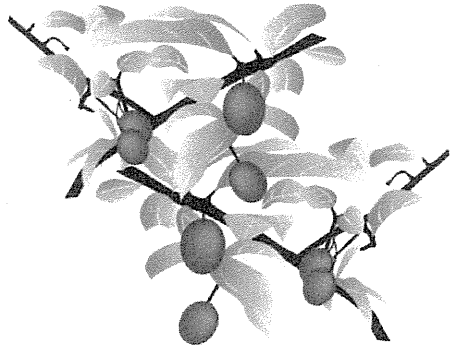

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読んで良し！　ひいて良し！

- この一冊で，緩和ケアに必須の知識が身につく！
- 若手ナースの学習に！　ベテランナースの後輩指導に！
- 読みやすい2ページ読み切りのQ&A方式！
- 『エビデンスレベル』を明記して，EBNに配慮！

総合医学社

Q26 オキシコドン内服薬について教えてください

A26

オキシコドンはモルヒネと同じ「オピオイド」で，モルヒネ製剤と比較して活性代謝産物が少なく，腎機能が低下した患者さんにも使用でき，がん性疼痛に使用する内服オピオイドの第一選択薬になりつつあります．

エビデンスレベルII

回答者
服部政治

1. オキシコドンの鎮痛効果[1)]

●オキシコドンの化学構造には初回通過効果を受けにくくする特徴があり，生物学的利用率は約60～90%と臨床使用されるオピオイドの中で最も高いです（モルヒネ20～30%）．このため血中濃度はモルヒネに比べて安定していると考えられています．

●オピオイド受容体ではμ，κ受容体に主に作用することで鎮痛効果を発揮する一方で，アセチルコリン遊離による鎮痛作用も併せもっています．

●さて，モルヒネを内服した場合は，モルヒネそのものと代謝産物のモルヒネ6グルコナイドが鎮痛効果を示します．そのため腎機能低下のある患者さんでは代謝産物が蓄積して副作用が増強したり，調節が難しくなっていました．オキシコドンの場合は，活性のある代謝産物（オキシモルフォン）が無視できる程度の量しかできないため，腎機能障害のある患者さんでも代謝産物の蓄積を考えなくてもよく，オキシコドンだけの薬理活性をみればいいので比較的安心して使用することができます．

2. オキシコンチン® 錠の早い作用発現時間と長い持続時間

●オキシコンチン® 錠は，内服してから1時間くらいで鎮痛効果が現れ，効果が12時間持続するとされています．この早い鎮痛効果の発現と長い持続時間は，製剤のコーティング技術とそれによってもたらされた二相性の放出機構（アクロコンチンシステム）に，その秘密が隠されています[2)]．

●オキシコンチン® 錠の外殻は，水に溶ける部分と水に不溶の部分とで構成され，まず内服すると水溶性の部分がすぐに溶け出して表層近くにあるオキシコドンが一気に放出されます．これが第一段階の放出で，早い鎮痛効果の発現の秘密です．その後，外殻に空いた穴を通して徐々に水溶性の部分が溶け出して徐放性を12時間保つとされています．

3. オキノーム® でのレスキュー対応

●オキノーム® 散は内服してから15～20分で鎮痛効果が現れ，効果は約6時間持続するといわれています．

●オキシコンチン® 錠を併用している時のレスキューとして使用され，その1回量の目安はオキシコンチン1日使用量の1/4～1/8とされています．

4. オキシコドンの副作用

●オキシコドンの副作用は，モルヒネと同様オピオイドに代表されるもので，嘔気・嘔吐・便秘・眠気・めまいなどがあります．重篤なものとして呼吸抑制がありますが，ほとんどの場合は過量投与が原因であるため慎重に使用していれば問題となることはありません．臨床で特に問題となるのは，嘔気，便秘，眠気でしょう．それぞれの副作用対策についてはQ24「モルヒネについて教えてください」を参照してください[3)]．

●オキシコドンとモルヒネの副作用の発現率で異なる点として明らかになっているのは，皮膚症状と精神症状です．これらの副作用はオキシコドンではモルヒネと比べると有意に少ないことが報告されています（**図1，2**）．

