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Review article

Dysregulated brain immunity and neurotrophin signaling in Rett syndrome and autism spectrum disorders ☆

Theoharis C. Theoharides [a,b,c,d,*], Marianna Athanassiou [a], Smaro Panagiotidou [a], Robert Doyle [e,f]

[a] Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA, USA
[b] Department of Internal Medicine, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA, USA
[c] Tufts Medical Center, Boston, MA, USA
[d] Department of Psychiatry, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA, USA
[e] Pediatric Psychopharmacology Unit, Massachusetts General Hospital, Boston MA, USA
[f] Harvard Medical School, Boston MA, USA

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ABSTRACT

Rett syndrome is a neurodevelopmental disorder, which occurs in about 1:15,000 females and presents with neurologic and communication defects. It is transmitted as an X-linked dominant linked to mutations of the methyl-CpG-binding protein (MeCP2), a gene transcription suppressor, but its definitive pathogenesis is unknown thus hindering development of effective treatments. Almost half of children with Rett syndrome also have behavioral symptoms consistent with those of autism spectrum disorders (ASDs). PubMed was searched (2005–2014) using the terms: allergy, atopy, brain, brain-derived neurotrophic factor (BDNF), corticotropin-releasing hormone (CRH), cytokines, gene mutations, inflammation, mast cells (MCs), microglia, mitochondria, neurotensin (NT), neurotrophins, seizures, stress, and treatment. There are a number of intriguing differences and similarities between Rett syndrome and ASDs. Rett syndrome occurs in females, while ASDs more often in males, and the former has neurologic disabilities unlike ASDs. There is evidence of dysregulated immune system early in life in both conditions. Lack of microglial phagocytosis and decreased levels of BDNF appear to distinguish Rett syndrome from ASDs, in which there is instead microglia activation and/or proliferation and possibly defective BDNF signaling. Moreover, brain mast cell (MC) activation and focal inflammation may be more prominent in ASDs than Rett syndrome. The flavonoid luteolin blocks microglia and MC activation, provides BDNF-like activity, reverses Rett phenotype in mouse models, and has a significant benefit in children with ASDs. Appropriate formulations of luteolin or other natural molecules may be useful in the treatment of Rett syndrome.

Contents

Abbreviations: ASD, autism spectrum disorders; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CSF, cerebrospinal fluid; CRH, corticotropin-releasing hormone; IL, interleukin; MCs, mast cells; MCAS, mast cell activation syndrome; mt, mitochondria; NT, neurotensin; TNF, tumor necrosis factor.

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* Corresponding author at: Molecular Immunopharmacology and Drug Discovery Laboratory, Department of Integrative Physiology and Pathobiology, Tufts University School of Medicine, 136 Harrison Avenue, Boston, MA 02111, USA.
E-mail address: theoharis.theoharides@tufts.edu (T.C. Theoharides).

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1. Introduction

Rett syndrome is a neurodevelopmental condition affecting about 1 per 15,000 females and is characterized by neurologic defects, mental retardation and seizures (Neul et al., 2010; Castro et al., 2013). Even though children with Rett syndrome show severe impairment in language and movement, they still make eye contact. About half of children with Rett syndrome also exhibit symptoms consistent with those of autism spectrum disorders (ASDs), also a neurodevelopmental condition. which affects almost 1/68 children but characterized by deficits in communication and sociability (Fombonne, 2009; Kogan et al., 2009; Volkmar et al., 2009).

In Rett syndrome over 2/3 of cases have been linked to specific sporadic de novo mutations (Matijevic et al., 2009; Matsuishi et al., 2011; Banerjee et al., 2012) affecting the gene for the methyl-CpG-binding protein (MeCP2), which is a general transcriptional repressor (Nguyen et al., 2012; Qiu et al., 2012; Ku et al., 2013; Na et al., 2013). In contrast, many gene mutations are associated with higher risk of ASD, but only explain a small percentage of cases (Weiss et al., 2009; Aldinger et al., 2011; Hallmayer et al., 2011; Williams, 2012).

DNA methylation at the C5 position of the cytokine residue of GpG dinucleotides generally leads to gene silencing (Feng and Fan, 2009), especially in the hypothalamus (Chahrour et al., 2008). Some papers have reported specific neuronal gene defects using MeCP2 null mice (Urdinguio et al., 2008), such as abnormal "axonal guidance" (Degano et al., 2009). Loss of MeCP2 also resulted in decreased production of biogenic amines (Samaco et al., 2009). However, it is still not known how the loss of the MeCP2 protein leads to the neurologic or other symptoms (Blackman et al., 2012).

