Monoaminergic system modulation in depression and alzheimer’s disease: a new stan...

Health & Medicine

Introduction

Many pathologies have been indicated as comorbid with Alzheimer's diseases (AD) and in particular neuropsychiatric disorders such as depression (Ownby et al., 2006 ; Sun et al., 2008). Indeed, depression is common in pre-clinical AD and may represent an early manifestation of this disease before the appearance of cognitive impairments (Geerlings et al., 2000 ; Visser et al., 2000). In this regard, much evidence endorses a strong relationship between depression and AD, so much that this mental illness has been proposed as a risk factor for AD or as a prodromic AD phase (Modrego and Ferrandez, 2004). The amyloid cascade hypothesis postulates that neurodegeneration in AD is related to abnormal accumulation of amyloid beta (Aβ) plaques in various areas of the brain. However, soluble forms of this peptide have been implicated in the development of early memory deficits as well as of neuropsychiatric symptoms (Rowan et al., 2005). Indeed, significant cognitive deficits have been directly attributed to soluble Aβ fragments (Mattson, 2004 ; Cleary et al., 2005), and increased levels of soluble Aβ oligomers have been linked to synaptic dysfunction (Hardy and Selkoe, 2002 ; Selkoe and Schenk, 2003). Meanwhile, it has been reported that in depressed patients, Aβ peptide levels are increased (Pomara and Sidtis, 2010). In good agreement, we have previously demonstrated that Aβ, intracerebroventricularly (icv) injected in rats 7 days earlier, evokes a depressive-like profile accompanied by lower cortical serotonin (5-HT) and neurotrophin content (Colaianna et al., 2010). Furthermore, we later reported that such impairment was associated with altered stress response and increased noradrenaline (NA) levels (Morgese

et al., 2014 , 2015). In addition, in the same model, cognitive impairment was demonstrated either acutely, such as 2 h after Aβ administration, or more enduringly, i. e., 7 days after the peptide central release (Morgese et al., 2014 ; Tucci et al., 2014 ; Mhillaj et al., 2018). Although the role of dopamine (DA) was less studied concerning depression and AD, recently, its role has been brought to the fore (Nobili et al., 2017) but is still in need of further evaluation.

The present review is aimed at summarizing the main knowledge related to biological and pathological substrates, such as monoamines and related molecules, commonly involved in AD and depressive pathology, with the scope of shedding light on possible therapeutic approaches.

Monoamine System in Depression and Alzheimer's Disease

Serotonergic System

The treatment of affective disorders is mainly based on the enhancement of the noradrenergic and serotonergic systems through selective or nonselective reuptake inhibitors. Such a pharmacological schedule sinks the roots on the catecholaminergic theory of affective disorders stating the crucial role of lower central NA and 5-HT availability in the insurgence of depression (Mann et al., 1986 ; Schildkraut, 1995 ; Mann, 1999). Alterations in these neurotransmitter systems have also been linked to neurodegenerative disorders such as AD. Impairment of the serotonergic system has been reported in the very early stages of AD (Versijpt et al., 2003 ; Egashira et al., 2005 ; Kepe et al., 2006), and substantial disruption of the serotonergic system in AD has been postulated according to both

clinical and *postmortem* studies (Morgan et al., 1987 ; Lanctot et al., 2001). In this regard, Aβ in its soluble forms, either monomeric or oligomeric, has been associated with the modulation of these systems. In particular, we have previously found that soluble Aβ injected icv in rats caused a significant reduction in 5-HT at the prefrontal cortex level, without interfering with the physiological functioning of other areas such as the striatum or the nucleus accumbens (Colaianna et al., 2010). These results indicated that the prefrontal cortex is an area highly sensitive to Aβ effects, and this area is also crucially involved in the etiopathogenesis of depressive phenomena. Indeed, impairment of 5-HT neurotransmission in the prefrontal area is central to both depressive disorders (Krishnan and Nestler, 2008) and several neurodegenerative diseases (Mattson, 2004 ; Egashira et al., 2005). Furthermore, we have more recently individuated the vulnerability of the hippocampal area to the action of exogenous Aβ icv injected. Indeed, we have found that this peptide can reduce 5-HT levels in the hippocampus, and this event is associated with a proinflammatory state and higher rate of activated microglia (Mhillaj et al., 2018). In addition, the treatment with a selective COX-2 inhibitor, such as celecoxib, was able to prevent the reduction in 5-HT levels, thus preventing the Aβ-induced depressive-like behavior and restoring Aβ plasma levels to control (Mhillaj et al., 2018 ; Morgese et al., 2018a). Accordingly, we have recently demonstrated that environmental factors, such as modified dietary factors, can lead to serotonergic impairment associated with increased levels of Aβ. In particular, we found that deficiency in polyunsaturated fatty acids of the omega 3 family, thus corresponding to a condition linked to a pseudoinflammatory

