Research on receptors related to acupuncture analgesia and positron emission tomography radioligands: a review

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As a traditional treatment method, acupuncture can be widely used to regulate physiological function as well as ameliorate pathologic processes, and the capital application is analgesia.

Many studies, including neurobiochemistry, histopathology and radioligand binding assay of receptor, showed that acupuncture analgesia (AA) was a complex physiological process mediated by various neurotransmitters, neuropeptides, modulators and receptors. However, the direct clinical evidence of these studies is limited as they were animal experiments. According to characteristics of receptor ligand-binding domains, positron emission tomography (PET) receptor imaging had its superiority in real-timely investigating the distribution (localization), quantity (density) and function (affinity) of the trace receptors in vivo with non-invasive approach. It would interpret the central action mechanism of AA and promote reasonable application of acupuncture if the PET receptor imaging should be used in AA research. As well-known, it is necessary for receptor imaging to select the suitable radioligand, therefore, the present article reviewed the central neuroreceptors related to AA and their respective radioligands labeled with [11] carbon (11C).

1 Opiate receptors

1.1 Opiate receptors related to AA As a treatment method of stimulation producing analgesia, acupuncture can relieve pain by activating the pain-related receptors in brain, where endogenous opioid peptides (EOPs) and their receptors are the major neurochemical substances involved in AA.

Opiate receptors (ORs) are always the prevalent spot in life science since they were discovered. In 1973, there was the first report that ORs can be found in human brain, and then formed the concept of three groups of ORs (μ, κ, δ). From 1970s, many EOPs were discovered sequentially, including enkephalin (ENK), β-endorphin (β-EP), dynorphin (DYN), etc., to 1990s, orphanin FQ receptor (OFQR) and the endogenous selective ligand of μ-OR were identified, to today, ORs have been researched more than thirty years, and four classes of OR ligands have been...
developed, including \( \mu, \kappa, \delta \), OFQR and endorphin (EM), DYN, ENK, orphanin FQ (OFQ) and their respective precursors\(^4\).

The previous studies of AA mechanisms found that naloxone, a \( \mu \)-receptor antagonist, could partially reverse the analgesic effects of acupuncture in mice\(^2\). The level of \( \beta \)-EP in human cerebrospinal fluid was elevated after electroacupuncture (EA), in addition, the analgesia could also be blocked by naloxone\(^2\). Further studies revealed that the release of EOPs and the activation of the ORs by EA were frequency-dependent. By intrathecal administration of various specific antagonists or antisera of OR subtypes, Han\(^5\) uncovered that 2 and 100 Hz EA induced analgesia effects were differentially reduced by blockade of \( \mu/\delta \) and \( \kappa \) receptors, strongly suggesting that low- and high-frequency EA were mediated by \( \mu/\delta \) and \( \kappa \) receptors in the rat spinal cord respectively under the physiological pain conditions. Three classes of EOPs (\( \mu, \kappa \), and \( \delta \)) could be released simultaneously by using low- and high-frequency EA alternately, resulting in the strongest analgesic effect. The experiment\(^6\) associated with the relationship between EA and pathologic pain displayed that both 2 and 100 Hz EA induced analgesic effects on inflammatory pain in rats were reduced by intrathecal administration of \( \mu \) and \( \delta \) receptor antagonists. However, there was no obvious effect with \( \kappa \) receptor antagonist. These observations manifested that EA induced the analgesic effects via activating \( \mu \) and \( \delta \) receptors but no \( \kappa \) receptor under the pathologic conditions, which possibly concerned with the differences of brain domains mediating high- and low-frequency EA and the receptor expression between the physiologic and pathologic conditions. If the animal species, types of pain, routes and doses of administration or sites of action were different, OFQ would generate differential responses to pain, such as algnesia, analgesia or inaction, which were potentially determined by stimulating the different OFQR subtypes\(^7\).

