Nicotinic acetylcholine receptor agonists may be a novel therapy for endometriosis

Yuan Wu b, Li-Ping Wang a, Jian-Qing Pan a,*

a Research Center for Neural Engineering, Shenzhen Key Laboratory for Neuropsychiatric Modulation, Shenzhen Institutes of Advanced Technology, Chinese Academy of Sciences, Shenzhen, China
b Department of Hepato-Biliary Surgery, the Affiliated Hospital of Guiyang Medical College, Guiyang, China

Article info
Article history:
Received 4 January 2011
Accepted 13 July 2011

Abstract
Endometriosis (EMs) is defined as the presence of tissue which somewhat resembles endometrial glands and stroma outside the uterus, and elicit an inflammatory response. This response is accompanied by angiogenesis, adhesions, fibrosis, scarring, neuronal infiltration, and anatomical distortion, resulting in pain and infertility. Owing to the side effects of the present medical treatment and the 10% incidence of recurrence after surgery, EMs is difficult to cure completely so far, that have given impetus to consider novel therapy. Since 1980s, cigarette smoking was found inversely related to the risk of having EMs and it is generally considered that nicotine may play a beneficial role in the pathological process of EMs. Recently, the anti-inflammatory and anti-nociceptive functions of nicotinic acetylcholine receptors (nAChRs) as well as the related mechanisms have become a research hotspot. Based on the above-mentioned, it suggests that the nicotinic acetylcholine receptor agonists may be applied for the treatment of EMs.

© 2011 Elsevier Ltd. All rights reserved.

Introduction
Endometriosis, a major contributor to pelvic pain and infertility, is characterized by endometrial-like tissue outside the uterus, primarily on the pelvic peritoneum, ovaries, and rectovaginal septum, and in rare cases on the organs outside the pelvis including diaphragm, pleura, pericardium, etc. The endometrial-like tissues elicit an inflammatory response which is accompanied by angiogenesis, adhesions, fibrosis, scarring, neuronal infiltration, and anatomical distortion, resulting in pain and infertility [1]. EMs is the third most common gynecological diseases among women 15–44 years of age. EMs affects 22% of women in their reproductive age and is associated with chronic pelvic pain, dysmenorrhea and dyspareunia [2]. Additionally, endometriosis can be diagnosed in 68% of patients suffering from infertility [3]. The traditional drug therapy is intended to reduce pain through a variety of mechanisms, including minimizing inflammation, interrupting or suppressing cyclic ovarian hormone production, inhibiting the action and synthesis of estradiol, and reducing or eliminating menses [4]. However, how to deal with the side effects such as nausea, amenorrhea, hypoestrogenism (vasomotor symptoms, vaginal dryness, decreased libido, irritability, loss of bone mineral density), and hyperandrogenic side effects (acne, edema, decreased breast size), remains a hard nut to crack [5]. Surgical approaches to relieve endometriosis-related pain can be used as first-line therapy or initiated after failed medical therapies. Hysterectomy and bilateral salpingooophorectomy are definitive surgical treatment for endometriosis [6]. In a retrospective analysis of women 10 years after hystectomy and bilateral salpingooophorectomy, there was a 10% incidence of recurrent symptoms [7]. Thus, EMs is difficult to cure completely so far, that have given impetus to consider novel therapy. Cigarette smoking is an established risk factor for cancer and cardiovascular disease, and is the leading cause of avoidable disease in most countries. Less well-known are possible beneficial effects, several studies suggest that there may be inverse associations of smoking with endometriosis [8–12]. Although in most cases the actual mechanism is understood only poorly or not at all, it is generally believed that the principal beneficial action is due to the nicotine administered, and that administration of nicotine without smoking may be as beneficial as smoking, without the higher risk to health due to tar and other ingredients found in tobacco [13,14]. Moreover, the anti-inflammatory and anti-nociceptive effects of nicotinic acetylcholine receptors as well as the related mechanisms have been well investigated [15]. Human endometriotic lesions were innervated by cholinergic, sensory and adrenergic nerve fibers, it suggests that these nerve may contribute a critical link in the generation of pain and inflammation in endometriosis [16]. Meanwhile, Remorgida et al. reported that large intestinal endometriosis does not lead to a systematic interference with the muscarinic acetylcholine receptor agonist carbachol [17]. These facts suggest that nicotinic acetylcholine receptors may be a novel therapeutic target.
Anti-nociceptive effects of the nicotinic acetylcholine receptors

