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Antidepressant drugs for beta amyloid-induced depression: A new standpoint?

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ABSTRACT

Mounting evidence suggests that depression represents a risk factor and an early manifestation of Alzheimer's disease (AD). Neuropsychiatric symptoms may derive from neurobiological changes in specific brain areas and may be considered prodromal of dementia. We have previously reported the depressive-like profile in rats receiving a single intracerebroventricular injection of soluble amyloid beta protein (ßA). Here, we verified the effect of different classes of antidepressants on the ßA-induced depressive behavior and on cortical monoamine levels. To these purposes, the forced swimming test was performed and cortical levels of serotonin (5-HT) and noradrenaline (NA) were quantified by high performance liquid chromatography (HPLC). We found that acute fluoxetine (20 mg/kg, s.c.), reboxetine (10 mg/kg, s.c.), and ketamine (15 mg/kg, i.p.) significantly reduced the immobility in ßA-treated rats compared to controls. Fluoxetine and reboxetine reversed 5-HT reduction, while βA-induced NA increase was further enhanced by all treatments. Treatments with fluoxetine, reboxetine and ketamine were able to revert soluble ßA-induced decrease of cortical BDNF levels, while only fluoxetine and ketamine, but not reboxetine, had the same effects on cortical NGF expression. Moreover, plasma soluble ßA-levels were lowered by fluoxetine, but not reboxetine and ketamine, treatments.

Our data suggest that different classes of antidepressants yield a short-acting effect on rat soluble ßA-induced depressive profile. Thus, we hypothesize a novel common mechanism of action of these drugs also based upon a "ßA lowering" effect. Although further investigations are still needed, our study might open a new scenario for unravelling the molecular antidepressant mechanisms of these drugs.

1. Introduction

Several epidemiological studies have confirmed the prevalence and the persistence of neuropsychiatric symptoms in Alzheimer's disease (AD) patients (Cherbuin et al., 2015; Mourao et al., 2016), represented by a heterogeneous group of non-cognitive symptoms and behaviors, such as delusions, depression and irritability. It has been estimated that the prevalence of these symptoms oscillates between 60% to 90% of cases, depending on either the selected population or the methodology of the studies (Cummings et al., 2016).

Among these symptoms, delusions and depression were the most persistent (Steinberg et al., 2004). These clinical manifestations can be the very first symptoms of a neurodegenerative process, thus being considered as prodromal of dementia (Andersen et al., 2005). It has been shown that a number of patients may develop depressive symptomatology in an early stage of neurological disorders, occurring before the appearance of cognitive impairments. Similarly, it has been reported that depressed individuals are nearly twice as likely to develop dementia, often in the form of AD, compared with non-depressed individuals (Jorm, 2001). Growing evidence has in most cases strengthened the notion that depression may represent a risk factor for AD development, even when it occurs earlier in life (Green et al., 2003; Sweet et al., 2004). Recently, it has been further confirmed that neurodegenerative disease may manifest as depressive traits in the early stages (Baquero and Martin, 2015).

As regard the association between depressive symptomatology and

Abbreviations: AD, Alzheimer's Disease; βA, amyloid beta protein; 5-HT, serotonin; NA, noradrenaline; HPLC, high performance liquid chromatography; DA, dopamine; Glu, glutamate; i.c.v., intracerebroventricular; FST, forced swimming test; SSRI, selective 5-HT reuptake inhibitors; NRI, NA reuptake inhibitors; NMDA, *N*-methyl-D-aspartate; PFC, prefrontal cortex; ANOVA, analysis of variance; BDNF, brain derived neurotrophic factor; NGF, nerve growth factor; CSF, cerebrospinal fluid; APP, Amyloid Precursor Protein; IL, interleukin

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cognitive impairments, similar findings in terms of prevalence rate have been found across different cultures, as well as in developing countries (Shah et al., 2005) and industrialized societies (Pinto et al., 2011), thus suggesting that the underlying mechanisms of neuropsychiatric symptoms could be considered as neurobiologically determined. Indeed, neuropsychiatric symptomatology should not be regarded as an emotional reaction but as an emerging neurobiology (Cummings et al., 2016). Thus, neuropathological hallmarks found in cognitive impairment might also be present in depressive states. Neuropsychiatric behaviors result from anatomopathological and biochemical changes within several brain regions. This is supported by neuropathological evidences, associated with underlying neurotransmitter system imbalances including noradrenaline (NA), dopamine (DA), acetylcholine, serotonin (5-HT), glutamate (Glu), gamma-aminobutyric acid and nitric oxide (Panza et al., 2010; Sweet et al., 2004; Wegener et al., 2004). Nevertheless, neurotransmission and other biological pathways and mechanisms involved in the association of cognitive deficits and depression remain not clearly understood. More recently, depressive signs have been potentially linked, in part, to the presence of soluble beta amyloid (ßA) in the brain. ßA peptides are physiologically produced from the ßA protein precursor through ß and gamma secretase cleavage (Zetterberg et al., 2010). They possess different brain area-selective neuromodulatory actions (Morgese et al., 2014; Morgese et al., 2017; Mura et al., 2010; Trabace et al., 2007).