1. 2 OR PET radioligands \(^{11}\)C-diprenorphine (DPN) and \(^{11}\)C-carfentanil (CFN) are the most frequently used OR PET radioligands recently. DPN, a nonselective OR partial agonist, can bind to \( \mu, \delta, \kappa \) receptors with characteristics of high affinity, low dissociation rate, and high ratio of specific/non-specific binding equally. CFN, a \( \mu \) receptor full agonist with high-selectivity, can still retain high affinity under condition of high sodium concentration in vivo, and easily be labeled with \(^{11}\)C\(^2\). Studies of brain OR system using PET have been applied for neurochemical mapping and studies of pain, emotion, drug addiction, movement disorders, neurodegeneration and epilepsy\(^8\). It should be paid close attention to that one group has studied AA by means of combining \(^{11}\)C-DPN PET imaging with functional magnetic resonance, which indicated greater \(^{11}\)C-DPN binding decreases during verum acupuncture in the right orbitofrontal cortex (OFC), left medial prefrontal cortex (PFC), right thalamus, and right insula, and greater \(^{11}\)C-DPN increases during verum acupuncture in the bilateral insula, right medial PFC/anterior cingulate cortex, left OFC, and right brainstem\(^9\).

Telbot et al\(^{10}\) observed the PET imaging of brain \( \kappa \) receptor with the pretreatment of naloxone in vivo in baboon by labeling \( \kappa \) receptor agonist GR89696 and its homogeneous isomer GR103545 with \(^{11}\)C. It exhibited that \(^{11}\)C-GR103545 was superior to \(^{11}\)C-GR89696 for imaging \( \kappa \) receptor with excellent brain penetration and uptake kinetics. Recently, Poinsel et al\(^{11}\) have investigated in vivo imaging the \( \kappa \) opioid receptor in mice by binding \(^{11}\)C-MeJDTrIc, which is the N-methylated derivative of JDTrIc, a selective \( \kappa \) receptor antagonist, and the results suggested that \(^{11}\)C-MeJDTrIc appeared to be a promising selective “lead” radioligand for \( \kappa \) opioid receptor PET imaging.

In the mid of 1990s, Madar et al\(^{12}\) had accomplished PET imaging of \( \delta \) opioid receptor in human brain with \( \text{N}^1\text{H}(\text{[\(^{11}\)C]methyl})\text{naltrindole (}\text{\(^{11}\)C-MeNTI})\), and demonstrated that \(^{11}\)C-MeNTI possessed a high selectivity for \( \delta \) receptor, and rapid washout in receptor-poor areas and prolonged retention in receptor-rich areas.

2 5-hydroxytryptamine receptors

2.1 5-hydroxytryptamine receptors related to AA

The family of 5-hydroxytryptamine (5-HT) receptors is fairly complicated. Nowadays, there are seven discoverable 5-HT receptors, including 5-HT\(_1\), 5-HT\(_2\), 5-HT\(_3\), 5-HT\(_4\), 5-HT\(_5\), and 5-HT\(_6\). 5-HT\(_1\) receptor is comprised of five subtypes, such as 5-HT\(_{1A}\), 5-HT\(_{1B}\), 5-HT\(_{1D}\), 5-HT\(_{1B}\), and 5-HT\(_{1F}\). 5-HT\(_3\) receptor can be subdivided to three subtypes, including 5-HT\(_{3A}\), 5-HT\(_{3B}\), and 5-HT\(_{3C}\). While, 5-HT\(_{5}\) receptor contains two subtypes as 5-HT\(_{5A}\) and 5-HT\(_{5B}\)\(^{13}\).

