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Celecoxib and omega-3 fatty acids alone and in combination with risperidone affect the behavior and brain biochemistry in amphetamine-induced model of schizophrenia

Alaa El-Sayed El-Sisi[a], Samia Salem Sokkar[a], Magda El-Sayed El-Sayad[a], Ehab Sayed Ramadan[b], Enass Yossef Osman[a,*]

[a] Department of Pharmacology and Toxicology, Faculty of Pharmacy, Tanta University, Egypt
[b] Department of Neuropsychiatry, Faculty of Medicine, University of Tanta, Egypt

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ABSTRACT

The implications of oxidative stress and neuro-inflammation in the pathogenesis of schizophrenia have been elucidated. Despite their effectiveness against positive symptoms of schizophrenia, antipsychotics have limited effectiveness against negative and cognitive symptoms and are associated with remarkable adverse effects. The use of celecoxib or omega-3 in schizophrenia may have beneficial effects. This study aimed to evaluate the possible efficacies of celecoxib, omega-3 or the combination of celecoxib + risperidone and omega-3+ risperidone compared to risperidone on the behavior and brain biochemistry in rats. In the present study, an amphetamine-induced model of schizophrenia in adult male rats was used to evaluate the effects of celecoxib, omega-3, celecoxib + risperidone and omega-3+ risperidone on the behavior of animals and on brain lipid peroxidation or tumor necrosis factor-alpha. In the water maze task, celecoxib, omega-3, celecoxib + risperidone, omega-3+ risperidone significantly decreased the latency time compared to amphetamine-treated group. Celecoxib, omega-3, celecoxib + risperidone, omega–3 + risperidone also significantly reversed the decreased spontaneous alternation induced by amphetamine in the Y-maze task. In the social interaction task, groups treated with celecoxib, omega-3, celecoxib + risperidone, omega-3+ risperidone spent less time to recognize foreign animals than animals in the amphetamine-treated group. Increased brain MDA and TNF-α levels due to amphetamine were significantly reduced in groups treated with celecoxib + risperidone or omega-3+ risperidone. The present findings showed that celecoxib or omega-3 can attenuate amphetamine- induced behavioral impairment and these effects may be associated with their ability to decrease lipid peroxidation and cytokine release. Celecoxib or omega-3 may be promising candidates as adjuvant therapy for schizophrenia.

1. Introduction

Schizophrenia is a debilitating psychiatric disease affecting approximately 1% of the world population [1,2]. The symptoms of schizophrenia are classified into positive symptoms, which represent distortion of normal functioning and include delusion and hallucinations, paranoia, agitation; negative symptoms, which represent deficits in functioning and include social withdrawal, affective flattening, and lack of motivation; and cognitive symptoms which comprise deficits in learning, memory, attention, and executive functions [3,4].

Despite the advances in understanding the pathophysiology of the disease, the exact mechanism by which schizophrenia develops remains unknown. Genetic factors, disturbances in neurotransmitters especially dopamine, serotonin and also environmental factors have been implicated in the etiology of schizophrenia [5–7]. Until now, most pharmacological treatments for schizophrenia were based on modulation of neurotransmitters, dopamine for the "typical", and serotonin, norepinephrine, acetylcholine, and histamine for the "atypicals" [8]. While effective

Abbreviations: MDA, malondialdeyde; TNF-α, tumor necrosis factor alpha; DA, dopamine; 5-HT, serotonin; NO, nitric oxide; IL-6, interleukin-6; COX-2, cyclooxygenase-2; PGs, prostaglandins; FA, fatty acids; AMPH, amphetamine; RIS, risperidone; CELECO, celecoxib; OMEG-3, omega-3 fatty acids.

* Corresponding author at: Faculty of Pharmacy, Tanta University, 32 EL–Geish street, Tanta, Egypt.
E-mail address: enassyoussefosman@yahoo.com (E.Y. Osman).

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in treating positive symptoms, current antipsychotics lack efficacy for negative and cognitive symptoms. Also, while the newer antipsychotics produce fewer motor side effects, they produce their own adverse effects such as weight gain and endocrinopathies. Consequently, the need for more effective and better-tolerated antipsychotic agents, and to identify new molecular targets has been emerged [9].

Oxidative stress is the loss of balance between antioxidant defense mechanisms and the production of endogenous reactive oxygen species. Brain is more vulnerable to the toxic effects of reactive oxygen species due to its high oxidative metabolic activity, low levels of antioxidant enzymes and high ratio of membrane polyunsaturated fatty acids [10]. Several authors have reported elevated levels of malondialdehyde and nitric oxide, along with lower levels of the antioxidants in the plasma, cerebrospinal fluid and peripheral tissues of schizophrenia patients [11–13].

The role of neuro-inflammation in schizophrenia has also been studied. Microglia hypothesis of schizophrenia stated that microglia (derived from peripheral macrophages) respond to minor pathological changes in the brain by releasing pro-inflammatory cytokines such as interleukin-6, tumor necrosis factor alpha and interferon gamma. Prolonged microglial hyperactivity leads to neuronal degeneration, neuronal apoptosis and brain damage [14]. One of the most important cytokines in the pathophysiology of schizophrenia is TNF-α. It plays a key role in orchestrating the complex events involved in inflammation and immunity [15]. Although majority of the studies have reported elevated levels of TNF-α in schizophrenic patients [16,17], some studies have observed decreases in TNF-α concentration [18].