Patients with Rett syndrome often have seizures, but those with ASDs have a number of other comorbidities including allergies, gastrointestinal symptoms and seizures (Bauman, 2010). There is new evidence that epigenetic regulation contributes significantly to neurodevelopmental and neurodegenerative diseases, Rett syndrome and those with ASDs (Herbert, 2010; Lilja et al., 2013; Rangasamy et al., 2013). We compare and contrast the clinical and pathological findings in Rett syndrome and ASDs (Table 1).

2. Methods

PubMed was searched since 1995 for papers reporting on Rett syndrome and/or ASD and any one of the following terms: allergy, atopy, brain-derived neurotrophic factor (BDNF), corticotropin-releasing hormone (CRH), cytokines, flavonoids, gene mutation, inflammation, mast cells (MCs), mitochondria, neurotensin (NT), phenotype, seizures, stress, subtype, treatment, and therapy. Papers were chosen for relevance, human data, and use of English language. Papers were excluded if they were published as "hypotheses" or if they were repetitive by the same authors.

Table 1
Differences and similarities between Rett syndrome and ASDs.

Characteristics	Rett syndrome	ASDs
Present in females	+	
More common in males		+
Neurologic symptoms	+	−
Behavioral symptoms	±	+
Eye contact	+	−
Decreased microglia phagocytosis	+	−
Microglia activation/proliferation	−	+
Neurotrophins (BDNF)	↓	↑ but defective signaling
MeCP2 mutation	+	−
Mitochondrial dysfunction	±	+
Brain autoantibodies	±	+
Brain inflammation	±	+
Seizures	+	±
Allergies/food intolerance	−	+
Gastrointestinal symptoms	−	+

3. Microglia and neurotrophins

A number of papers have reported altered microglial function in Rett syndrome (Maezawa et al., 2011; Derecki et al., 2012; Tsai, 2012; Zachariah et al., 2012; Derecki et al., 2013). In fact, neuron-only expression of normal MeCP2 was not sufficient to reverse the Rett phenotype in mice; instead brain-wide expression was needed suggesting the importance of glia cells, astrocytes or some other brain cell type (Guy et al., 2007; varez-Saavedra et al., 2007). For instance, astrocytes from Rett syndrome patients can spread MeCP2 deficiency (Maezawa et al., 2009). Correction of MeCP2 deficiency in myeloid cells of *MeCP2*-null mice was sufficient to correct most symptoms associated with Rett phenotype, but strangely only if phagocytic activity of microglia was intact (Derecki et al., 2013). There is also increased glia neurodensity in Rett syndrome suggesting inflammatory astrocytosis (Armstrong, 2005). Microglial–MC interactions are considered important in neuroinflammatory diseases (Skaper et al., 2012). Interestingly, the MC-derived protease tryptase induced microglia activation (S. Zhang et al., 2012).

A neuroinflammatory process (Zimmerman et al., 2005), as evidenced by strong activation of microglia and astroglia, along with increased expression of MCP-1 and tumor necrosis factor (TNF)-α, had been reported in ASDs (Vargas et al., 2005), and has since been confirmed. However, "atypical wiring" may be more important than active inflammatory process (Rodriguez and Kern, 2011; Morgan et al., 2012).

Lack of brain-derived neurotrophic factor (BDNF) has been implicated in many neuropsychiatric diseases (Autry and Monteggia, 2012), including Rett syndrome (Li and Pozzo-Miller, 2014). A number of papers have reported reduced blood and cerebrospinal fluid (CSF) levels of BDNF in patients with Rett syndrome (Katz, 2014), and in a mouse model of Rett syndrome (Schaevitz et al., 2010). In fact, loss of MeCP2 has been correlated with reduced levels of neurotrophic factors including BDNF (Abuhatzira et al., 2007). In contrast, BDNF has been largely found to be elevated in patients with ASDs (Nishimura et al., 2007; Sadakata et al., 2012; Ricci et al., 2013), but this increase may be the result of defective signaling (Correia et al., 2010).

4. Autoimmunity

Increasing reports suggest that Rett syndrome and ASDs may have some aspects of immune dysfunction (Derecki et al., 2010). ASDs in particular have been considered having an autoimmune (Ashwood and Van de Water, 2004; Gesundheit et al., 2013; Theoharides et al., 2013) and having some neuroimmune component (Theoharides et al., 2009). MeCP2 has been shown to be an autoantigen associated with increased susceptibility to systemic lupus erethymatosus (Webb et al., 2009). Autoantibodies against the brain have been reported in the serum of Rett syndrome patients (Klushnik et al., 2001). In the case of ASDs, 30% of patients had elevated antibody levels directed against the cerebellum (Wills et al., 2009; Rossi et al., 2011; Braunschweig and Van de Water, 2012). The Autism Phenome Project reported that 42% of 3 year old children with ASDs had plasma antibodies against