In the past, it has been widely accepted that progressive brain deposition of ßA proteins in neuritic plaques was a prominent feature of AD. Indeed, therapeutic strategies have been targeted against ßA depositions (see (Awasthi et al., 2016) for review) or acetylcholinesterase inhibition (Grutzendler and Morris, 2001; Trabace et al., 2000).

Recent studies suggest that early memory impairments might be explained by the presence of soluble forms of ßA peptides, rather than aggregated forms. Interestingly, several lines of evidence suggest that elevated levels of cerebral soluble ßA peptides, especially $ßA_{1–42}$, may also be associated with a high incidence of depression.

We have previously reported a depressive-like profile induced by a single intracerebroventricular (i.c.v.) injection of soluble ßA peptide in rats. Soluble ßA treated-rats exposed to the forced swimming test (FST) showed an increase in the immobility frequency, which has been shown to mimic a typical state of “behavioral despair”. This behavioral alteration was associated to significant reduction in cortical 5-HT and neurotrophin levels, suggesting that soluble ßA was able to induce a depressive-like state (Colaianna et al., 2010). In good agreement with our results, data from preclinical research have associated various risk factors for depression with increased soluble ßA production in the brain (Catania et al., 2009). Furthermore, plasma ßA disturbances in humans have been reported, although with conflicting results (Pomara et al., 2006; Qiu et al., 2007). Very recently, Yasuno and coworkers confirmed the presence of cortical amyloid burden in cognitively intact patients with depressive episodes, which were more likely to have underlying AD neuropathology (Yasuno et al., 2016). Thus, depressive symptoms may increase the predictive power for the identification of future AD cases.

Our aim was to investigate the effect of different classes of antidepressants on the depressive profile induced by exogenous soluble ßA in the brain, by using the FST paradigm. This test is useful to assess the capacity of antidepressant agents to switch passive behavior in active forms of coping (Cryan et al., 2002a).

To this end, we used acute fluoxetine (a selective 5-HT reuptake inhibitor, SSRI) and reboxetine (a NA reuptake inhibitor, NRI) to evaluate whether these drugs could alleviate or reverse soluble ßA-induced behavioral despair. Moreover, we also investigated the effects of ketamine [a *N*-methyl-D-aspartate receptor (NMDA) antagonist] administration on this animal model, as several clinical data reported rapid and powerful antidepressant effects of a single administration of a sub-psychomimetic dose of ketamine (Autry et al., 2011; Engin et al., 2009). Finally, as the alteration of serotonergic and noradrenergic systems may be primarily involved in the development of depressive symptomatology (Ressler and Nemeroff, 2000), we investigated whether serotonergic and noradrenergic neurotransmissions were affected by antidepressant treatments in the prefrontal cortex (PFC) of soluble ßA-treated rats.

2. Material and methods

2.1. Animals

All experiments were conducted on male Wistar rats (250–275 g, Harlan, S. Pietro al Natisone, Udine, Italy). Rats were group housed (three to four per cage) and maintained 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). Food and water were available ad libitum. 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, anyway all efforts were made to minimize the number of animals used and their suffering.

2.2. Surgery and soluble ßA infusion

The soluble ßA peptide was purchased from Tocris (Bristol, UK) and was dissolved in sterile double-distilled water (vehicle) at a concentration of 4 μM. All solutions were freshly prepared. Surgery procedures were performed as previously described (Colaianna et al., 2010).

Briefly, rats were anesthetized and secured in a stereotaxic frame (David Kopf Instruments, Tujunga, CA, USA). The skin was cut to expose the skull and a hole was drilled to insert the infusion needle (30-gauge stainless steel tubing; Cooper's Needles, Birmingham, UK). Coordinates for i.c.v. infusions were based on the atlas of Paxinos and Watson (1998): AP = − 0.5, ML = + 1.2 and DV = − 3.2 from bregma, with the incisor bar set at − 3.3 mm. Soluble ßA (5 μl) was delivered through a 25 μl Hamilton microsyringe at 2 μl/min infusion rate. Control rats were infused with vehicle only, because reverse soluble $ßA_{42–1}$, used in preliminary experiments, had no effect on the measured parameters and was indistinguishable from vehicle alone (unpublished observations). All experimental procedures were performed 7 days after i.c.v. administration (sham-operated or soluble ßA-treated groups).

2.3. Pharmacological treatments and experimental design

Fluoxetine hydrochloride and reboxetine mesylate were purchased from Sigma-Aldrich (Milan, Italy), dissolved in dH_2O (vehicle) and given subcutaneously (s.c.) 24, 5 and 1 h before the behavioral performance in the FST (test phase) at a dose of 20 mg/kg and 10 mg/kg, respectively. Ketamine hydrochloride was purchased from Sigma-Aldrich (Milan, Italy), dissolved in saline (vehicle) and administered intraperitoneally (i.p.) at a dose of 15 mg/kg. Animals received treatment with ketamine hydrochloride 1 h before FST (test phase).

Doses of fluoxetine and reboxetine used in this work were chosen according to (Cryan and Lucki, 2000; Cryan et al., 2002b, 2005b). The protocol we used was chosen as it results in prolonged brain penetration of the compounds, mimicking a state of subchronic drug exposure and, consequently, a continuously elevated drug concentration in the rat (Slattery and Cryan, 2012). Doses of ketamine used in the present work were chosen based on a previous study reporting that acute ketamine