Omega-3 fatty acids play vital roles in brain function, normal growth and development [19]. They are located at the core of the walls of brain cells thus providing them the flexibility necessary to receive the signals from other cells [20]. The therapeutic effects of omega-3 fatty acids in schizophrenia may result from altered membrane fluidity and receptor responses following their incorporation into cell membranes [21]. They also interact with the dopaminergic and serotonergic systems through modulation of receptor-coupled arachidonic acid release [22].

Celecoxib is a non-steroidal anti-inflammatory drug acts by cyclooxygenase-2 enzyme inhibition which is the enzyme responsible for the synthesis of prostaglandins, prostacyclins, and thromboxanes [23]. In addition to their involvement in inflammatory cascade, prostaglandins participate in synaptic plasticity through several mechanisms, including modulation of adrenergic, noradrenergic, and glutamatergic neurotransmission [24]. Studies have shown that celecoxib can serve as a beneficial add-on therapy in psychiatric disorders [25,26].

Despite their well-established pharmacological effects in many disease conditions, celecoxib and omega-3 fatty acids have not been extensively studied in schizophrenia. The current study aimed to elucidate the effects of omega-3 fatty acids and celecoxib alone or in combination with risperidone on the amphetamine-induced behavioral impairment using the water maze, Y-maze and social recognition tasks. The brain tissue malondialdehyde and TNF-α levels were also estimated.

2. Materials and methods

2.1. Animals

All experimental procedures were carried out in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and with the approval of Ethics Committee of faculty of Pharmacy, Tanta University, Egypt. Adult white male albino rats obtained from the animal house of the National Institute of Ophthalmology, Cairo, Egypt, and weighing 150–180 g were used in the present study The animals were kept in climate-controlled (22 °C) with light–dark cycle of 12 h; water and food were provided ad libitum throughout the treatment.

2.2. Drugs and reagents

Amphetamine sulfate (d-isomer) was purchased as a white powder from Sigma Aldrich (U.S.A). 2,5- dimethyl–celecoxib was purchased as a white powder from Sigma Aldrich (U.S.A.). Omega-3 fatty acid was purchased as soft gelatin capsules (180 mg eicosapentanenoic acid (EPA) + 120 mg docosahexaenoic acid (DHA)/capsule) from Sedico (Egypt). Risperidal was purchased as 1 mg/ml solution from Janseen Cilag (France). Rat Tumor necrosis factor alpha ELISA kit was purchase from Bioscience (U.S. A). All other chemicals were of analytical grade.

2.3. Drug administration

The study used a total of 98 animals, which were divided randomly into seven groups of 14 rats each.

Group I: Rats were injected with control vehicle (saline and DMSO) s.c or i.p, respectively at a dose volume of 0.5 ml/100 g body weight each for five consecutive days. This group was co-currently carried out with Amphetamine- treated groups to serve as a control group. Group II: Rats were injected with amphetamine (2.5 mg/kg, s.c) every other day for a total of five doses [27] Group III: Rats were injected with risperidone (0.1 mg/kg, i.p) [27] 20 min before amphetamine every other day for a total of five doses. Group IV: Rats were injected with celecoxib (5 mg/kg,i.p.) 20 min before amphetamine every other day for a total of five doses [28]. Group V: Rats received omega-3 fatty acids (0.1 g, p.o.) 20 min before amphetamine every other day for a total of five doses [29]. Group VI: Rats were injected with a combination of risperidone and celecoxib 20 min before amphetamine every other day for a total of five doses. Group VII: Rats were injected with a combination of risperidone and omega −3 fatty acids 20 min before amphetamine every other day for a total of five doses. Randomly chosen rats were divided in two main categories (7 rats each). The first category was used for evaluation of the behavioral parameters 24hr after the last dose treatment and the second category was used for estimation of biological parameters.

2.4. Behavioral testing

2.4.1. Swimming test

A rectangular glass tank (140cm × 70 cm diameter × 60 cm high) was filled to 30 cm deep with water that was made opaque by addition of milk powder at a temperature (26 °C). A stainless steel ramp was placed within the pool, submerged approximately 2 cm below the surface of the water. The platform was placed in the center of the west quadrant for each trial. Before the start of training, animals were habituated to the pool without a platform 1 min per day for 3 days. The experimenters and extra maze cues remained constant throughout testing [30]. To test for spatial memory as an indicator for the cognitive performance of rats, a simple water maze apparatus and procedure were designed as follows: The rats were trained to locate the hidden platform in the water pool. During training, animals were required to locate the submerged platform by using extra maze cues. The rat was placed into the pool, facing the wall of the tank and allowed 120 s to locate and climb onto the submerged platform on which it was allowed to stay for 30 s., before the next training trial. If it failed to find the platform within 120 s., it was guided gently onto platform. The behavior of the animal in the swimming pool was observed in order to evaluate the latency time (the time to reach the hidden platform) on each day of testing. The mean latency for each group