Nicotinic acetylcholine receptors have been confirmed to participate in manipulating pain transmission in the central nervous system (CNS). Activation of cholinergic pathways by nicotine and nicotinic agonists was observed to elicit anti-nociceptive effects in a variety of pain tests [18]. It has been well known that the anti-nociceptive effect of nAChRs is due to the activation of their subtypes, including α4β2 and α7 nAChRs [19]. The α4β2 subtype is the major neuronal nAChRs in the brain [20]. Marubio et al. investigated the mechanism of nicotine-elicted anti-nociception using both α4 and β2 knock-out mice. Nicotine naturally has anti-nociceptive effects when measuring supraspinal responses to pain stimuli. These nicotine-elicted anti-nociceptive effects were attenuated in either β2 or α4 knock-out mice, which indicates that both subunits contribute to the anti-nociceptive effects of nicotine. Deletion of either α4 or β2 nAChRs subunits, which together form a high-affinity receptor for nicotine, reveals that nAChRs is an important component of the nicotinic anti-nociceptive pathway [21]. Moreover, blocking α7 nAChR with a-BGTX resulted in decreased anti-nociceptive effects of DMXB (3-(2,4-dimethoxybenzyl) and 4-OH-DMXB which are α7 nAChR agonists. In short, both the α4β2 and α7 nAChRs which contribute to anti-nociceptive effects are candidate targets for controlling the pain of EMs.

Mechanisms of α7-mediated anti-inflammatory effects

Another anti-inflammatory pathway called the “cholinergic anti-inflammatory pathway” has been revealed. The α7 nAChR is generally considered to be the most important therapeutic target which mainly expresses on the membrane of immune cells, including monocytes, macrophages, T and B lymphocytes, dendritic cells [22,23]. It has been demonstrated that α7 nAChR affect immune cells via triggering various signaling mechanisms, that probably interact with each other to achieve the anti-inflammatory effects, including the Jak2-STAT3 and NF-κB signaling pathways [24]. Briefly, nicotine inhibits the production of proinflammatory mediators in human monocytes by suppression of I-κB and NF-κB transcriptional activity through α7 nAChR [25]. On the other hand, STAT3, a potential negative regulator of inflammatory responses, is phosphorylated by the tyrosine kinase Jak2 that is recruited to the α7 nAChR. The phosphorylated STAT3 leads to the down regulation of the proinflammatory cytokine genes. Immunoprecipitation studies support previous findings showing that nicotine exposure recruits Jak2 and lead to an increased association between the kinase and α7 receptors [26]. Studies of mice macrophages with deficient STAT3 illuminated that vagus nerve stimulation does not reduce peritoneal cytokine levels or intestinal inflammation as it does in control group [24]. These data support the interaction of JAK2 and α7 nAChR, also indicate the critical role of α7 nAChR in the cholinergic anti-inflammatory pathway. The anti-inflammatory effect of α7 nAChR has been studied via different models of inflammation [27–31]. These studies support a potential role for α7 nAChR in the regulation of inflammatory processes. Thus, it is suggested that α7 nAChR agonist may be a novel therapy to control the inflammation of EMs.

Conclusion and prospect

According to the scientific analysis above, it is suggested that the nAChR agonists exhibit promising therapeutic effects in the treatment of EMs and should be treated as a novel therapy for EMs. To evaluate our hypothesis, we suggest that the in vivo and in vivo research on EMs related cells and animal models are required to evaluate the safety and efficacy of the nAChR agonists. After that, clinical research should be performed to estimate the efficacy of the nAChR agonists and provide stronger evidence for potential application in the future.

Conflicts of interest statement

None declared.

References


