Group 2 included 112 patients who underwent open gastrectomy or open colectomy and postoperative continuous epidural analgesia. In both groups, patients with chronic pain or severe systemic disease, patients who took any analgesics, psychotherapeutic drugs, anti-anxiety drugs, or anticonvulsants were excluded. There was no difference in age, body height or weight between patients with or without the minor G allele of the rs3845336 SNP in both groups. Carriers of the minor G allele had higher opioid requirements in Group 1, while reporting higher pain scores in Group 2. Altogether, carriers of the minor G allele exhibited enhanced pain-related phenotypes after gastrointestinal surgery, in contrast to reduced pain-related phenotypes after orthognathic surgery. These results suggest that this SNP enhances pain-related phenotypes after gastrointestinal surgery, possibly through impairment of Ca,2,3 VACCCs responsible for activation of visceral inflammatory pain stimulus-elicited antinociception.

PT636

Association between the rs7583431 single-nucleotide polymorphism close to the activating transcription factor 2 (ATF2) gene and the analgesic effect of fentanyl in the preoperative cold pressor-induced pain test

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Abstract

Background: Activating transcription factor 2 (ATF2) is a member of the leucine zipper family of DNA-binding proteins and is widely distributed in tissues. Several recent studies have demonstrated that this protein is involved in mechanisms related to pain and inflammation. However, polymorphisms of the ATF2 gene are unclear that encodes the human ATF2 influence pain sensitivity. The ATF2 gene is known to be highly polymorphic. Thus the present study examined associations between the analgesic effect of fentanyl in the preoperative cold pressor-induced pain test and polymorphisms in the ATF2 gene in 355 Japanese patients who underwent orthognathic surgery.

Result: In the present study, 39 single nucleotide polymorphisms (SNPs) were polymorphic, and a total of 2 linkage disequilibrium blocks with 7 Tag SNPs (rs1153711, rs1153702, rs7583431, rs2302663, rs3845744, rs1205399, and rs268214) were observed in the region within and around the ATF2 gene. Thus, we further analyzed associations between these Tag SNPs and clinical data. Result of multiple testing such as Bonferroni adjustments, for the rs7583431 SNP, the analgesic effect of fentanyl in the preoperative cold pressor-induced pain test of the subjects in the AA group was significantly greater than in the AC + CC group (Mann-Whitney U-test, P = 0.007).

Conclusions: The present findings may contribute to adequate postoperative pain relief in individual patients. Although more research on the genetic factors that influence opioid sensitivity is necessary, postoperative analgesic requirements may be predicted before surgery by analyzing the ATF2 SNP, together with other polymorphisms in the genes that are reportedly associated with opioid sensitivity, such as OPRM1 and GIRK2.

PT637

[11C]- (R)-PK11195 positron emission tomography in patients with complex regional pain syndrome: a pilot study

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Abstract

Complex regional pain syndrome is characterized by severe and chronic pain, but the pathophysiology of this disease is not clearly understood. The primary aim of our study was to explore neuroinflammation in patients with complex regional pain syndrome (CRPS) using positron emission tomography (PET), with an 18kDa translocator protein (TSPO) specific radioligand [11C]-(R)-PK11195. [11C]- (R)-PK11195 PET scans were acquired for eleven patients with CRPS (age, 30-55 years) and twelve control subjects (age, 30-52 years). Parametric image of distribution volume ratio (DVR) for each participant was generated by applying a relative equilibrium-based graphical analysis. The DVR of [11C]- (R)-PK11195 in the caudate nucleus ($t_{95} = -3.209, p = 0.002$), globus pallidus ($t(21) = -2.045, p = 0.027$), putamen ($t_{95} = -2.492, p = 0.011$), nucleus accumbens ($t_{95} = -2.218, p = 0.019$), thalamus ($t_{95} = -2.395, p = 0.013$), postcentral gyrus ($t_{95} = -1.996, p = 0.03$) and precentral gyrus ($t_{95} = -1.839, p = 0.04$) were significantly higher in CRPS patients than in healthy controls. In patients with CRPS, there was a strong positive correlation between the DVR of [11C]- (R)-PK11195 in the caudate nucleus and the pain score, the Visual Analogue Scale ($r = 0.639, p = 0.034$) and affective subscales of McGill Pain Questionnaire ($r = 0.604, p = 0.049$). We demonstrated that neuroinflammation in CRPS patients from basal ganglia (BG) to cortical region. Our results suggest that microglial pathology can be an important pathophysiology of CRPS. Association between the level of caudate nucleus and pain severity indicated that neuroinflammation in this region might play a key role. These results may be essential for developing effective medical treatments.

PT638

Translational research of chronic pain patients using human blood-induced microglia-like (iMG) cells

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Abstract

Fibromyalgia is a refractory disease characterized by chronic pain, the cause of which has not yet been elucidated due to its complex pathology. Recently, activation of immune cells in the brain called microglia has attracted attention as a potential underlying pathological mechanism in chronic pain. Until recently, however, technological and ethical considerations have limited the ability to conduct research using human microglia. We have developed a technique to create human-induced microglia-like (iMG) cells from human peripheral blood monocytes.

