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Short communication

Sub-chronic celecoxib prevents soluble beta amyloid-induced depressive-like behaviour in rats

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ABSTRACT

Background: Depression and Alzheimer's disease (AD) are co-morbid conditions. Neuropsychiatric symptoms have been reported as prodromal symptoms of AD-like dementia and soluble forms of beta amyloid peptide (Aβ), the main constituent of insoluble plaques typical of AD brains, have been implicated in such an effect. We have previously shown that intracerebral injection of Aβ can evoke a depressive-like state in rats, accompanied by neurochemical and neuroendocrine alterations reminiscent of depressive symptoms in humans. AD and depression are crucially linked by neuroinflammation and cyclooxygenase II (COX-2) enzyme involvement is an intriguing field of research. Indeed, its pharmacological inhibition has shown both antidepressant and Aβ modulating effects.

Methods: Male rats were exposed to sub-chronic celecoxib (15 mg/kg/day sc for 8 days), a selective COX-2 inhibitor or vehicle (saline), starting from the day before central intracerebroventricular injection of Aβ peptide (5μL of 4 μM solution or vehicle for sham). Animals were tested for depressive-like behaviour by using the forced swimming test paradigm and prefrontal serotonin (5-HT) content and plasma Aβ levels were further evaluated.

Results: We found that celecoxib treatment prevented the pro-depressive effects induced by Aβ. Moreover, it also prevented the reduction in 5-HT content in prefrontal cortex of Aβ-treated rats and decreased their plasma Aβ levels.

Conclusions: Taken together, our data indicate that celecoxib could be a suitable pharmaceutical tool for the treatment of depressive state related to increased Aβ levels.

1. Introduction

Depressive states have been linked to the development of neurodegenerative disorders such as Alzheimer's disease (AD). Indeed, depression is a common feature in early AD representing a clinical manifestation of this disease before cognitive decline (Visser et al., 2000). Depression has been indicated as a risk factor for AD and depressed subjects, mild cognitive impaired, show more than twice the risk of developing AD-type dementia than non-depressed (Modrego and Ferrandez, 2004). In this regard, neuropsychiatric symptoms have been reported as prodromal symptoms of dementia deriving from neurobiological changes in specific cerebral regions (Andersen et al., 2005). Soluble forms of beta amyloid peptide (Aβ), the main constituent of insoluble plaques typical of AD brains, rather than the aggregated form, have been implicated in such an effect. According to the *amyloid cascade hypothesis*, Aβ peptide production is based on the so called *amyloidogenic pathway*, consisting of sequential proteolytic cleavage of the amyloid precursor protein by β- and γ − secretases (Selkoe and Hardy, 2016). Although Aβ holds important physiological properties, it can also impair neurotransmission. Accordingly, we have previously demonstrated in rats that a single intracerebral injection of Aβ can evoke a depressive- like state accompanied by reduction in serotonin (5-HT) and neurotrophin levels (Colaianna et al., 2010) and altered hypothalamic pituitary adrenal (HPA) axis response and NA levels (Morgese et al., 2015; Morgese et al., 2014). Furthermore, a depressive-like state induced by lifelong exposure to an unbalanced fat diet was associated with increased plasma Aβ levels (Morgese et al., 2016). Neuroinflammation represents a common link between depression and AD and the cyclooxygenase II (COX-2) enzyme seems to play a crucial role. In particular, increased expression of COX-2 has been associated with alteration in stress response in animal model of depression (Cassano et al., 2006; Guo et al., 2009). In further agreement, celecoxib, a COX-2 inhibitor, showed antidepressant properties as adjuvant therapy in clinical trials (Akhondzadeh et al., 2009; Muller et al., 2006). Thus, in the present study, we tested in vivo the effect of sub-chronic celecoxib administration on the Aβ-induced model of depression and

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we combined *ex-vivo* 5-HT and Aβ quantifications in order to evaluate a possible mechanism of action.

2. Materials and methods

2.1. Animals

All experiments were conducted on male Wistar rats (275–300 g, Harlan, S. Pietro al Natisone, Udine, Italy) kept under controlled conditions of temperature (22 ± 1 °C), humidity (55 ± 5%) and lighting (12 h light/dark cycle; lights on from 7:00 AM to 7:00 PM) with free access to food and water. Procedures involving animals and their care were conducted in conformity with the institutional guidelines of the Italian Ministry of Health (D.L. 26/2014), the Guide for the Care and Use of Mammals in Neuroscience and Behavioral Research (National Research Council 2004), the Directive 2010/63/EU of the European Parliament and of the Council of 22 September 2010 on the protection of animals used for scientific purposes. All procedures involving animals were conducted in accordance to ARRIVE guidelines. Animal welfare was daily monitored through the entire period of experimental procedures. No signs of distress were evidenced and all efforts were made to minimize the number of animals used and their suffering.

2.2. Aβ administration and experimental design

The $A\beta_{1\text{-}42}$ peptide (Tocris, Bristol, UK) was dissolved (4 μM, Aβ) in sterile double-distilled water (vehicle, sham) and centrally released into the right ventricle (icv) as previously described (Tucci et al., 2014). All experimental procedures were performed 7 days after icv administration.