The nuclei raphe magnus (NRM), which is a crucial site in the ascending and descending pathways of pain modulatory system, contains abundant 5-HT neurons. The electrolytic lesion of NRM and the blockade of 5-HT biosynthesis could produce inhibition of AA. Furthermore, blockade of 5-HT receptors by using 5-HT receptor antago-
nists almost abolished AA\textsuperscript{[13]}. Chang et al\textsuperscript{[14]} found that (1) intraventricular injection of exogenous 5-HT exhibited an analgesic effect, which partially mimicked the analgesic actions of EA; (2) the antinociception of EA at different frequencies was attenuated after reducing biosynthesis of 5-HT by administration of the 5-HT inhibitor; and (3) the 5-HT\textsubscript{1A} and 5-HT\textsubscript{3} receptor antagonists, pindobind-5-HT\textsubscript{1A}, respectively blocked three different frequencies of EA-induced analgesia, but the antinociceptive effect of 100 Hz EA was potentiated by the 5-HT\textsubscript{3} receptor antagonist, ketanserin. These observations well documented that 5-HT\textsubscript{1A} and 5-HT\textsubscript{3} receptors partially mediate the analgesic effects of EA, but that the 5-HT\textsubscript{3} receptor is conversely involved in the nociceptive response.

2.2 5-HT Receptor PET Radioligands  The representative is 5-HT\textsubscript{1A} receptor PET radioligands. Most of 5-HT receptor tracers belong to the following structural families: (1) compounds with structural similarity to the 5-HT\textsubscript{1A} antagonist, N-[2-4-(2-methoxyphenyl)-1-piperazinyl]ethyl]-N-(2-pyridinyl) cyclohexane carboxamide (WAY100635); (2) derivatives of the 5-HT\textsubscript{1A} agonist, 8-hydroxy-2-(di-n-propylamino) tetralin (8-OH-DPAT). At present, PET tracers imaging 5-HT\textsubscript{1A} receptor successfully are mostly 5-HT\textsubscript{1A} antagonists\textsuperscript{[15, 16]}.

WAY100635 is a 5-HT\textsubscript{1A} receptor antagonist with high affinity and selectivity. \textsuperscript{11}C-WAY100635 is the most commonly used tracer for 5-HT\textsubscript{1A} receptor \textit{in vivo}. Kumar et al\textsuperscript{[15]} have reported that there had a good correlation between regional distribution volumes of 5-HT\textsubscript{1A} receptor derived from PET studies using \textsuperscript{11}C-WAY100635 and \textit{in vitro} binding levels from studies on postmortem brain tissue using \textsuperscript{11}H-8-OH-DPAT. DWAY is a minor metabolite of WAY100635. Studies with \textsuperscript{11}C-DWAY in animal experiments and human volunteers have a substantially greater intensity of signal per unit of radioactive dose as compared to \textsuperscript{11}C-WAY100635\textsuperscript{[15]} CPC-222, a structural analogue of WAY100635, has the characteristics of high yield, metabolic stability and high yield to non-target ratios in human brain\textsuperscript{[12]}. (R)-RWAY is a reverse amid of WAY100635, which is used for imaging 5-HT\textsubscript{1A} receptors in rodents and nonhuman primates. \textsuperscript{11}C-CUMI-101, a 5-HT\textsubscript{1A} receptor agonist, has been applied to image 5-HT\textsubscript{1A} receptor in baboon brain, and further studies are required to determine whether \textsuperscript{11}C-CUMI-101 is a suitable PET tracer for the reliable quantification of 5-HT receptor levels in human being\textsuperscript{[12]}. For the 5-HT\textsubscript{2A} receptor, PET imaging probes such as \textsuperscript{11}C-MDL 100907, \textsuperscript{12}F-altanserin are used for human brain\textsuperscript{[14]}. 5-HT\textsubscript{1A} and 5-HT\textsubscript{3} receptor radioligands aforementioned can be employed to investigate AA. Besides, the radioligands of 5-HT\textsubscript{3} receptor related to AA still remain in process of study.