This study was conducted to observe microglia activation in patients with fibromyalgia at the cell level using iMG technique. iMG cells were created from 14 patients with fibromyalgia and 10 healthy individuals, and analyzed at the molecular cell level. No significant difference in phagocytic capacity was observed between iMG cells derived from healthy participants and patients with fibromyalgia. Interestingly, however, TNF-α gene expression level and protein concentrations significantly increased in ATP-stimulated iMG cells from patients with fibromyalgia compared to cells from healthy individuals. Moreover,
significant correlations were observed between ATP-induced TNF-α expression level and clinical parameters of subjective pain and other mental manifestations of fibromyalgia. These findings suggest that the microglia in patients with fibromyalgia are hypersensitive to ATP. TNF-α produced by microglia may be a key factor underlying the complex pathology of fibromyalgia.

PT639
Vasodilator action of glucagon-like peptide-2 in the mouse dura matter: implication in migraine
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Abstract
Objective: It was previously reported that increasing serum level of glucagon-like peptide-2 (GLP-2) is a risk factor of migraine in human. The headache phase of a migraine attack is thought to originate in vasodilation of meningeal blood vessels followed by activation of the nociceptive trigeminal nerve innervating these vessels. However, it is unclear how GLP-2 acts on this pathway. In the present study, we investigated the effects of GLP-2 on the diameter of meningeal blood vessels, and determined the target cells of GLP-2 in the meningeal tissue.

Methods: Meningeal preparations were isolated from male ddY mice (5–6 weeks). GLP-2 (10–100 nM) was perfused, and the meningeal arteriolar diameter was measured using infrared-differential interference contrast microscopy. The nitric oxide synthase (NOS) inhibitor, L-nitro-arginine-methyl-ester (L-NAME), was co-perfused with GLP-2. Mice were fixed by cardiac perfusion with 4% paraformaldehyde, and GLP-2 receptors were detected with immunofluorescence staining in the meningeal tissue.

Results: GLP-2 (100 nM) dilated the meningeal blood vessels, which was prevented by the co-treatment with L-NAME. In the immunofluorescence staining, GLP-2 receptor-like immunoreactivities were detected in the macrophage marker Iba-1 positive cells, but not in the meningeal artery and isolectin B4, a marker of nociceptive C-fiber, positive neurons.

Conclusion: GLP-2 dilates the meningeal blood vessels via macrophage NOS-independent mechanisms. This supports a crucial role of GLP-2 in the development of migraine.

Policy of full disclosure: None.

PT640
The dysfunction of brain free fatty acid receptor GPR40/FFAR1 signaling relate to the development of chronic pain
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Abstract
Previously, we have demonstrated that the activation of the GPR40/free fatty acid receptor 1 (GPR40/FFAR1) signaling may play an important role in the regulation of the descending pain control system. Here, we examined the involvement of hypothalamic GPR40/FFAR1 signaling in the development of chronic pain. We used GPR40/FFAR1 knock out (GPR40KO) mice or wild type (WT) mice. A plantar incision was performed in mice. The complete Freund’s adjuvant (CFA) was intraplantary injected in mice. Mechanical allodynia and thermal hyperalgesia were evaluated using von Frey filaments and plantar test, respectively. The repeated administration of GW1100, a GPR40/FFAR1 antagonist, CFA or incision-induced mechanical allodynia compared to vehicle treated mice. The repeated GW1100 treated mice significantly increased phosphorylated ERK (p-ERK) in the spinal cord after low threshold touch stimulation. The level of the hypothalamic docosahexaenoic acid (DHA), a GPR40/FFAR1 agonist, significantly increased at 2 days after surgery compared to sham group. Furthermore, GPR40KO mice were exacerbated incision-induced mechanical allodynia, but not thermal hyperalgesia compared to WT mice. Our findings suggest that the dysfunction of this signaling pathway may be associated with the development of chronic pain.

PT641
Genome-wide association study identifies candidate loci associated with postoperative fentanyl requirements after laparoscopic-assisted colectomy
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Abstract
Objective: Although laparoscopic surgery is often categorized as ‘minimal invasive surgery’ mainly because of small skin incisions, postoperative pain is not ‘minimal’ after laparoscopic surgery because of development of visceral pain. Therefore, opioid analogues are frequently required after laparoscopic surgery. Further, pain intensity and/or opioid requirements after laparoscopic surgery are highly variable among patients. Such individual differences in pain and/or opioid sensitivity may at least partly be attributable to genetic factors. We conducted a genome-wide association study (GWAS) in patients undergoing laparoscopic-assisted colectomy (LAC) to identify potential candidate single nucleotide polymorphisms (SNPs) that may significantly contribute to such individual differences.

Methods: We conducted a three-stage GWAS by using whole-genome genotyping arrays with more than 900,000 markers in 350 patients undergoing LAC, in whom postoperative pain control was managed with intravenous fentanyl patient-controlled analgesia. We further investigated whether one of the best candidate SNPs identified with the GWAS (rs2076222 SNP) significantly affects pain sensitivity in 500 healthy volunteers.

Results: As a result of GWAS in surgical patients, a SNP mapped to 1q32, rs2076222 had highly significant associations with postoperative analgesic requirements; the subjects with the C allele (A/C and C/C) required more fentanyl and more rescue analgesics for postoperative analgesia, compared with those without this allele (A/A), while C allele carriers tended to report higher pain scores during the early postoperative period, compared with non-carriers. In healthy volunteers receiving the mechanical pain perception threshold was lower in C allele carriers, compared with non-carriers. The genes located in this region were found to include LAMB3, encoding laminin, beta 3.