Mini Review

Are δ-Opioid Receptor Agonists with Facilitating Effects on Fear Extinction Learning Candidates for the Treatment of Post-Traumatic Stress Disorder?

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ABSTRACT

Several lines of evidence have suggested that Delta Opioid Receptor (DOP) system is involved in the mechanisms underlying the pathophysiology of fear and anxiety, as DOP is abundant in brain regions involved in emotion regulation systems. Recently, DOP agonists have attracted much attention as a promising new psychotropic agent for anxiety. Post-Traumatic Stress Disorder (PTSD) is a condition in which an individual who has experienced a traumatic event continues to have recurrent flashbacks of the event, resulting in increased fear and anxiety. In the pathophysiology of PTSD, persistence of traumatic fear memories and impairment of fear extinction have been implicated. Several studies have focused on pharmacological agents to facilitate fear extinction. However, because of difficulties in the regulation of fear memory to specifically induce extinction, no clinically usable treatments have been developed to date. We recently found that a novel selective DOP agonist KNT-127 produced robust anxiolytic-like effects, and demonstrated facilitating effects on fear extinction learning in fear conditioning test of mice, a widely accepted model of PTSD that is frequently used to examine fear memory not only in rodents but also in humans. Interestingly, another DOP agonist SNC80 did not cause any facilitating effects, although anxiolytic-like effects were observed. Previous studies have shown that SNC80 effectively induces the recruitment of β-arrestin, whereas KNT-127 is an intermediate its recruiters, although the inhibitory effects on the forskolin-induced cAMP production in HEK293 cells expressing DOP showed similar effects on both these drugs. Although DOP agonists have a common robust anxiolytic-like effect, the mechanism of extinction-facilitating effect of DOP agonists is a different from the anxiolytic-like effect. The mechanism may involve the β-arrestin independent properties of DOP agonists. We propose that biased DOP agonists are expected to be an excellent candidate compound as therapeutic targets for PTSD.

Key Words: Delta opioid, Anxiety, Fear memory, Biased ligand, Extinction, Cognitive behavioral therapy

Abbreviations: AMDD: Anxious Major Depressive Disorder, CS: Conditioned Stimulus, GPCR: G-Protein-Coupled Receptor, PTSD: Post-Traumatic Stress Disorder.

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INTRODUCTION

Several lines of evidence have suggested that the Delta (δ) Opioid Receptor (DOP) system is involved in the mechanisms underlying the pathophysiology of fear and anxiety, as DOP is abundant in brain regions involved in emotional regulation systems [1]. A previous study indicated that DOP-deficient mice exhibit strong anxiety-like and depressive-like behaviors, and DOP is thought to be involved in the control of these behaviors [2]. Other studies have shown that changing opioid signaling have been observed with currently used treatments for depression and pathophysiology of Post-Traumatic Stress Disorder (PTSD) [3-5]. In addition, there have been many suggestions that DOP agonists produce potent anti-depressant and anxiolytic-like effects in rodents. Thus, DOP has become an attractive target for psychotropic drugs. However, several prototype DOP agonists have been reported to have severe side effects, such as seizures in rodents and monkeys, which have limited their clinical development [6]. Recently, novel selective and potent DOP agonists that do not produce convulsions have been developed, unlike prototype DOP agonists. We found that a DOP agonist with a morphine structure, KNT-127, produced no convulsive effects, even at 100 times higher doses, indicating anti-depressant and anxiolytic-like in rodents [7]. Recently, in a placebo-controlled pilot trial, the selective DOP agonist AZD2327 was reported to likely have a better anxiolytic effect profile in patients with Anxious Major Depressive Disorder (AMDD) [8]. Now, DOP agonists have attracted much attention as a promising new psychotropic agent for anxiety disorders, including PTSD.

CURRENT STATUS AND ISSUES IN THE DEVELOPMENT OF THERAPEUTIC DRUGS FOR PTSD

PTSD is a condition in which, after facing the danger of death, the memory of the experience keeps coming back like a flashback or nightmare, regardless of one's will, resulting in increased anxiety and tension, and a loss of reality. In the pathophysiology of PTSD, persistence of traumatic fear memories and impairment of fear extinction has been implicated [9–11]. Fear extinction is an inhibitory learning process by which a fear response developed in traumatic event is reduced after long or repetitive retrieval of the memory of the event and is considered as biological process underlying exposure therapy, one of a form of cognitive behavioral therapy, for the treatment of PTSD [12,13]. From a clinical point of view, therefore, facilitating fear extinction has attracted attention as an effective method to enhance the exposure therapy [14].

In laboratory experiment, fear conditioning test is widely accepted as a model of PTSD and frequently used to examine fear memory not only in rodents but also in humans [15-17]. Briefly, fear extinction is assessed using a serial re-exposure protocol. First, subjects are exposed to an Unconditioned Stimulus (US), such as electrical foot shock in combination with a Conditioned Stimulus (CS), such as a tone, light, or experimental context. Next, subjects are re-exposed to the same CS without US presentation as the memory retrieval session. When the duration of the memory retrieval session is long enough, or the session is repeated over time, fear extinction occurs and reduces the fear response. In rodents, fear memory is evaluated by measuring a fear response termed freezing behavior, which is complete immobilization except for body movements necessary for respiration [18]. Another method used to evaluate fear extinction is the fear potentiated startle paradigm [13]. Rodents that have undergone fear conditioning show a stronger startle response to acoustic sound presentation. Fear conditioning can also be utilized in humans [19].