state (Solbrig et al., 2010 ; Graeber et al., 2011), led to a depressive-like phenotype characterized by reduced 5-HT content and higher Aβ levels (Morgese et al., 2017). Accordingly, an anti-inflammatory diet, such as a diet enriched in omega 3 fatty acids, was able to prevent the reduction in 5-HT caused by Aβ injection, preventing the depressive phenomenon (Bove et al., 2018 ; Morgese et al., 2018b). Likewise, depressed patients showed higher risk for the development of AD (Kessing and Andersen, 2004). On the other hand, *postmortem* studies performed in AD patients revealed low 5-HT and relative receptor content (Reynolds et al., 1995). An *in vitro* model of familiar AD confirmed these observations, since cells overexpressing APP gene with the Swedish mutations associated with familial AD, indicated an altered sensitivity of the serotonergic system and 5-HT $_{1B}$ receptor subtype in particular (Tajeddinn et al., 2016). Furthermore, in a double transgenic model of early AD, fluoxetine, an antidepressant drug acting as serotonin-selective re-uptake inhibitors (SSRIs), ameliorated the impairment of spatial learning by preventing neuronal loss (Ma et al., 2017) and delayed the cognitive decline associated with synaptic changes (Zhou et al., 2018). Accordingly, clinical evidence revealed that SSRIs significantly improve depressant symptoms and daily activities in AD patients (Werner and Covenas, 2015). This point is very intriguing considering that cognitive decline is recognized also as a clinical feature of depressive state. Interestingly, serotonergic system activation was reported to negatively modulate interstitial Aβ content. Indeed, in transgenic animal models of AD, the enhancing of 5-HT signaling, through the administration of SSRI antidepressants, rapidly reduced Aβ production *in vivo via* activation of

extracellular regulated kinase (ERK) and the α-secretase-mediated pathway (Cirrito et al., 2011 ; Fisher et al., 2016). Indeed, the sequential proteolytic cleavage of amyloid precursor protein (APP) can also occur *via* α-secretase, leading to the production of α-CTF later transformed by γ-secretase into AICD and p3 peptides (Chow et al., 2010). This pathway is recognized as the non-amyloidogenic pathway since APP is cleaved by α-secretase in the Aβ region, yielding to lower Aβ production (Chow et al., 2010). This pathway has been described as neurotrophic and neuroprotective (Chow et al., 2010); therefore, therapeutic strategies steered at pushing APP processing toward α-secretase-mediated derivatives are under the spotlight. Furthermore, a PET imaging study carried out in cognitively normal individuals evidenced lower Aβ accumulation in consequence to increased 5-HT signaling (Sheline et al., 2014), and retrospective analysis on patients under antidepressants further confirmed this finding (Vlassenko et al., 2011). In this regard, we have recently demonstrated that fluoxetine treatment not only could restore 5-HT content in animals centrally injected with Aβ characterized by depressive-like phenotype but also reduced Aβ plasma levels (Schiavone et al., 2017). In further agreement, activation of serotonergic receptors, such as 5-HT $_4$, 5-HT $_6$, and 5-HT $_7$, corresponded to lower Aβ content, whereas the opposite effect was retrieved after simultaneous pharmacological blockade of 5-HT $_4$ and 5-HT $_7$ (Cho and Hu, 2007 ; Fisher et al., 2016). 5-HT $_4$ partial agonists have been proposed as fast-acting antidepressants (Lucas et al., 2007 ; Vidal et al., 2014) and have been shown to ameliorate cognitive deficit in anxiety/depressive models (Darcet et al., 2016). In good agreement, pharmacological activation of 5-HT $_4$

receptors was shown to enhance short- and long-term memory function (Meneses, 2007), endorsing the hypothesis of a putative role of these drugs for the amelioration of symptomatology of depression in AD. With regard to other receptor subtypes, it has been shown that APP can be released upon activation of 5-HT $_{2A}$ and 5-HT $_{2C}$, and activation of 5-HT $_{2C}$ receptor promotes the expression of neprilysin, a well-characterized Aβ degrading enzymes (Tian et al., 2015). However, it should be considered that both 5-HT $_{2C}$ agonists and antagonists have been evaluated as antidepressants (Cryan and Lucki, 2000 ; Steardo et al., 2000 ; Cryan et al., 2005).