3 Gamma-aminobutyric acid receptors

3.1 Gamma-aminobutyric acid receptors related to AA Gamma-aminobutyric acid (GABA) is the most important inhibitory transmitter in central nervous system (CNS). GABA receptors include three subtypes, GABA\textsubscript{A}, GABA\textsubscript{B}, and GABA\textsubscript{C}. Both GABA\textsubscript{A} and GABA\textsubscript{B} are Cl\textsuperscript{−} channel receptors, and GABA\textsubscript{B} is G protein-coupled receptor.

A series of studies concerned with AA and GABA\textsubscript{A} receptor showed that acupuncture could elevate the pain threshold in the rats with radiant heat stimulus, and the elevation of the pain threshold could not be reversed by intracerebroventricular injection of bicuculline, which is an antagonist for GABA\textsubscript{A} receptor. It also exhibited that GABA\textsubscript{A} receptor in brain might not be implicated in AA, but at spinal level, GABA\textsubscript{A} receptor was contributed in acupuncture-induced spinal segmental inhibition\textsuperscript{[17]}. Zhu et al\textsuperscript{[17]} summarized that intracerebroventricular and intrathecal injections of GABA or baclofen, a GABA\textsubscript{B} receptor agonist, induced the dose-dependent analgesic effect by activating GABA\textsubscript{B} receptor. Possibly, GABA is engaged in AA via GABA\textsubscript{B} receptor in brain, however in spinal cord, both GABA\textsubscript{A} and GABA\textsubscript{B} receptors take part in AA.

3.2 GABA receptor PET radioligands  \textsuperscript{11}C-flumazenil, a radiotracr for brain GABA\textsubscript{A}/benzodiazepine (GABA/BZD) receptor with high specific binding \textit{in vivo}, is widely used for numerous neurological and psychiatric disorders, such as epilepsy, stroke, anxiety disorders, and dementia etc. Some subsequent tracers for BDZ receptor, such as \textsuperscript{11}C-PKI1195, \textsuperscript{11}C-DAA1106, \textsuperscript{11}C-Ro-151788, \textsuperscript{11}C-Ro-154513 and \textsuperscript{11}C-PBR28, can also be applied for GABA\textsubscript{A} receptor imaging \textit{in vivo}. \textsuperscript{11}C-GP62349, an antagonist for GABA\textsubscript{B} receptor, would be hopeful to become the suitable PET ligand for GABA\textsubscript{B} receptor\textsuperscript{[18]}. It can be seen that the actual effects of different GABA receptor types contributed in AA might be validated with the help of the specific PET radioligands.

4 Noradrenaline receptors

4.1 Noradrenaline receptors related to AA Noradrenaline (NA) receptors, which are a group of receptors binding with catecholamines and cate-
cholamine analogues, include \( a_1 \), \( a_2 \) and \( \beta \) three major types according to their pharmacological characteristics. On the basis of molecular cloning technique, nine subtypes of NA receptor have been obtained; \( a_{1A} \), \( a_{1B} \), \( a_{1D} \), \( a_{2A} \), \( a_{2B} \), \( a_{3C} \), \( \beta_1 \), \( \beta_2 \), and \( \beta_3 \). NA receptors widely distribute in CNS. The major NA receptors in brain are \( a_1 \) and \( \beta_1 \), and in spinal cord are \( a_{1D} \) and \( a_{3A} \).[19]

Catecholamines (CAs) also participate in alleviating pain with \( \alpha \) receptor besides regulating the cardiovascular function and emotion activity. CA would induce different analgesic effects along with the variations of administration routes[19]. The most of central noradrenergic neurons locate in the bulbus medullae and pons of variolus, which deliver the ascending and descending fibers to brain and spinal cord, and organize the ascending and descending pathways. The former projects to limbic system via ventrolateral funiculi and evokes the releasing of NA in periaqueductal gray matter, ganglion habenulae and preoptic area by stimulating the ascending NA system, and as a result, the analgesia is impeded by \( \alpha_1 \) receptor. While the latter reaches to spinal dorsal horn via dorsolateral funiculus, inducing the releasing of NA in dorsal horn by activating the descending NA system, and the analgesia is enhanced by \( a_2 \) (\( a_{2A} \)) receptor[19]. The mechanism of AA is similar to that mentioned above. Kim et al.[20] reported that intrathecal injection of yohimbine, an antagonist of \( a_2 \) receptor, reduced the EA-induced analgesic effects on neuronal mice obviously, and it was ineffective for injection of furazosin, which is an antagonist of \( \alpha_1 \)-receptor. Whereas, intracerebroventricular injection of clonidine, an agonist of \( \alpha \)-receptor, relieved the analgesic effect; phenolamine, an antagonist for \( \alpha \)-receptor, strengthened the AA effect[20].