5. 他のオピオイドとの強さの比較

●日本で使用できる強オピオイドは，モルヒネ，オキシコドン，フェンタニルに代表されます．内服モルヒネを1とした時，オキシコドンは1.5倍の強さがあり，フェンタニルは100倍の強さがあるといわれ[4)]，これを「効力比」といいます（**図3**）．逆に，ある痛みを取るのに必要なモルヒネ量を1とした時，必要となるオキシコドンの

量は2/3，フェンタニルは1/100となり，これを「等鎮痛用量」といいます．**表1**に各オピオイド間の等鎮痛用量を示します．効力比や等鎮痛用量は比較的低用量～中等量のオピオイドでは妥当性がありますが，高用量の場合はあてにならなくなるので注意が必要です．

6. オキシコドン製剤のこれから

●オキシコドン製剤は，欧米では，古くは1914年から抜歯後の鎮痛薬として使用されてきた医療用麻薬です．また1995年には米国でオキシコンチン®錠が発売になり，世界では内服オピオイドの第一選択薬となっています．本邦でも2003年にオキシコンチン®錠が，2007年にオキノーム®散が発売となり，がん性疼痛管理の主役になりつつあります．最近では，オキノーム®散の10mg規格が出たため，さらに使いやすくなっています．

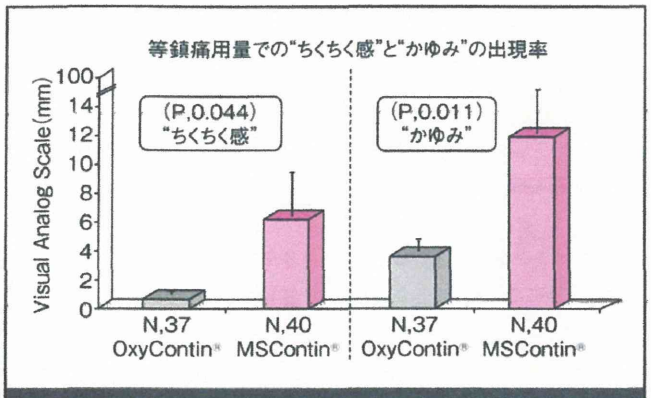

図1　オキシコドンとモルヒネの皮膚症状発現率のちがい

(Euro J Pain 1998 ; 2 : 239-249)

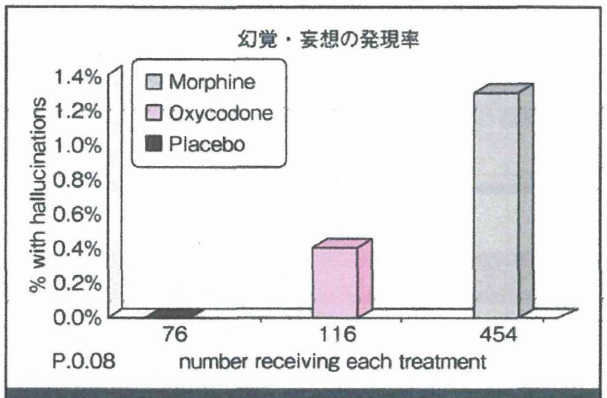

図2　オキシコドンとモルヒネの精神症状発現率のちがい

(EFIC 1997 ; 366)

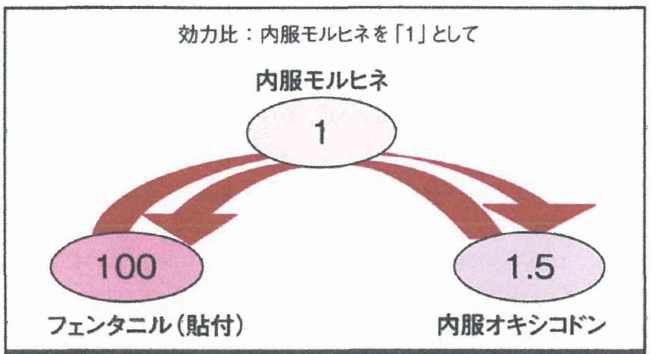

図3　オピオイド・ローテーション時の効力比（当科仕様）

表1　オピオイド・ローテーション時の等鎮痛用量換算表（当科仕様）

オキシコドン徐放剤	硫酸モルヒネ徐放剤	経皮吸収型フェンタニル貼付剤（デュロテップMTパッチ）
20～60mg/日	30～90mg/日	25μg/時（4.2mgパッチ）
60～100mg/日	90～150mg/日	50μg/時（8.4mgパッチ）
100～140mg/日	150～210mg/日	75μg/時（12.6mgパッチ）

