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The BTBR mouse model of idiopathic autism – current view on mechanisms

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Abstract

Autism spectrum disorder (ASD) is the most commonly diagnosed neurodevelopmental disorder, with current estimates of more than 1% of affected children across nations. The patients form a highly heterogeneous group with only the behavioral phenotype in common. The genetic heterogeneity is reflected in a plethora of animal models representing multiple mutations found in families of affected children. Despite many years of scientific effort, for the majority of cases the genetic cause remains elusive. It is therefore crucial to include well-validated models of idiopathic autism in studies searching for potential therapeutic agents. One of these models is the BTBR $T^{+}Itpr3^{tf}$/J mouse. The current review summarizes data gathered in recent research on potential molecular mechanisms responsible for the autism-like behavioral phenotype of this strain.

Keywords

BTBR; social behavior; repetitive behavior; neuroanatomy; pharmacological manipulations; molecular mechanisms

1. Introduction

Despite decades of research, autism spectrum disorder (ASD) remains the most commonly diagnosed neurodevelopmental disorder. Current epidemiology studies place its prevalence at as high as 1 in 45 children (Zablotsky et al. 2015) or, using a more conservative questionnaire, 1 in 68 children (Christensen et al. 2016) in the US. National statistics for ASD prevalence vary across countries but in most of them the numbers oscillate around 1% of the population (for review see, Elsabbagh et al. 2012).

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The etiology of the disorder remains unclear, with genetic, epigenetic and environmental factors interacting to produce a very heterogeneous group of patients sharing a similar behavioral profile. Recent studies point to over a hundred affected genes, with the majority being *de novo* mutations and copy number variants (Huguet et al. 2013, Jeste and Geschwind, 2014, Iossifov et al. 2016). Nevertheless, only a small percentage of cases is associated with known mutations, leaving the majority of cases to be described as idiopathic. In a recent work Iossifov and collaborators (2014), screened over 2500 simplex families (families in which only one child was diagnosed with ASD) to find that de novo missense mutations and de novo likely gene-disrupting (LGD) mutations contribute to 12% and 9%, respectively, of ASD diagnoses. Upon inclusion of copy number variants into these numbers, de novo mutations were found responsible for 30% of simplex cases and 45% of female cases of ASD.

Preclinical animal studies rely on well-validated rodent models to facilitate an understanding of clinical conditions. In the absence of a clear genetic, molecular, physiological or structural mechanism, animal models of ASD are typically validated in terms of two main behavioral clusters: 1. social behavior and communication impairments and 2. excess of repetitive behaviors (DSM-V, APA). The BTBR $T^{+}Itpr3^{tf}$/J mouse (BTBR), originally bred for studies on insulin-resistance, diabetes-induced nephropathy and phenyloketonuria, was identified only a decade ago as displaying strong and consistent autism-relevant behaviors (Bolivar et al. 2007, Moy et al. 2007, Nadler et al. 2006). Here we will summarize the data from recent genetic and proteomic studies identifying several clusters of genes and proteins differently expressed in the BTBR mice, as compared with C57BL6/J (B6) mice (unless otherwise noted). The latter strain is commonly used as a highly social “control” for autism-related studies employing BTBR mice. We will also discuss recent developments in the search for the neuroanatomical correlates of autism-like behaviors of the BTBR mouse, as well as possible molecular mechanism responsible for this phenotype.

2. Altered gene and protein expression in the BTBR mouse

Recent research has provided several gene expression and proteomic studies emphasizing the unique phenotype of the BTBR mouse strain. The inositol triphosphate receptor 3 gene (*Itpr3*), was identified as responsible for the mouse tufted (tf) locus (Ellis et al. 2013), which resulted with a change of the strain name from BTBR T^{+}tf/J to BTBR $T^{+}Itpr3^{tf}$/J. More importantly, the deletion within the *Itpr3* gene was found to cause indifference of BTBR mice to sweet, Polycose, umami, bitter, and calcium tastes (Tordoff et al. 2013), which in turn affects their food intake (preferential fat consumption, as compared to carbohydrate-rich diet, Tordoff et al. 2014). In the light of these results, the reports of impaired social communication of food-preference in this strain (McFarlane et al. 2008), as well as the use of BTBR mice to validate food reward based tasks (Martin et al. 2014) need to be reconsidered.

