Kaohsiung Veterans General Hospital

Research Program

Program Name：

The relationship between chronic OA pain and cognition deficits in OA patients.

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CONTENT

A THESIS ABSTRACT

Key Words：

[KEY1] Chronic pain	[KEY2] osteoarthritis	[KEY3] cognition deficits
[KEY4]	[KEY5]	[KEY6]

Program Abstract:

In the previous studies, which revealed that because neural systems involved in cognition and pain processing are closely linked, they may affect with each other. In addition to sensory symptoms, cognitive functioning is thought to be affected in chronic pain patients. Pain uses cognitive resources, alters neural plasticity and affects expression and activity of a variety of chemical and cellular neuromediators. There are several brain regions such as amygdala and hippocampus which are most commonly activated during pain processing.

Osteoarthritis (OA) of the knee is one of the leading causes of disability among noninstitutionalized elderly adults

One population-based study revealed that osteoarthritis increases the risk of cognitive deficits diseases such as dementia. However the possible mechanism had not be elucidated. Recent study revealed that OA-induced hyperalgesia was associated with increased NGF/TrkA signaling. NGF activation of ERK/MAPK may play a role in centralization of OA pain. Otherwise NGF has also been shown to produce a dramatic upregulation of brain-derived neurotrophic factor (BDNF) in trkA-expressing DRG cells, and there is now growing evidence that BDNF may serve as a central regulator of excitability and is a neuromodulate or of central pain processing. On the other hand, in previous studies they showed that BDNF plays a critical role in synaptic plasticity, memory processes and storage of long-term memory. The BDNF/TrkB system in the hippocampus plays a crucial role not only in the memory acquisition, but also in the retention and / or recall of spatial memory.

Besides ongoing pain in chronic knee OA is characterized by increased brain activity in limbic-affective regions thus providing novel evidence for a strong emotional component of arthritis pain. There are feedback loops exist between pain, emotion and cognition. How is the role of BDNF in such loop? Especially in circuit between amygdala and hippocampus? The objective of the study was the evaluation of association between pain characteristics and cognitive functions in severe knee OA patients. Besides, we will try to explore the possible mechanisms by which chronic OA like pain develops to cognitive deficits in animal models. The relationship between BDNF levels in body fluids (serum and CSF) and pain characteristics and

cognitive function was also evaluated in the whole sample.

B BACKGROUND AND PURPOSE

Importance and research status of this project at home and abroad, and indicate important documents。

The International Association for the Study of Pain (IASP) defines pain as ‘‘an unpleasant sensory or emotional experience associated with actual or potential tissue damage, or described in terms of such damage.’’ This definition is based on the concept of pain as a perception rather than as a purely sensory modality, and consider the fact that for pain to be consciously experienced, cognitive processing is required. Thus in 2016, Williams, A.C. et al [1] proposed an updated definition of pain as ‘‘Pain is a distressing experience associated with actual or potential tissue damage, with sensory, emotional, cognitive and social components.’’ The authors added cognitive and social components in pain definition. They may have hypothesized that because neural systems involved in cognition and pain processing are closely linked, they may affect with each other.

Chronic pain is defined as pain persisting for 3–6 months or longer generally exceeds the duration of the precipitating noxious stimulus or injury, and may be neuropathic, inflammatory or idiopathic in nature [2]. Chronic pain are most common reasons for seeking medical attention and is reported by 20 to 50 percent of patients seen in primary care [3]. In addition to sensory symptoms, cognitive functioning is thought to be affected in chronic pain patients.

There was a detailed review in 2011 [4], Moriarty, O. et al. reviewed both clinical and preclinical studies that have investigated pain-related alterations in cognition. In some previous studies they reviewed, which showed that chronic pain patients performing poorly compared with controls on some cognitive function such as spatial, verbal, working memory capacity and recall, recognition memory, long-term spatial memory and general cognition. In chronic pain of animal models, both inflammatory pain and neuropathic pain models revealed decreased cognitive performance in chronic pain animals. In this review the authors have proposed a model to explain the

potential mechanisms involved in pain-related cognitive impairment. This model is based on the three theories of (1) competing limited resources, (2) neuroplasticity and (3) dysregulated neurochemistry. Pain uses cognitive resources, alters neural plasticity and affects expression and activity of a variety of chemical and cellular neuromediators. There are six brain regions most commonly activated during pain processing: the insular cortex, the prefrontal cortex, the anterior cingulate cortex, periaqueductal gray, amygdala and hippocampus.

Considering feasibility of biological fluids collection in clinical settings, I would like to more explore neuromediator theory for further study. Besides considering patient in my clinical settings, I would like to choose osteoarthritic (OA) like pain model for further study.