オキシコドン徐放剤＝2/3 硫酸モルヒネ徐放剤
フェンタニルパッチ＝1/100 硫酸モルヒネ徐放剤
（Medicament News 第1770号，2003より改変して引用）

ワンポイントアドバイス

1）オキシコドンは経口オピオイドの第一選択薬といえるでしょう．
2）便秘対策を忘れずに．注意深い監視・調節を！
3）低用量製剤（5mg）があるので細かい用量調節が可能．
4）強オピオイドであり，モルヒネ，フェンタニル同様，痛みに応じて増量することが可能です．

参考文献

1）小川節郎："ペインクリニシャンのためのオピオイドの基礎と臨床" 真興交易医書出版部，2004
2）並木昭義，表　圭一："オピオイド Opioid" 克誠堂出版，pp20-32，2005
3）武田文和："がんの痛みの鎮痛薬ー治療マニュアルー改訂第2版" 金原出版，2005
4）小川道雄："一般病棟における緩和ケアマニュアル" へるす出版，2005

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総合医学社

Q24 モルヒネ（内服・注射・坐薬）について教えてください

A24

モルヒネはオピオイド受容体に作用する医療用麻薬（オピオイド）の代表的なもので，医療の現場で古くから強力な鎮痛薬として使用されています．日本では，がん性疼痛に対する治療薬として多くの剤型が発売されています．

エビデンスレベルⅠ

回答者
服部政治

1. モルヒネの鎮痛効果

●モルヒネは，μ，δ，κオピオイド受容体に作用し，**中枢神経系における痛覚伝達の抑制と下行性抑制系を賦活化させることで鎮痛作用を発揮するとされています**（図1）[1]．

●なかでも鎮痛効果を主に司っているμ受容体は，神経終末や中枢神経系に多く分布しています．つまり，モルヒネが体に投与されると，痛みが最初に伝達される一次感覚神経終末のμ受容体に作用し，神経伝達物質のグルタミン酸やサブスタンスPの遊離を抑制します．同時に，脊髄後角神経の興奮を抑えることでより痛み刺激を伝導しにくくします．また，下行性痛覚抑制系を賦活化させることでさらに痛覚を伝導しにくくします．さらに上位中枢にも作用して，大脳皮質や視床での痛覚伝達も抑制されます．

2. モルヒネ製剤の種類

●モルヒネは最も多く剤型の揃った薬剤です．2009年現在本邦で使用可能なモルヒネ製剤とその特徴を**表1**に示します[2]．散剤，錠剤，顆粒剤，細粒剤，坐薬，注射薬があります．それぞれの剤型や投与経路で作用発現時間，持続時間は少しずつ異なりますので，投与する時の患者さんの状態（内服可能か否かなど）や痛みの特徴（持続的に痛いのか，時々強い痛みが襲うのかなど）を考慮し，**適した剤型・規格を選ばなくてはなりません．**

3. モルヒネ製剤の使い分け

●二通りの分け方があります．それは，a）痛みのパターン，b）投与経路で選ぶことになります．

a）痛みのパターン

●がんの痛みを，持続する痛みと突出する痛みに分けると，持続する痛みには徐放性のものを，突出する痛みには速効性のものを投与します（図2）．

●**作用発現時間が早く持続時間の短いものをレスキュー剤として，持続時間の長いもの（徐放製剤）を持続痛に対する薬剤として使用します．**

b）投与経路

●モルヒネを使用する場合，経口投与が第一選択となります．しかしながら病期や病態によっては投与経路を変更しなくてはなりません．一般的な選択基準を以下に示します．

① 経口投与	→	推薦される一般的な投与経路
② 経直腸投与	→	経口不能な場合に選択
③ 皮下・筋肉内	→	消化管吸収ができない時，急な激痛（筋肉内）
④ 静脈内	→	消化管吸収ができない時，急な激痛，痛みの変動が激しい時
⑤ 硬膜外腔	→	痛みが限局している時，モルヒネ総投与量を減らしたい時
⑥ くも膜下腔	→	難治性がん性疼痛の時，①～⑤で除痛できない時，除痛するには鎮静以外に方法がない時，全身に多発する難治性がん性疼痛の時など