The first genetic comparisons between BTBR and B6 mice were done almost a decade ago (see McFarlane et al. 2008) and yielded several single nucleotide polymorphisms (SNPs) in the BTBR genetic background. The most interesting finding was a nonsynonymous coding region polymorphism in the *Kmo* gene encoding kynurenine 3-hydroxylase, an enzyme

regulating the metabolism of kynurenic acid (a glutamate antagonist). Further studies showed that deficiency in cholinergic transmission and increased levels of kynurenic acid in the prefrontal cortex of BTBR mice may be responsible for their inaccurate performance in the 5-choice serial reaction time task (McTighe et al. 2013).

Quantitative Trait Loci analysis using F2 intercross between the BTBR and B6 strains identified loci for autism-relevant traits and commissural morphology on chromosomes 1, 3, 9, 10, 12, and X (Jones-Davis et al. 2013). Additionally, four novel QTL for commissural morphology were found on chromosomes 4, 6, and 12. Detailed analysis yielded several candidate genes in the domains of developmental proteins (including genes regulating cell cycle, cell adhesion, axon growth/guidance and actin binding), synaptic proteins, kinases and immune and heat shock proteins.

Recently, Daimon and collaborators (Daimon et al. 2015) collected transcriptomic and proteomic data indicating differential expression of several genes and proteins in the hippocampus and cortex of BTBR and B6 mice. Among others, brain derived neurotrophic factor [*Bdnf*], p21-activated kinase type1 [*Pak1*] and cortistatin [*Cort*] were downregulated in BTBR hippocampus and cortex. While solute carrier family 25 [mitochondrial carrier; phosphate carrier], member 3 [*Slc25a3*] was downregulated in cortical samples, Serpin peptidase inhibitor, clade A [*Serpina*] was found decreased in the hippocampi of BTBR mice. Signaling pathway analysis (Ingenuity Pathway Analysis and Kyoto Encyclopedia of Genes and Genome) identified numerous down and up-regulated pathways. While transcripts related to gap junction, long-term depression and potentiation, Parkinson's disease, and adherence junction were upregulated, pathways related to metabolic stress response were downregulated. Others, such as members of MAPK signaling pathway, were both up and downregulated. These data are in line with previous reports showing BDNF deficiency (in adult BTBR mice, Scattoni et al. 2013, Stephenson et al. 2011) and MAPK signaling disruption (Faridar et al., 2014, Seese et al., 2014, reporting increased p-ERK levels, but fewer double labeled p-ERK/PSD95 puncta). The high level of p-ERK in the prefrontal cortex, but not in the cerebellum or total level, was associated with impaired juvenile sociability (Faridar et al. 2014) and adult memory formation in the Object Location Memory task (Seese et al. 2014).

Levels of other ASD-relevant mRNAs were also altered. These included: Caskin 1, which binds to Neurexin 1, and Homer31, which binds to Shank 1 and 3. The use of *Textrous!* natural language processing-based informatics analysis allowed for extraction of functional groups of altered genes. These included: *axon guidance*, *neurogenesis* and *regulation of actin cytoskeleton* (Daimon et al. 2015).

A recent comparison of transcriptomic data from BTBR and Engrailed ($En2^{-/-}$) hippocampi showed a total of 153 genes similarly deregulated in both ASD models (Provenzano et al. 2016). Pathway analysis revealed that these were involved in abnormal behavioral response, chemokine/MAP kinase signaling, as well as in dysfunction of the immune system and abnormal synaptic transmission/seizures.

Another proteomic study of BTBR cortex showed that apart from aberrant regulation of actin cytoskeleton BTBR mice have down-regulated levels of the stable tubule only polypeptide protein (STOP) and myelin-related proteins (e.g. myelin basic protein, MBP and myelin associated glycoprotein, MAG). They also displayed reduced levels of staining with ferric alum, indicating myelin disruption, in comparison to B6 controls (Wei et al. 2016a). These results are in line with histopathological examination of BTBR brain tissue (Stephenson et al. 2011), which showed reduction of myelin markers such as 2′,3′-cyclic nucleotide 3′-phosphodiesterase (CNPase) and MBP, as well as an increase in the oligodendrocyte precursor NG2. MBP and CNPase were expressed in small ectopic white matter bundles within the cingulate cortex. Contrary to the findings of Heo et al. (2011), Stephenson and colleagues found no evidence of gliosis, but described the orientations of glial fibers as altered in specific white-matter areas.