4.2 NA receptor PET radioligands NA receptors imaging with PET is mostly used to explore the modulation of sympathetic nervous system in various cardiac diseases. At present, multiple presynaptic tracers have been introduced, but the availability of radioligands for the postsynaptic NA receptors is deficient. For \( \alpha \) receptor relevant to AA, \(^{11}\)C-GB67, a pharmacologic analogue of the \( \alpha_1 \) receptor antagonist prazosin, has the characteristics of high selectivity, good potential and fast binding for \( \alpha_1 \) receptor subtype. However, larger clinical studies are still needed to confirm its usefulness and practicability. \(^{11}\)C-CGP12177 is a nonselective, hydrophilic \( \beta \) receptor antagonist which produces good-quality PET images of the heart. However, the radiolabeling via \(^{11}\)C-phosgene is laborious, and in addition specific yields of the tracer are variable and often low. \(^{11}\)C-CGP12388 is developed as an alternative for clinical use, and it has similar potency to \(^{11}\)C-CGP12177. Safe and efficient use of \(^{11}\)C-CGP12388 in the quantification of receptor density has been shown in human body[21]. Nevertheless, the effects of \( \beta \) receptor in AA seem to be weak, thus, the values of \( \beta \)-receptor radioligands in the study of AA are limited at present.

5 Dopamine receptors

5.1 Dopamine receptors related to AA According to the receptor signal transduction and the diversity of ligands binding, dopamine (DA) receptors consist of two families: \( D_1 \) and \( D_2 \). Five DA receptor subtypes, \( D_1 \), \( D_2 \), \( D_3 \), \( D_4 \), and \( D_5 \) receptors, are named from cloning technique. The \( D_1 \) family contains \( D_1 \) and \( D_2 \) subtypes, while the \( D_2 \) family is composed of \( D_2 \), \( D_3 \), and \( D_4 \) subtypes.

Gao et al.[22] found that dopaminergic system could influence algesia and AA. Intrathecal injection of LY171555, a selective agonist for \( D_2 \) receptor, or injection of emetomorphine, a \( D_1 / D_2 \) receptor agonist, produced analgesic effect (dose-dependent) and potentiated AA. Injection of SKF38393, a selective agonist for \( D_1 \) receptor, was ineffective on both algesia and AA. While injection of SCH23390, a selective antagonist for \( D_1 \) receptor, or injection of sulphiride, a selective antagonist for \( D_2 \) receptor, could attenuate acupuncture-induced analgesia. To summarize, at the spinal level, \( D_2 \) receptor is implicated in algesia modulation, and both \( D_1 \) and \( D_2 \) receptor participate in AA. Wang et al.[23] reported that \( L \)-tetrahydrodopalmatine, a DA receptor antagonist, could potentiate AA. Injections of SKF38393, a selective antagonist for \( D_1 \) receptor, and quinpirole, a selective antagonist for \( D_2 \)-receptor, were performed via nucleus accumbens of mice respectively; the former reduced the potentialization for AA by \( L \)-tetrahydrodopalmatine, and the latter was inactive. It illustrated that DA receptors had a bidirectional effect on AA, which mimics NA receptors. It could weaken AA by stimulating brain DA receptors (the major is \( D_2 \) receptor), and in contrast, activating the spinal cord DA receptors (the major is \( D_1 \) receptor) could enhance AA.