●**このように，患者さんの痛みのパターンやモルヒネの吸収可能な経路を考慮しながら疼痛管理を行うことが必要**です．⑤，⑥に関しては麻酔科ペインクリニック医師に協力を要請するようにしましょう．

●また，投与経路によって鎮痛に必要なモルヒネの量も異なってきます．一般的に経口のモルヒネ量を1とした時，皮下・静脈内投与では1/2～1/3の量で，硬膜外腔では1/10～1/20の量で，くも膜下では1/100～1/200の量で同じ鎮痛効果が得られるとされています．そのためモ

ルヒネの副作用で増量できない場合などは，**投与経路を変えることで総投与量を減らすことも可能**となります．

4. モルヒネの副作用対策

●モルヒネの副作用はオピオイドの副作用に代表されるもので，嘔気・嘔吐，便秘，眠気，皮膚掻痒，めまい，せん妄などがあります．重篤なものとして呼吸抑制がありますが，ほとんどの場合は過量投与が原因であるため慎重に使用していれば問題となることはありません．臨床で特に問題となるのは，嘔気，便秘，眠気でしょう．

a）嘔気・嘔吐

●モルヒネ投与開始時期の嘔気は中枢のドーパミン受容体の刺激によるものが多く，プロクロルペラジン（ノバミン®）やハロペリドール（セレネース®）などを使用します．投与開始から2週間以上経って出現した嘔気・嘔吐では，胃内容停滞によるものが考えられるのでドンペリドン（ナウゼリン®）やメトクロプラミド（プリンペラン®）を使用します．

b）便　秘[3]

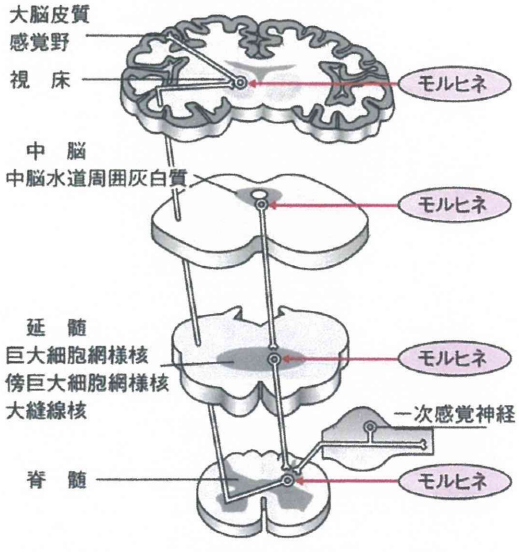
●**便秘対策は，モルヒネに限らずオピオイド使用時には大変重要**になります．水分摂取，食物繊維の摂取，適度な運動という便秘対策の基本は忘れないようにしなくてはなりません．食物繊維はなかなか十分量摂取することができませんが，最近では**食物繊維だけを製品化した「サンファイバー®」**などがあるので，有効に利用してみるのも一つの手です．一般的な考え方としては，塩類下剤のマグネシウム製剤などで便を柔らかく維持し，大腸刺激作用のあるセンナ剤やピコスルファートを投与します．オピオイドを開始したと同時に必ず便の性状の観察と便秘薬の細かい調節をするようにしましょう．

c）眠　気

●眠気は投与開始時期，増量期に起こることが多いですが，ゆさぶっても起きないような状態や呼吸抑制が起こるようでない限りは，**眠気は耐性ができやすいので2～3日は様子をみるようにしましょう**．

d）せん妄[4]

●腎機能が低下している患者さんでは，モルヒネの代謝産物の蓄積によってせん妄や幻覚などの精神症状が出やすいので注意が必要です．モルヒネが原因と思われるせん妄が出現した場合は，痛みの訴えがなくなれば50%ずつ減量していきます．ただし，モルヒネ投与中の患者さんでせん妄症状が起こった場合，脱水，高カルシウム血症，低ナトリウム血症，高アンモニア血症，脳転移，悪液質，ステロイド投与，全身状態の悪化，通常の心因反応など他の要素が原因のことが多いので，モルヒネを減量・中止するだけではなく，**せん妄出現時には他の原因検索と対策をすることを忘れないようにしましょう**．



モルヒネは，大脳皮質や視床などの上位中枢に作用するほか，脊髄にも直接作用し痛覚情報伝達を抑制する．さらに，中脳にある中脳水道周囲灰白質や延髄網様体にある巨大細胞網様核，傍巨大細胞網様核，大縫線核に作用し，下行性痛覚抑制系を賦活化する．