Analysis of fetal brain proteins showed a decreased level of glial fibrillary acidic protein, as well as increased BDNF and MBP levels in BTBR compared to FVB/NJ mice. No significant difference was obtained for NGF (nerve growth factor) between the two strains (Hwang et al. 2015). The upregulation of BDNF expression at an early developmental stage (in stark contrast to the BDNF signaling deficiency in later life of BTBR mice) is in line with clinical data showing increased plasma BDNF in children with ASD (Wang M. et al. 2015).

A proteomic analysis of hippocampi and cortices in aged BTBR mice identified several elevated synaptic proteins (Jasien et al. 2014) including: spinophilin, Synapsin 1 (and p-Synapsin 1), PSD95 and NeuN in the hippocampus and spinophilin, p-Synapsin 1 and NeuN in the cortex. However, BDNF levels were reduced in these aged animals. Advanced bioinformatics analyses (iTRAQ, followed by gene ontology, KEGG and Ingenuity Pathway Analyses) together with *Textrous!* analysis found several differentially regulated pathways for BTBR mice, such as upregulated excitatory amino acid synaptic activity and downregulated protein kinase activity (cortex), and upregulated heat shock factors and proteins involved in synaptic pathophysiology and downregulated proteins responsible for oligodendrocyte generation and CNS myelination (hippocampus). The analysis also identified novel functional association of neuronal Wasp (Wiskott-Aldrich syndrome protein) with the ASD profile of the BTBR mice. Wasp has been indicated as playing a role in neuroprotection related to BDNF deficiency in this strain (Jasien et al. 2014). KEGG analysis also pointed to aberrant mammalian target of rapamycin (mTOR) pathway signaling in the cortex of BTBR mice. This is in line with the pharmacological result obtained by Burket and colleagues (Burket et al. 2014) showing that rapamycin, an mTORc1 inhibitor, improved sociability in this strain.

Apart from the differential gene expression patterns, BTBR mice exhibit increased epigenetic alterations to the DNA in the cerebellum (Shpyleva et al. 2014). Elevated levels of 8-oxo-7-hydrodeoxyguanosine, [8-oxodG] the most studied oxidative DNA lesion and an oxidative stress marker, and increased 5-methylcytosine [5mC] were associated with reduced expression of the 8-oxoguanine DNA-glycosylase 1 [*Ogg1*]; and increased expression of de novo DNA methyltransferases 3a and 3b [*Dnmt3a* and *Dnmt3b*]. Similar changes were

observed for human postmortem analysis of cerebellar epigenetic changes in ASD patients (Shpyleva et al, 2014).

In sum, the BTBR background is characterized by multiple genetic and epigenetic aberrations. Recent, improved protocols for *in vitro* fertilization in this strain (Baan et al. 2016) open the possibility for generation of transgenic mutants on BTBR background (e.g. with gene editing tools such as CRISPR/Cas9 plasmids), which should verify the role of many of the suggested candidate genes in the development of the ASD-like profile of BTBR mice. While pathway analyses point to disruption of several inter and intracellular signaling pathways, many genes and proteins involved in the development and maintenance of proper connectivity within the brain were also affected. The latter results in the unique neuroanatomical profile of the BTBR mouse.

3. Neuroanatomy of the BTBR mouse: impaired axon guidance and neurogenesis

Many neuroanatomical similarities between the BTBR mouse model and certain subpopulations of ASD patients were recently pointed out (for review see Ellegood and Crawley, 2015). The recent return of BTBR neuroanatomy to autism-related research focus was fueled by the development and popularization of neuroimaging techniques allowing for a more systematic overview of brain morphology aberrations. Until 2013 most information about aberrant brain connectivity in BTBR mice, including the striking complete agenesis of corpus callosum (aCC) and reduction in the hippocampal commissure, came from postmortem histological assessments (Bohlen et al. 2012, Jones-Davis et al. 2013, Kusek et al. 2007, Wahlsten et al. 2003). Similar, changes in the shape and localization of many brain structures, including the hippocampus and amygdala (Mercier et al. 2012), and the formation of Probst bundles were recently confirmed using these neuroimaging techniques (Dodero et al. 2013, Ellegood et al. 2013, Fenlon et al. 2015, Sforazzini et al. 2016, Yang et al. 2009). Analogous neuroanatomical aberrations were reported for a subpopulation of ASD patients (Bridgman et al. 2014, Packer, 2016, Wegiel et al 2010).