Cite this article as: Saitoh A, Kawaminami A, Yamada D. Are δ-Opioid Receptor Agonists with Facilitating Effects on Fear Extinction Learning Candidates for the Treatment of Post-Traumatic Stress Disorder? J Basic Clin Pharma.2021;12:92-94.

It should be noted that the relapse of fear response after exposure therapy is one of the problems observed after the exposure therapy in the treatment of PTSD. In animal study, there are several types of fear relapse:

1. Spontaneous recovery, a phenomenon where extinguished fear response reappear with the passage of time after extinction training.

2. Renewal, a phenomenon where changes in the context evoke a recovery of fear response to an extinguished CS when the subjects re-exposed to a different CS where extinction training conducted and

3. Reinstatement, a phenomenon where an extinguished fear response recovers after the presentation of an even weaker US in the extinction context after extinction training.

A great amount of research has conducted to establish the methods that prevent the relapse of fear. Numerous studies have assessed pharmacological agents capable of facilitating fear extinction and preventing recovery of fear response, a partial agonist for NMDA receptors, D-cycloserine, AMPA receptor potentiator, 4-(2-(phenylsulfonylamino)ethylthio)-2,6-difluoro-phenoxyacetamide (PEPA), a selective reuptake inhibitor of endocannabinoids, AM404, and a histone deacetylase inhibitor, valproic acid facilitate fear extinction [12,20-23]. However, because of difficulty in the regulation of fear memory to specifically induce extinction, these drugs are unavailable for the clinical use to date. In actual clinical practice, monoaminergic antidepressants such as selective serotonin reuptake inhibitors have been used to treat PTSD, but their therapeutic effects have been insufficient. Today, there is a need for the development of psychotropic drugs with novel mechanisms that have a reliable therapeutic effect.

FACILITATING EFFECTS ON FEAR EXTINCTION LEARNING OBSERVED WITH DOP AGONISTS

We recently found that systemic administration of KNT-127, a selective DOP agonist, has an extinction-facilitating effect in the fear conditioning test. Mice were contextually fear conditioned with eight foot shocks (0.8 mA, 1 s duration, 30 s interval). Twenty-four hours after conditioning, mice were re-exposed to the same context without presentation of foot shocks. Next, 30 min before re-exposure, the mice were intraperitoneally injected with KNT-127. On day 3, the mice were re-exposed to the same context without foot shocks and KNT-127. In the behavioral test on day 3, mice treated with KNT-127 showed significant reduction in freezing behaviors. These results suggested that in contextually conditioned fear, KNT-127 produced the anxiolytic-like effect on day 2 and then facilitating effect on fear extinction learning on day 3. This protocol is generally used to assess drug effects on extinction facilitation. Interestingly, although another DOP agonist SNC80 also produced the decreases in the freezing behaviors on day 2, SNC80 produced no effects on the day 3. These results suggested that SNC80 produced anxiolytic-like effects, while no effects on the extinction learning [24]. This notion is supported by the fact that clinically available anxiolytic drug, Benzodiazepines, significantly reduce freezing behavior only in the re-exposure on day 2, but not that on day 3 [25].

RECENT STUDIES SUGGEST THAT DOP AGONIST MAY HAVE BIASED LIGANDS

DOP is a G-protein-coupled receptor (GPCR) that binds primary to the inhibitory Gi/o family. It is now widely recognized that GPCRs actually exist in multiple conformations and that ligands can stabilize different active states. For example, there are two types of DOP agonists depending on the difference in receptor internalization. Recent study using β-arrestin knockout mice indicates that high (SNC80) and low (ARM390) internalizing DOP agonists may also differentially recruit arrestin isoforms [26]. More recently, it is indicated that the anxiolytic-like effects of SNC80 was abolished in β-arrestin knockout mice [27]. Previous studies have shown that SNC80 effectively induces the recruitment of β-arrestin 1 and 2, whereas KNT-127 is an intermediate β-arrestin 2 recruiters, although the inhibitory effects on the forskolin-induced cAMP production in HEK293 cells expressing DOP showed similar effects on both SNC80 and KNT-127 [28]. Taken together, we propose that facilitating effects of fear extinction learning observed in mice treated with KNT-127 may be mediated by an independent mechanism of β-arrestin signaling.

Many pharmaceutical companies have tried to develop several compounds, since DOP agonists are expected to be strong analgesics without the risk of addiction. TAN-67 was the first non-peptide DOP agonist and, since then, SNC80 and its derivatives were most frequently developed [29-30]. Unfortunately, the prototype DOP agonist-like SNC80 resulted in severe adverse effects, including convulsion and catalepsy, in rodents and monkeys. These adverse effects remain major issues limiting the clinical development of DOP agonists [31]. Recently, our group succeeded in synthesizing a novel DOP agonist termed KNT-127 [6,32]. KNT-127 produced neither convulsions nor catalepsy, even at a 100-fold higher dose than that required for antidepressant-like or anxiolytic-like effects in rodents [7]. However, the agonists did not show a strong morphine-like analgesic effect, which inevitably led to clinical indications as antidepressant and anxiolytic drugs.

CONCLUSION

Although DOP agonists have a common robust anxiolytic-like effect, it has been suggested that fear extinction learning by DOP agonists occurs through a mechanism different from that of the anxiolytic-like effect. This mechanism may involve b-arrestin-independent properties of DOP agonists. In summary, we propose that biased DOP agonists as excellent candidate compounds for PTSD therapy.

DISCLOSURES

There are no conflicts of interest to declare.

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