5.2 DA receptor PET radioligands Dopaminergic system imaging is widely applied for a variety of brain disorders such as Parkinson’s disease, Huntington’s chorea, schizophrenia, etc. \(^{11}\)C-raclopride and \(^{11}\)C-N-propylnoraporphin, \( D_2 / D_3 \) receptor antagonists, are mostly employed for investigating the distribution of striatal \( D_2 / D_3 \) receptors. Recently, the studies on DA receptor
tracers with high affinity have increased, such as $^{11}$C-FLB457 and some tracers labeling with $^{18}$F, also analogues of raclopride, which have been employed for the visualization of extrastriatal (cortex) DA receptors in vivo. In addition, $D_1/D_2$ receptor excitatory tracers such as $^{11}$C-(+)-PHNO were produced subsequently, which might have superior sensitivity and affinity in comparison with the inhibitory tracers\textsuperscript{[16]}

For the $D_1$ receptor system, $^{11}$C-SCH2399086 and $^{11}$C-NNC112 are the widely used $D_1$ receptor PET tracers. The defect of both is their poor selectivity due to the partial affinity to 5-HT\textsubscript{2A} receptor\textsuperscript{[16]}

Apart from DA receptors, the variation of presynaptic DA transport (DAT) protein also reflects the function of dopaminergic system. $^{11}$C-\textbeta-CFT [2β-carbomethoxy-3β-(4-fluorophenyl) tropane] is the representative of DAT PET tracers labeled with $^{11}$C.

6 Acetylcholine receptors

6.1 Acetylcholine receptors related to AA Central acetylcholine (ACh) receptors comprise muscarinic (M) receptor and nicotinic cholinergic (N) receptor as same as the peripheral ACh receptors. There are five pharmacological subtypes, $M_1$, $M_2$, $M_3$, $M_4$, and $M_5$, according to their different affinity. And also, cloning study manifested five structural subtypes, $m_1$, $m_2$, $m_3$, $m_4$, and $m_5$. $m_1$, $m_2$, $m_3$, were corresponded to $M_1$, $M_4$, $M_5$, respectively, while $m_4$ and $m_5$ are similar to $M_3$. Central N receptor has 12 subunits known from cloning technology, including $\alpha_2$, $\alpha_3$, $\alpha_4$, $\alpha_5$, $\alpha_6$, $\beta_2$, $\beta_3$, $\beta_4$, and $\beta_5$. Central N receptor exists as pentamer and mostly of two $\alpha_4$ subunits and three $\beta_2$ subunits ($\alpha_4\beta_2\beta_2\alpha_4\beta_5$)\textsuperscript{[11-16].}

Central cholinergic system also plays an important role in AA. The metabolism of ACh in CNS accelerates during acupuncture, thus, the AA effect is strengthened. Inhibiting ACh biosynthesis by intracerebroventricular injection of hemicholine, or blocking M receptor by injection of atropine, could attenuate AA. Whereas, interrupting the degradation of ACh by intracerebroventricular injection of calabarine or injection of exogenous ACh could elevate the pain threshold and reinforce AA\textsuperscript{[1].}

6.2 ACh receptor PET radioligands $^{11}$C-4-NMBA, $^{11}$C-3-NMNB and $^{11}$C-bezotropine are the available PET radioligands currently with non-selectivity for M receptor, which can be applied to research the function of M receptor involved in AA. The studies on selective tracers for M receptor subtypes remain in progress. $^{11}$C-nicotine was used in human body to image the N receptors, but the PET images were plagued with high nonspecific binding\textsuperscript{[16]}. $^{11}$C-CHIBA-1001 has been successfully used to image $\alpha_2$ subunit of central N receptor in monkey brain by some groups recently\textsuperscript{[24]}. The roles of N receptors in AA might be revealed by using PET imaging with these radioligands in the future.