In association with aCC, BTBR mice also exhibit gross alterations in the morphology of the brain ventricles and the reduction of the lateral ventricle subventricular zone neurogenic niche heparan sulfate fractones (Mercier et al. 2012, Meyza et al. 2012), a feature also found in ASD children (Pearson et al. 2013). Heparan sulfate (HS) is an extracellular matrix proteoglycan involved in both axonal guidance and dendritic spine formation (Perez et al. 2016). The HS deficiency in BTBR mice occurs in association with the downregulation of exostosin 1 expression (http://phenome.jax.org) and a reduction in plasma sulfate concentrations (Corley et al. 2012). A role of HS in development of autism-like behavioral profile was demonstrated with the use of a conditional knockout of EXT1 (Ext1CKO, *CaMKII-Cre2834;Ext1*$^{flox/flox}$, Irie et al. 2012). These mice, much like BTBR mice, displayed abnormal social interactions, increased repetitive behaviors and impaired ultrasonic vocalization.

As indicated by transcriptomic and proteomic studies, axon guidance, neurogenesis (Daimon et al. 2015) as well as myelination (Wei et al. 2016a) and oligodendrocyte generation (Jasien

et al. 2014, Wei et al. 2016a) are differently regulated in BTBR brains as compared with B6 mice. The combination of the acallosal phenotype with decreased neurogenesis (Stephenson et al. 2011) displayed by BTBR mice provides a unique opportunity to study the role of both of these factors in the development of normosocial behaviors. Until now, only juvenile neurogenesis was reported necessary (Wei et al. 2011), while a callosal dissection experiment by Yang and collaborators (Yang et al. 2009) indicated that the early postnatal physical absence of the corpus callosum did not affect sociability in normally developing mice.

The development of magnetic resonance scanners yielding resolution high enough to track morphological aberrations in mouse brains has allowed for postmortem diffusion tensor imaging and tractography (DTI and DTT, Dodero et al. 2013, Ellegood et al. 2013 and 2015, Kerever et al. 2015) followed by tract-based spatial statistics (TBSS) and voxel based morphometry. A DTI scan combined with detailed histological assessment employing modified CLARITY and CUBIC techniques and two-photon microscopy identified what had been considered a novel interhemispheric commissure in the rostral region of the third ventricle (Miller et al. 2013) as a part of the ventral hippocampal commissure connecting to the fimbria of the hippocampus (Kerever et al. 2015). While there are reports of other commissural changes in BTBR mice, these are inconsistent: Fenlon and collaborators (Fenlon et al. 2015) found that, contrary to previous reports (Ellegood et al. 2013), the anterior commissure was reduced, rather than enlarged, in BTBR mice.

Meta-analysis of MRI data from 26 mouse models of autism revealed abnormalities in multiple brain regions including parieto-temporal lobe, cerebellar cortex, frontal lobe, hypothalamus, and the striatum, that grouped into three clusters based on connectivity (Ellegood et al. 2015). These included: a limbic system cluster (including the bed nucleus of the stria terminalis, amygdala, hypothalamus, lateral septum, hippocampus, and olfactory regions); a white matter cluster (the cerebral peduncle, corpus callosum, internal capsule, and fimbria); and structures connecting cerebellar regions and the inferior colliculus. Clustering between mouse models revealed three major groups. One (including *Shank3*, *En2*, *Fmr1* and *Nrxn1α* mutants) displayed an enlarged corpus callosum, fimbria, and fornix, as well as an increased size of frontal and parieto-temporal lobes and decreased cerebellar cortex. A second group showed decreases in corpus callosum, internal capsule and cerebral peduncle, as well as in the globus pallidus, hippocampus and striatum. BTBR mice fell into this cluster together with *AndR*, *Gtf2i* (dp/dp), *Itgβ3*, 15q11–13, *Slc6A4* KI (129), and *Nlgn3* KI mice. A third cluster, consisting of 16p11, BALB/c, *Cntnap2* (−/−), *Gtf2i* (+/−), *Mecp2, Slc6A4* KI (B6), *Slc6A4* KO, and XO mice was characterized by decreased size of frontal and parieto-temporal lobes and an increase in the size of the cerebellum.