As regard to 5-HT $_{2A}$ receptors, genetic polymorphisms have been described in AD patients affected by major depression (Holmes et al., 2003) and, in AD patients, lower binding to these receptors has been identified (Versijpt et al., 2003). In addition, intra-hippocampal injection of Aβ was associated with a significant reduction in 5-HT $_{2A}$ expression (Christensen et al., 2008). However, the effects of the activation of these receptors may vary depending on the cerebral pathway involved. Indeed, 5-HT $_{2A}$ knocked down mice showed an altered phenotype with depressive-like symptoms (Popa et al., 2005), and 5-HT $_{2A}$ antagonists have been evaluated as antidepressants (Zhang and Stackman, 2015); thus, a better understanding would help the developing of targeted compounds. On the other hand, 5-HT $_{6}$ receptors represent a novel therapeutic strategy in AD. Indeed, clinical trial for studying the efficacy and tolerability of the 5-HT $_{6}$ receptor antagonist, SB-742457, in subjects with mild-to-moderate and probable AD, revealed a safe profile and possible utility in improving cognitive symptoms of AD (Maher-Edwards et al., 2010). However, antagonists of these receptor

subtypes have been indicated as useful also in the treatment of non-cognitive symptoms associated with AD (Garcia-Alloza et al., 2004). However, despite early positive findings, larger phase-III trials have failed to demonstrate any statistically significant impact on cognition for either idalopirdine or intepirdine, two 5-HT $_6$ antagonists, as adjunct to cholinesterase inhibitors. Paradoxically, 5-HT $_6$ receptor agonists also hold cognitive enhancing properties (Khoury et al., 2018). Likewise, polymorphism of these receptors has been associated with altered response to antidepressant treatment in major depressive disorder (Lee et al., 2005), although contrasting results have been reported (Wu et al., 2001); hence, further research is warranted.

Noradrenergic System

The noradrenergic system is also implicated in the etiopathogenesis of both depression and AD. However, it has been recognized that the cause of depression is more complex than just an alteration in the levels of 5-HT and/or NA, being more directly caused by dysfunction in brain areas or neuronal systems modulated by monoamine systems (Delgado and Moreno, 2000). It has been postulated that antidepressants, by enhancing neurotransmission in normal noradrenergic or serotonergic neurons, can restore lost functions in affected brain areas under monoamine control through a time-dependent process (Delgado and Moreno, 2000). Indeed, noradrenergic and serotonergic systems are strictly interconnected and control each other *via* heteroreceptors. In particular, a negative feedback has been hypothesized considering that increased 5-HT levels correspond to NA release, which in turn inhibits further 5-HT release *via* α $_2$ AR activation (

Mongeau et al., 1997). This process is mediated through inhibitory α $_2$ receptors (α $_2$ AR) at 5-HT terminal levels and 5-HT $_3$ receptors at NA terminals. Interestingly, increased α $_2$ AR have been found in *postmortem* brains of depressed patients (Meana et al., 1992 ; Ordway et al., 1994), and a theory of α $_2$ AR supersensitivity in depression was postulated early on Charney et al., 1981 . In this regard, increased α2-adrenoceptor density was retrieved in most regions of a rat model of depression, such as the flinders sensitive rat (Lillethorup et al., 2015) and in patients with depressive disorders (Cottingham and Wang, 2012). Interestingly, it has been postulated that tricyclic compounds can bind α2AR, thus functioning as arrestin-based ligands, and such an effect can explain their antidepressant property (Cottingham et al., 2015). Beta-arrestins are a small family of regulators of G protein-coupled receptors that regulate desensitization, internalization along, and initiation of their own signaling of such receptors (Jiang et al., 2013). Long-term activation of these receptors causes endocytosis and downregulation through the recruitment of α $_2$ AR/arrestin complex (Cottingham et al., 2015). The NA system is deeply affected also in neurodegeneration and in early AD (Haglund et al., 2006). Indeed, α2A adrenergic receptors modulate APP endocytic sorting and promote Aβ generation through disrupting APP interaction with a vacuolar protein sorting (Vps10) family protein, a family of receptors that plays a decisive role in controlling the outcome of APP proteolytic processing (Chen et al., 2014). In addition, this study pointed to the use of α2A antagonists as a new direction for AD treatment. In this light, another putative target for the generation of novel AD treatments is targeting β-arrestin. Indeed, increased β-arrestin 1