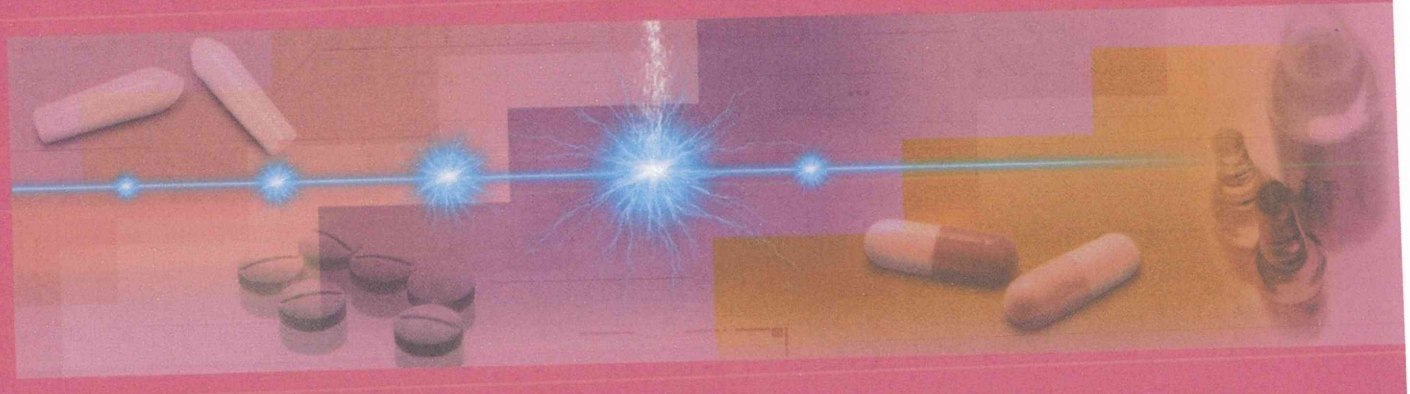
図1　モルヒネの鎮痛作用機構
―脳・脊髄におけるモルヒネの作用点―

（文献1より転載）

看護のすべてがわかる!

Expert Nurse Guides

がん性疼痛ケア完全ガイド



編集

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神経ブロック

Points

- **神経ブロックとは、痛みの伝達を抑える（または絶つ）方法である。奏効するとオピオイドなど鎮痛薬を減量することができる。**
- **神経ブロック（特に神経破壊）はペインクリニック専門医など技術を習得した医師によって実施されるべきである。**
- **持続硬膜外ブロック（硬膜外腔・脊髄くも膜腔への持続投与）の場合、体外デバイスが必要となるため、実施前に、転院先や在宅でも管理可能かどうかを十分に検討する必要がある。**

神経ブロックとは

●神経ブロックとは、下記に示す方法により、痛みを伝達する神経（末梢神経、神経節、脊髄、脳神経）の伝達路を遮断もしくは破壊して、痛みを取り除く方法である。

①麻酔薬を使用して神経を麻痺させる方法
②ステロイドなどで神経の炎症を抑える方法
③アルコール・フェノール・物理的焼灼などで神経を破壊する方法
④脊髄近傍にオピオイドを投与する方法　など

●がん性疼痛では、WHOで示されている疼痛治療段階（3段階除痛ラダーなど）にかかわらず、有益性があると判断された場合には、神経ブロックを実施すべきである。

1．がん性疼痛に対する神経ブロック療法

●がん性疼痛の治療として行われる神経ブロック療法は、**①神経破壊**と、**②オピオイド／局所麻酔薬の持続投与**の2つに大別できる（**表1**）。

1）神経破壊

●神経破壊には、神経を破壊する薬剤（99.5%アルコール、7%フェノールグリセリンなど）を使用して破壊する方法と、神経を物理的に焼灼して破壊する方法（高周波熱凝固術など）がある。

●アルコールやフェノールによる神経破壊は、知覚神経だけでなく運

COMMENTS

高周波熱凝固術とは

- 高周波で加熱することで、ターゲットとなる神経を焼灼し、痛みの伝導を遮断する方法。
- 高周波熱凝固装置は、電気メスや電子レンジなどと同じ原理が使用された装置である。