BTBR structural MRI data was also recently used for the development of semi-automated registration-based procedures for voxel based morphometry, and cortical thickness estimation (Pagani et al. 2016). The latter was found generally reduced in BTBR mice, with no particular cell population affected more than others (Fenlon et al. 2015).

Resting-state BOLD functional magnetic resonance imaging (rsfMRI) was used to verify intra-hemispheric connectivity impairments in the anaesthetized BTBR mouse (Sforazzini et

al. 2016). Inter-hemispheric connectivity was found to be present (synchronous rsfMRI signal) in the area of the visual cortex, but detailed analysis employing recombinant rabies virus tracing found no evidence for monosynaptic connections between the two hemispheres in this region. A recent work by Cheng and collaborators (2016) showed, however, that the patterning of retinal fibers within the dorsal lateral geniculate nucleus of both neonatal and adult BTBR mice was disrupted, with a much higher degree of overlap of ipsi- and contralateral fibers, than in B6 mice. Generally, however, aberrations in ipsilateral connections were found in the fronto-cortical regions, but not in the posterior parts of the cortex, and for subcortical fronto-thalamic and striatal fibers.

4. Molecular mechanisms

4.1. Excitatory/Inhibitory imbalance

Excitatory/Inhibitory (E/I) neurotransmission imbalance has been proposed as a focal mechanism in autism-like behaviors (for review see: Uzunova et al. 2016). Consonant with such an imbalance, Wei et al. (2015, 2016b) reported a decreased KCl-evoked glutamate release from synaptoneurosomes in both young adult (8 weeks) and aged BTBR mice. A rescue of that phenotype was obtained by blockade of IL-6 signaling through *i.c.v.* administration of sgp130Fc protein (Wei et al. 2016c). Reduced coherent network oscillations, as well as increased GABAergic and reduced glutamatergic currents were also observed in the early postnatal CA3 field of hippocampi of BTBR mice (Cellot et al. 2016). On the other hand, the frequency of spontaneous inhibitory post-synaptic current (IPSC) was found significantly reduced, while the amplitude and the frequency of spontaneous excitatory post-synaptic current (EPSC) increased in BTBR hippocampal slices from adult (6–10 m.o.) mice. Both were normalized by clonazepam treatment (Han et al. 2014). While these two lines of evidence seem contradictory, the latter is supported by several pharmacological studies (summarized in Table 1), reporting the effectiveness of many categories of drugs affecting E/I balance in reversing at least one domain of autism-relevant behaviors in the BTBR mouse. Drugs acting at glutamatergic or GABAergic sites (mGluR5 antagonists; agonist of the NMDA receptor and AMPAKINEs; as well as positive allosteric modulators of GABAA receptors--the effect being specific for the α2,3 subunit; and selective GABAB receptor agonists) have been useful.

Also an mTORc1 inhibitor, rapamycin, has been considered to be a potential E/I imbalance treatment, due to its role in regulating cell metabolism and protein synthesis (Uzunova et al. 2016). In BTBR mice it was reported capable of reversing social behavior deficits (Burket et al. 2014). Similar, histidine, lysine and threonine rich diet, reportedly inhibiting mTOR1 pathway in the prefrontal and somatosensory cortices but not amygdala of the BTBR mice, reduced their excessive selfgrooming while leaving social approach unaltered (Wu et al. 2016).

Exposure to a ketogenic diet restored sensorimotor E/I balance in the BTBR mouse (Smith et al. 2016). Simultaneously, it improved sociability and the transfer of food preference as well as reduced excessive grooming in these mice (Ruskin et al. 2013). The mechanism through which a ketogenic diet influences either of the two remains elusive. Several explanations have been proposed, including a shift from glucose to ketone bodies

metabolism in the brain, anticonvulsive properties of certain components of the diet, and a change in electrolyte balance (acidosis). A recent report by Newell and collaborators (2016) suggests that ketogenic diet may also reduce otherwise elevated numbers of certain gut microbiota, characteristic of ASD phenotype. Whether any of these are actually responsible for the alleviation of ASD-like symptoms in BTBR mice is not known at this point.

