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Editorial

The Progression of the Role of Fluoxetine in Aggression

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Abstract

Aggression is a prevalent symptom of many neurological disorder and serotonin alteration is supposed to play an important role in it. Therefore, fluoxetine, one of the most widely prescribed selective serotonin reuptake inhibitor, is widely applied to treat agonistic behavior. Intriguingly, fluoxetine displayed biphasic effect on aggressive behavior. This overview briefly updates the role of fluoxetine in aggressive behaviour as well as its potential mechanism, and speculates the possible opportunity for the future study.

Keywords: *Aggression; Fluoxetine; Serotonin*

Aggression behavior is a prevalent phenotype/ symptom of several central nervous system disorders, such as schizophrenia, posttraumatic stress disorder, major manic depressive disorder and epilepsy. A large body of studies in humans and animals elucidate the critical role of serotonin in agonistic behavior. It is demonstrated that serotonin plays an important role in aggression because it is reported that heightened agonistic behaviors are associated with the reduction of serotonin metabolite 5-HIAA in the cerebrospinal fluid and decreased serotonin turnover ratios [1], and supplemental tryptophan diet can increase brain serotonin and attenuate aggressive behavior [2-4]. Therefore, the pharmacologic agent which acts on serotonin becomes a promising therapeutic treatment. Fluoxetine, one of the most popular serotonin reuptake inhibitor, is widely used to manage aggressive behavior. The current article overviews the role of fluoxetine in aggression in these decades and updates its progress.

Fluoxetine, a selective serotonin reuptake inhibitor, was initially developed to cure depression in the early 1970s and was approved by US FDA in 1987. From then on, fluoxetine became one of the most widely prescribed antidepressants for decades [5]. Furthermore, people started to realize that fluoxetine can reduce aggressive like behavior [6]. During these decades, extensive studies have been conducted to investigate the effect of fluoxetine on aggression. Intriguingly, fluoxetine exhibits biphasic effect on agonistic behaviour which is complicated as it relates to the dose, type of aggression and test time.

Previous preclinical studies revealed fluoxetine attenuated various aggressive behavior in rodent and non-human primates [7,8]. Similarly, pervious clinical evidences also displayed that fluoxetine exerted suppressive effect on aggressive behaviors in patients with mental retardation, personality disorder and depression [5,9-11]. Serotonin alteration is supposed to play an important role since the reduction of serotonin metabolite 5-HIAA in the cerebrospinal fluid and decreased serotonin turnover ratios are associated with heightened attack behaviors [1], and fluoxetine injection decreases serotonin rate of fall in rat brain after inhibiting serotonin synthesis. [12], indicating the anti-aggressive efficacy of fluoxetine derives from inhibiting serotonin reuptake and enhancing serotonin level in the synapse. Moreover, the later evidence suggested that fluoxetine caused reduction of brain allopregnanolone down-regulation plays more important role in its anti-aggression effect [13]. However, current study shows that high dose of fluoxetine 16 mg/kg heightened defensive aggression behavior 24 hours after injection, and decreased serotonin turnover ratios in frontal cortex and hypothalamus at the same time point, suggesting attenuated serotonin activity in these brain regions could be associated with observed enhanced attack behavior following fluoxetine administration [14]. Furthermore, some clinical evidences displayed fluoxetine increased aggressive and impulsive behaviors of depressive patients [11,15,16] which were consistent with preclinical outcome, and the likely reduction of serotonin synthesis in the

orbitofrontal cortex may contribute to this heightened aggression [17]. Moreover, the predisposition factors which affect individual's response to fluoxetine treatments [18] and interactions between environment and gene may also play a role in this heightened aggression [19]. Furthermore, present investigation revealed that gender difference plays an important role on effect of fluoxetine since fluoxetine escalated aggression in females and substantially attenuated aggression in males [20]. Although a number of studies investigated the function of fluoxetine on aggression, there are still more mechanisms underlying its complicated effects remain to be clarified, for example, if fluoxetine exerts its effect by altering serotonergic DRN-PFC (dorsal raphe nucleus- prefrontal cortex) pathway. The future of the study will be undoubtedly bright and will guide us to explore better therapy.

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Conflicts of Interest

None declared.

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