levels were shown in a transgenic animal model of AD as well as in *postmortem* study (Liu et al., 2013). In keeping in mind a parallel route for depression and AD, β-arrestin signaling has also been associated with antidepressant properties of drugs (Golan et al., 2013). Overexpression of β-arrestin 2 was associated with increased Aβ production. In particular, experimental conditions able to silence the β-arrestin 2 gene corresponded to Aβ rate of production by regulating γ-secretase activity (Thathiah et al., 2013). Accordingly, Pontrello et al. found that the loss of dendritic spine in hippocampal neurons caused by Aβ was prevented by deleting β-arrestin-2 (Pontrello et al., 2012). On the other hand, polymorphisms in the gene encoding for β2 adrenergic receptor have been associated with an increased risk of developing sporadic late onset AD (Yu et al., 2008), while alterations in β adrenergic receptors were reported in depressed patients (Mann et al., 1986). Indeed, much evidence indicates that activation of these receptors yield to antidepressant effects (Overstreet et al., 2008 ; Gu et al., 2012). Nonetheless, Aβ interacts with the noradrenergic system directly binding to β-adrenergic receptors (Igbavboa et al., 2006 ; Wang et al., 2011). Aβ may cause desensitization and subsequently internalization of β2 adrenergic receptors in prefrontal cortical neurons (Wang et al., 2011). Furthermore, β2 adrenergic receptor activation mediates phosphorylation of tau after Aβ exposure both *in vivo* and *in vitro* (Wang et al., 2013). On the other hand, we have found that central icv injection of Aβ increases noradrenergic tone after either 2 h or after 7 days from the central injection, probably reflecting a neuroprotective phenomenon (Morgese et al., 2014 , 2015), considering that, NA is protective against neuroinflammatory processes. Accordingly, NA

is able to modulate glial activation, and pharmacological strategies finalized to increase NA are considered a valid approach for neurodegenerative diseases (Braun et al., 2014). *In vitro* studies have evidenced that neuroprotective effects of noradrenergic locus coeruleus (LC) afferents against Aβ rely on the stimulation of neurotrophic NGF and BDNF autocrine or paracrine loops *via* beta adrenoceptor activation of the cAMP response element binding protein pathway (Counts and Mufson, 2010 ; Liu et al., 2015). After Aβ exposure, lower NA concentrations in LC projecting areas facilitate the inflammatory reaction of microglial cells, thus impairing microglial migration and phagocytosis, ultimately decreasing Aβ clearance (Heneka et al., 2010). Accordingly, progression of AD is paralleled by the loss of noradrenergic function in LC (Kelly et al., 2017), indicating the crucial role of this system in neurodegeneration.

Dopaminergic System

As regards the dopaminergic system, impairment of its neurotransmission has been implicated in many diseases including depression (Schmidt et al., 2001), and several pre-clinical studies have indicated the involvement of dopaminergic, either D1, D2, or D3, in antidepressant effects (Pytka et al., 2016). In good agreement, it has been shown that pure dopaminergic drugs, such as pramipexole, DA precursors, and DA reuptake inhibitors, show therapeutic efficacy in depression (El Mansari et al., 2010 ; Belujon and Grace, 2017). In addition, neurodegenerative diseases associated with the loss of dopaminergic function, such as Parkinson’s or Huntington’s diseases, have high comorbidities with depression and anxiety (Dale et al., 2016 ; Schrag and Taddei, 2017 ; Smeltere et al., 2017).

Concerning AD, it was shown that prefrontal cortical and hippocampal areas showed lower DA receptor expression (Kemppainen et al., 2003 ; Kumar and Patel, 2007). Interestingly accumbal expression of D2-like receptors, dopaminergic transporter, and tyrosine hydroxylase enzyme was found altered in AD brains (Rinne et al., 1986 ; Allard et al., 1990 ; Murray et al., 1995 ; Joyce et al., 1997). Imaging studies evidenced atrophy of this area in a cohort of AD patients (Pievani et al., 2013). Aβ administration disrupts the cholinergic control of DA release, particularly in the nucleus accumbens (Preda et al., 2008), but we also reported a blunting of DA release in the prefrontal cortex of rat after icv injection of the peptide (Trabace et al., 2007). In addition, the increase in DAnergic tone has been proposed as a possible therapeutic strategy for AD, considering that dopaminergic dysfunction plays a pathogenic role in cognitive decline (Martorana et al., 2009 , 2013 ; Koch et al., 2014 ; Martorana and Koch, 2014). Furthermore, selective DAnergic neuronal degeneration in ventral tegmental area was demonstrated in AD transgenic mice at pre-plaque stages, suggesting that lower hippocampal and accumbal DA outflow correlate to memory deficits and dysfunction of reward processing (Nobili et al., 2017).

Conclusions

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. Unfortunately, few pharmacological tools are available for dementia; thus, the need for novel therapeutic strategies is very compelling. Future studies aimed at elucidating the mechanisms through which drugs modulating monoamine release may prove helpful in individuating novel

strategy for slowing down cognitive impairment in pre-clinical AD phase, often associated with mood alterations, taking into account their effects on Aβ production/clearance, aggregation status, and neuroinflammatory-induced pathways. Furthermore, some of these molecules are already commercialized; thus, such a novel potential therapeutic approach for AD treatment may become rapidly clinically suitable.

Author Contributions

MM and LT helped in study design, drafting, revising, and accepting of the final version of the manuscript.

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Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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