Oxytocin is of particular interest in the context of E/I imbalance and ASD due to its ability to promote the formation of GABAergic synapses (Theodosis et al. 2006). Mice lacking oxytocin receptors were reported to have decreased number of hippocampal GABAergic synapses leading to an increased ratio of glutamatergic/GABAergic synapses and increased seizure susceptibility. These mice also display impaired social behavior and cognitive flexibility (Sala et al. 2011). Single-dose oxytocin supplementation trials have reported increased retention of social information and reduced repetitive behaviors in ASD patients (Hollander et al. 2003, 2006). Intranasal OT administration also produced positive effects on empathic accuracy (Guastella et al. 2010) and trust (Andari et al. 2010). Chronic intranasal oxytocin administration in BTBR mice, however, did not result in improvement of either juvenile reciprocal social interactions or three-chambered social approach. It also did not affect repetitive self-grooming, open-field exploratory activity or fear-conditioned learning and memory (Bales et al. 2014). This unexpected lack of effect could be due to the elevated baseline plasma oxytocin levels observed in BTBR mice (Silverman et al. 2010 b). An oxytocin receptor blocker, L368,899, was effective at reversing the increase in social approach (but not in social novelty preference or the reduction in grooming) caused by electroconvulsive therapy in BTBR mice (Hagen et al. 2015). Another possibility is that chronic intranasal administration is not a suitable method for oxytocin supplementation for mice. A recent study by Huang et al. (2014) demonstrated impaired sociability of B6 mice treated that way, while in prairie voles chronic intranasal oxytocin supplementation resulted with deficient pair bonding (Bales et al. 2013).

4.2. Impairments in monoaminergic (5HT, DA) and cholinergic transmission

Impairments in monoaminergic neurotransmission have been associated with the severity of symptoms in ASD patients (Cartier et al. 2015, Gangi et al. 2016, Muller et al. 2016). BTBR mice were reported to have higher hippocampal $5HT_{1A}$ receptor density (Gould et al. 2011, 2014) as well as lower [(3)H] cyanoimipramine and citalopram binding to the serotonin transporter (SERT, Gould et al. 2011). Increased 8-OH-DPAT-stimulated GTPγS binding in the BTBR hippocampus indicated an elevated capacity of $5HT_{1A}$ receptors to activate G-proteins (Gould et al. 2011). At the same time, fewer serotonergic cells were reported in the hippocampus of BTBR mice as compared to B6 mice (Guo and Commons, 2016). This, however, was compensated by increased number of serotonergic cells in brain areas projecting to the hippocampus, especially in the median raphe.

Dopaminergic neurotransmission in the BTBR mouse was also altered (Squillace et al. 2014). While D_1 receptor activation seemed intact, D_2 receptor function was impaired, resulting in hypoactivation of the reward system in a functional magnetic resonance imaging (fMRI) scan upon GBR 12909 (dopamine reuptake inhibitor) challenge.

Many agents acting via monoaminergic pathways have been tested for their efficacy in reversing autism-like behaviors in the BTBR mouse (summarized in Table 1). Risperidone, an atypical antipsychotic, affecting both serotonergic and dopaminergic transmission had no effect on sociability (Chadman 2011, Gould et al. 2011) and anxiety (Chadman 2011). It did, however, decrease the repetitive behavior of the BTBR mice (Gould et al. 2011) and improve reversal learning in the probabilistic learning paradigm (Amodeo et al. 2014 a). The latter effect, as well as decrease in grooming, was also obtained with *i.p.* administration of a novel 5HT2A antagonist, M100907 (Amodeo et al. 2014 a, 2016a) as well as with microinfusions of that drug to the dorsomedial striatum, but not to the orbitofrontal cortex (Amodeo et al. 2016b). Fluoxetine, a potent SERT blocker, on the other hand, improved social approach, but had no effect on the repetitive behavior (Gould et al. 2011) and anxiety level (Chadman 2011). Similar effects were observed for buspirone, a 5HT1A receptor partial-agonist (Gould et al. 2011). The effect of citalopram, a selective serotonin reuptake inhibitor (SSRI), was tested using the tail suspension test (Crowley et al. 2005). BTBR mice proved to be very responsive to it. Administration of dietary tryptophan improved social approach, without affecting social novelty preference, reduction of excessive grooming or the number of marbles buried by the BTBR mice (Zhang et al. 2015). Also, a commonly used painkiller, acetaminophen (paracetamol), acting as a 5HT agonist, increased social approach (but not social novelty preference) in the three-chambered apparatus (Gould et al. 2012). Several psychostimulant drugs, acting at the dopaminergic circuitry, affect the behavior of BTBR mice. D-amphetamine increased the number but decreased the duration of social sniffing and reduced the excessive grooming (Silverman et al. 2013 b). 3,4-Methylenedioxymethamphetamine (MDMA, ecstasy) as well as methamphetamine and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP, a neurotoxin destroying dopaminergic neurons) did not affect BTBR locomotor activity, while (−)-trans-Δ9-tetrahydrocannabinol (THC) reduced spontaneous, repetitive wheel running in this strain (Onaivi et al. 2011).