PET imaging agents for central acetylcholinesterase (AChE) activity, such as $^{11}$C-MPSA (N-methyl-3-piperidylaceta) and $^{11}$C-MPIA (N-methylpipericin-4-ylacetate), have been investigated for visualizing AChE activity in human body, and PET studies showed a widespread reduction of AChE activity in the cerebral cortex of Alzheimer’s disease patients\textsuperscript{[30].}

7 Excitatory amino acid receptors

7.1 Excitatory amino acid receptors related to AA

Aminoglutaminic acid (Glu) is considered as the major excitatory amino acid (EAA) in CNS, and the next is aspartate (Asp). Some other EAAs with strong excitatory effects also are identified in recent years, including N-methyl-D-aspartate (NMDA), quisqualic acid (QA), kainic acid (KA), and amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA). In mammalian brain, there are five categories of EAA receptors at least, respectively named NMDA receptor, AMPA receptor, KA receptor, L-2-amino phosphono-butyric acid (L-AP) receptor and metabotrophic glutamate receptor (mGluR). The former four are classified into ionotropic receptor, and the latter G protein-coupled receptor\textsuperscript{[11-16].}

Multiple researches discovered that AA could be enhanced efficiently by blockade of NMDA or AMPA/KA receptors, while activating AMPA/KA receptor would result in algesia. Choi et al\textsuperscript{[25]} found that in complete Freund’s adjuvant (CFA)-induced inflammation model, EA lessened both inflammation agent-induced pain responses and expression of NR\textsubscript{1} and NR\textsubscript{2} (NMDA receptor subtypes) in the spinal cord. Wang et al\textsuperscript{[26]} summarized that EA and NMDA or AMPA/KA receptor antagonists have a synergic antinociceptive action against inflammatory pain. EA-induced analgesic effects on inflammation mice could be potentiated by combining EA with NMDA or AMPA/KA receptor antagonists, especially with NMDA antagonist. However, it was ineffective while using NMDA or AMPA/KA receptor antagonists alone.

7.2 EAA PET radioligands

Despite strenuous efforts, no suitable PET radioligand currently ex-
ists for the imaging of NMDA and AMPA/KA receptors contributed in AA in human body. One group recently reported a novel, selective, and high-affinity mGluR5 antagonist that showed promise as a PET radioligand for the imaging of mGluR5 in human being. This new compound, $^{11}$C-ABP688, displayed an in vivo distribution pattern in rodents and human subjects, being consistent with the known regional density of mGluR5$^{[16]}$. However, the correlation between mGluR5 and AA needs to be verified.

8 Others

Beside the central neurotransmitter-receptor mentioned above, there are some other neuropeptides, neurosteroids and their respective receptors involved in AA, such as cholecystokinin receptor, angiotension II receptor, and estrogen receptor. PET radioligands for these receptors are rarely reported at present, which would have extensive study prospects.

Consequently, there are multiple and diverse central neurotransmitter-receptor contributed in AA, and the most of which have their specific PET radioligands (Table 1). PET receptor imaging has been widely employed for exploring a great deal of psychiatric and neurological disorders currently, but it is still at the initial stage in the field of acupuncture. It can be confirmed that identification of more suitable PET radioligands for receptors and developing of various clinical and experimental studies relevant to acupuncture would provide new insights into the neurophysiological and biochemical mechanisms of AA, and facilitate the development of nuclear medicine and traditional Chinese medicine.

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<th>Receptors</th>
<th>Effects in AA by activating receptors</th>
<th>Radioligands with $^{11}$C</th>
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<tr>
<td>OR $\mu/\delta$</td>
<td>Mediate low frequency EA (physiological pain) Mediate EA (pathological pain)</td>
<td>$^{11}$C-DPN $^{11}$C-CFN $^{11}$C-MeNTI</td>
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<td>$\kappa$</td>
<td>Mediate high frequency EA (physiological pain) Inaction (pathological pain)</td>
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<td>Synergism</td>
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**REFERENCES**