Celecoxib (Pfizer, Milan, Italy) was dissolved in saline and given subcutaneously (sc) at a dose of 15 mg/kg/day for 8 days. Drug treatment (celecoxib or vehicle) started 24 hours before surgery.

2.3. Forced swimming test

During the preconditioning period, animals were individually placed and videotaped in inescapable Perspex cylinders (diameter23 cm; height 70 cm) filled with a constant maintained 25 °C temperature water at a height of 30 cm for 15 min. As previously described (Zotti et al., 2013), 24 hours later (test day), each rat was positioned into the water-filled cylinder. This 5 min session was video-recorded and subsequently scored by an observer blind to the treatment groups. The following frequency (every 5 sec) behaviours were measured: struggling (tentative of escape), swimming (moving around the cylinder) and immobility (floating making only the necessary movements to keep head above the water).

2.4. Monoamine quantification

Rats were euthanized and brains were immediately removed and cooled on ice for dissection of PFC according to the atlas of Paxinos and Watson (1998). Tissues were frozen and stored at −80 °C until analyses. 5-HT and 5-HIAA concentrations were determined by HPLC coupled with an electrochemical detector (Ultimate ECD, Dionex Scientific, Milan, Italy) as previously described (Morgese et al., 2017). 5-HT turnover was calculated as 5-HIAA/5-HT ratio.

2.5. ELISA quantifications

Plasma samples were analyzed for Aβ by using ELISA kits (CloudClone Corporation, Houston, Texas, USA), according to the manufacturer's instructions. Duplicate analyses were carried out to avoid intra-assay variations.

2.6. Statistical analysis

Results were expressed as mean ± S.E.M. Statistical analyses were performed using Graph Pad 5.0 (GraphPad Software, San Diego, CA) for Windows. Data were tested for normality and then analysed by using two-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparison test. P value was set at 0.05.

3. Results

Aβ central injection evoked a depressive-like profile in treated rats as revealed by the increased frequency in immobility behaviour and reduced frequency of swimming (Fig. 1A-B, two-way ANOVA followed by Bonferroni's multiple comparisons test, $P < 0.0001$ and $P < 0.01$ for veh group Aβ-treated rats compared to sham, respectively) with no differences in struggling (Fig. 1C, two-way ANOVA followed by Bonferroni's multiple comparison test, n.s.). Celecoxib administration (15 mg/kg/day sc for 8 days) prevented Aβ pro-depressive effects, either for immobility or swimming frequencies (Fig. 1A-B, two-way ANOVA followed by Bonferroni's multiple comparison test, $P < 0.05$ for Aβ group celecoxib-treated versus veh rats, respectively).Behavioural outcomes were supported by neurochemical data. As shown in Fig. 1D, Aβ administration significantly reduced prefrontal 5-HT levels and subchronic celecoxib treatment reversed such an effect. No alteration was retrieved in 5-HT metabolism (Fig. 1E, two-way ANOVA followed by Bonferroni's multiple comparison test, $P > 0.05$). Furthermore, celecoxib administration significantly reduced plasma Aβ levels 7 days after icv release of the peptide (Fig. 2, two-way ANOVA followed by Bonferroni's multiple comparisons test).

4. Discussion

In the present study, we showed that sub-chronic treatment with the COX-2 inhibitor celecoxib reversed the pro-depressive effects induced by a single icv administration of Aβ in rats. In particular, we found that celecoxib prevented the increase in immobility and the decrease in swimming frequency, as well as the reduction in PFC 5-HT content induced by the peptide. In addition, an Aβ-lowering effect was also described. We have previously found that central Aβ administration induces a depressive-like behaviour in rats and conditions leading to increased Aβ levels correspond to such behavioural outcome (Colaianna et al., 2010; Morgese et al., 2017). Here we found an antidepressant property of celecoxib. This result is in line with other observations either in animal models (Cassano et al., 2006) or in clinical trials (Muller et al., 2006). Nevertheless, this is the first report linking such beneficial effect in the animal model of Aβ-induced depressive like behaviour. A possible mechanism could rely on the reduction in proinflammatory response secondary to Aβ injection. In this regard, we have previously found that some Aβ-related effects on neurotransmission are mediated by IL-1 receptors (Morgese et al., 2015). Indeed, we found that Aβ increases central IL-1β (Mhillaj et al., 2018), a cytokine crucial for depression and stress response, and COX-2 expression. Accordingly, celecoxib treatment prevented those effects endorsing a possible protective property against depressive state induced by stress. In keeping with this hypothesis, both Aβ and COX-2 have been linked to alteration in stress response (Morgese et al., 2014; Myint et al., 2007). COX stimulationcan activate central stress response, by increasing prostaglandin E_2 (PGE_2) release, an eicosanoid enhanced in biological fluids of depressed patients (Muller et al., 2006), and in our animal model Aβ injection increased COX-2 expression (Mhillaj et al., 2018). In this light, a proposed mechanism of action of celecoxib in stress-related depression model was the central reduction of COX-2 expression (Guo et al., 2009). Interestingly, it was reported that another possible mechanism explaining the antidepressant effect of celecoxib was the enhancement of glucocorticoid receptor function (Hu et al., 2005). Alterations in stress response can also interfere with serotonergic