In a study of Annals of Rheumatic diseases in 2016 [5], it revealed that OA-induced hyperalgesia was independent of joint pathology and were strong correlated with augmentation of nerve growth factor(NGF)/ tropomyosin receptor kinase A (TrkA) signaling. This study revealed that whether in mice synovium or in OA patient's synovium, OA-induced hyperalgesia was associated with increased NGF/TrkA signaling. Thus, the authors proposed that NGF activation of ERK/MAPK may play a role in centralization of OA pain. Initially, NGF/TrkA signaling promotes peripheral sensitization in the OA joint, then retrograde transport to dorsal root ganglion (DRG), amplification of input resulted in central sensitization.

NGF has also been shown to produce a dramatic upregulation of brain-derived neurotrophic factor (BDNF) in trkA-expressing DRG cells, and there is now growing evidence that BDNF may serve as a central regulator of excitability [6].

Among neurotrophins, BDNF is the most abundant and widely distributed in the central nervous system. BDNF is expressed in small and medium-sized sensory neurons of the DRG, and is synthesized by the type of DRG cells which express trkA and neuropeptide CGRP [7]. The expression of BDNF mRNA and protein is dramatically up-regulated in models of inflammatory pain.

In the previous study [8], they administrated systemic NGF treatment, a procedure that mimics peripheral inflammatory states, it resulted in raises BDNF levels in sensory neurons and increases nociceptive spinal reflex excitability. This increased central excitability is reduced by trkB-IgG, a BDNF "antagonist." And if with intrathecally administered NGF, it has much more potent effects than systemic NGF on BDNF levels [7]. Thus, we know that BDNF is a neuromodulator of central pain processing.

How is the exact role of BDNF in central sensitization pain from peripheral nociceptors, to spinal level and brain level? In Rheumatology International 2014 [9], this study was to analyze the levels of BDNF in both the plasma and synovial fluid of patients with primary knee osteoarthritis compared with control individuals and to investigate the relationship between BDNF levels and self-reported pain. This study showed systemic BDNF (i.e., plasma levels) of the knee OA patients were significantly higher than that of the healthy controls, but synovial fluid BDNF levels are normal. And plasma BDNF levels significantly correlated with self-reported pain (Western Ontario and mcmaster universities Osteoarthritis Index, WOMAC). In spinal level, previous animal studies have shown that inflammation is accompanied by an upregulation of BDNF in both types of ganglia. Microglia have been identified as a major source for the synthesis and release of BDNF responsible for increasing neuronal excitability by causing disinhibition in dorsal horn neurons in the spinal cord [10]. In DMM OA animal model, which leads to late stage dorsal horn microgliosis. The microgliosis is associated with joint damage and accompanying persistent pain [11]. At the brain level, BDNF has also been shown to activate descending nociceptive facilitation in the nucleus raphe magnus, periaqueductal gray, and rostral ventromedial medulla. In which brain regions, BDNF shifts the balance from descending nociceptive inhibition toward nociceptive facilitation [12-14]. Previous study reported that under chronic stress, it leads to increased BDNF mRNA and protein level in basal lateral amygdala [15]. However, BDNF level is decreased in the hippocampus, include subfields CA1, CA2, and CA3 either in acute pain or chronic pain and stress (acute or chronic treatments) [16,

17].

On the other hand, in previous studies they showed that BDNF plays a critical role in synaptic plasticity, memory processes and storage of long-term memory [18, 19]. In one animal models study [18], BDNF is released in the hippocampus of well-taught rats during maze performance, and thereby TrkB activation is seen immediately after the maze training. The BDNF/TrkB system in the hippocampus plays a crucial role not only in the memory acquisition, but also in the retention and / or recall of spatial memory.

According the above studies, we know that BDNF level are increased both in peripheral nociceptors and at the spinal level. In brain level, BDNF level increased in nucleus raphe magnus, periaqueductal gray, rostral ventromedial medulla, amygdala. Except in hippocampus, BDNF level is decreased. Why is discrepancy of BDNF level in brain regions? Especially between amygdala and hippocampus, they are important regions of modulating pain and memory function. The amygdala is specialized for input and processing of emotion, while the hippocampus is essential for declarative or episodic memory [20]. Is there any specific pathway between these two regions? There are some recent studies to illustrate how amygdala and hippocampus work synergistically to form long-term memory. The basolateral amygdala nucleus (BL) is divided into anterior part (BLa) and posterior part (BLp). Both BLa and BLp project directly to ventral hippocampal CA1 (vCA1). BLp–vCA1 projection is more intensive than BLa–vCA1 projection [20]. Activation of BLa–vCA1 inputs induces anxiety and social deficits [21]. Activation of BLp–vCA1 inputs control emotion-modulated spatial memory [22]. From the above animal studies, we noted that circuits between BLA and hippocampus CA1 regions control emotional and cognitive expression. So, how is the affective effect in OA patients? From the PET image findings, in which revealed arthritic pain is associated with increased activity in areas of the brain that play a role in affect, aversive conditioning, and motivational responses [23]. Besides by use of arterial spin labelling (ASL) MRI for cerebral blood flow mapping, which showed that areas with significant associations between CBF and reported ongoing OA pain

intensity additionally controlled for pain catastrophizing and trait-anxiety scores [24]. Ongoing pain in chronic knee OA is characterized by increased brain activity in limbic-affective regions thus providing novel evidence for a strong emotional component of arthritis pain [24]. According the above studies, which revealed that pain can have a negative effect on emotions. Conversely, a negative emotional state can lead to increased pain, whereas a positive state can reduce pain and improve cognition. There are feedback loops exist between pain, emotion and cognition [25]. How is the role of BDNF in such loop? Especially in circuit between amygdala and hippocampus?

As for clinical study, there is a study[26] used Taiwan National Health Insurance Research Database (NHIRD) data base which revealed that osteoarthritis increases the risk of dementia. The adjusted hazard ratio(HR) for dementia was 1.25 for patients with OA. The results of this study indicated that OA is an independent risk factor for dementia. The authors proposed that inflammation and depressed symptoms are possible mechanisms of OA which develop dementia.

Therefore, the objective of the study was the evaluation of association between pain characteristics and cognitive functions in severe knee OA patients. The relationship between BDNF levels in body fluids (serum and CSF) and pain characteristics and cognitive function was also evaluated in the whole sample.

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C METHODS AND STUDY PROCEDURE

This study was approved from the Institutional Review Board of Kaohsiung veterans general hospital (IRB No. VGHKS19-CT2-21). Written informed consent was received from the OA and control group patients before their participation in the study. We totally enrolled 60 patients (30 OA group and 30 control group) who were scheduled to receive elective surgery which need spinal anesthesia.

- The inclusion criteria of OA group are:

1. Age is more than 20 years old,
2. American Society of Anesthesiologists (ASA) class I–III.

- The exclusion criteria of OA group are:

1. Unwilling to participate,
2. age is lesser than 20 years old,
3. autoimmune diseases,
4. previous knee injury or infection history,
5. brain region disease ex: stroke or brain tumor...etc,
6. mild cognitive impairment, dementia or other neurogenerative diseases,
7. cancer, and
8. other chronic pain.

Control group patients were included based on ASA class I–III, age > 20 years old, scheduled to receive elective general surgery or urological surgery with spinal anesthesia such as hernioplasty, ureteroscopy and laser stone fragmentation, and transurethral resection of the prostate…etc. The exclusion criteria of control group are the same as those of OA group patients plus with OA pain.

All patients will receive the following questionnaires on the day before their surgery: the Western Ontario and McMaster universities Osteoarthritis Index (WOMAC) and the cognitive abilities screening instrument (CASI). Otherwise, we used geriatric depression scale (GDS-15) for evaluation of emotion especially for participant of age > 65 years old.

VGHKS19-CT2-21 CASE REPORT

Case Report Form

Case No:_____

I Basic information：

No.：_____ Sex：☐1.M ☐2.F

Age：_____ Weight：____kg Height：____cm BMI：_____kg/m^2

Date：____/____/_____ ASA：____

Group：☐1. Osteoarthritis group ☐2. Control group

II History：

☐Smoking ☐Drinking ☐Education level(☐Junior high school, ☐Senior high school, ☐University, ☐Graduate school)

☐HTN ☐DM ☐Autoimmune disease ☐Hyperlipidemia ☐CAD ☐COPD

☐CVA ☐Parkinson disease ☐Painkillers(☐No ☐Yes，_____)

☐Duration of pain(☐<=Three months ☐3~6 months ☐> 6 months

III Results of questionnaires

1. CASI C-2.0

LTM	STM	ATTEN	MENMA	ORIEN	ABSTR	LANG	DRAW	ANML	CASI	MMSE

2. WOMAC

Pain	Stiffness	Body function	Total score:__/ 96 = __%

3. GDS-15

Total score	1(0-4)	2(5-9)	3(10-15)

IV Postoperative evaluation

1. ☐Headache：☐0 None ☐1 Mild ☐2 Moderate ☐3 Severe
2. ☐Lumbar soreness/Backache：☐0 None ☐1 Mild ☐2 Moderate ☐3 Severe
3. ☐Nausea/Vomiting：☐0 None ☐1 Mild ☐2 Moderate ☐3 Severe
4. ☐Side effects of blood extraction：☐Bruises ☐Infection

D EXPECTED WORK ITEMS AND SPECIFIC RESULTS

Contribution to clinical or academic

Through this study, it is expected to explore the associations of cognitive deficits caused by knee osteoarthritis.