While no differences were found between acetylocholinesterase (AChE) expression in the forebrain of BTBR and B6 mice (Stephenson et al. 2011), lower basal levels of extracellular acetylcholine were reported for BTBR prefrontal cortex (McTighe et al. 2013). Oxotremorine, a muscarinic receptor (mAChR) agonist, decreased repetitive behaviors (grooming and marble burying) in BTBR mice (Amodeo et al. 2014 b). Nicotine, a nicotinic receptor (nAChR) agonist, in low doses improved sociability and in high doses decreased grooming (Wang L. et al. 2015). Donepezil, an acetylocholinesterase inhibitor (AChEI) increased both social approach and social novelty preference (including social sniffing time) in the three chambered social approach task and reduced behavioral rigidity in a water t-maze task and jammed running wheel assay (Karvat and Kimchi 2014).

4.3. Other mechanisms

Prenatal valproate is considered a potent autism-causing environmental factor (for review see Roullet et al. 2013) due to its function as histone deacetylase inhibitor (HDACI). Another HDACI, sodium butyrate, was recently tested in adult BTBR mice (Kratsman et al. 2016). It enhanced preference for social novelty and lowered, otherwise exacerbated repetitive behavior. It had, however, no effect on excessive grooming displayed by these mice.

SR1078, an agonist at the retinoic acid receptor-related orphan receptor α (RORα, nuclear receptor deficiently expressed in many ASD patients), was found to decrease repetitive behaviors (both grooming and marble burying) in BTBR, but not B6 mice (Wang et al 2016). Administration of SR1078 also increased the expression of several genes, including *Bmal1, Clock, and Npas2* as well as *A2bp1*, *Cyp19a*, and *Itpr1* in the brains of BTBR mice.

BTBR mice also showed reduced stereotypy after administration of GW7647, a nuclear peroxisome proliferator-activated receptor agonist (PPAR-α, D'Agostino et al. 2015). The physiological function of this receptor is to regulate lipid homeostasis, but its disrupted expression results in cognitive inflexibility and perseveration.

In sum, pharmacological evidence points to a multiple neurotransmitter imbalance, as well as selective disruption of intracellular signaling in the brains of BTBR mice. It is therefore possible that the common factor(s) responsible for the autism-like behavioral phenotype of this mouse strain lie downstream from these pathways.

5. Other physiological aberrations reported for the BTBR strain

5.1. Stress hormones

Reports of increased anxiety in BTBR mice have been inconsistent (Moy et al. 2007, Pobbe et al. 2011, Silverman et al. 2010 b). However, BTBR mice consistently display increased baseline corticosterone levels (Benno et al. 2009, Frye and Llaneza, 2010, Silverman et al. 2010 b) as well as high glucocorticoid receptor mRNA levels in the brain (Silverman et al. 2010 b). The levels of corticoliberin (CRF) and its mRNA were comparable to those measured in B6 mice (Silverman et al. 2010 b). Social novelty was found to elicit stronger increases in corticosterone level in adolescent (5 weeks old) BTBR mice than in adult BTBR mice (Gould et al. 2014). The corticosterone level in 5 week old BTBR mice was also much higher than that of both 5 and 16 week old B6 and 129S1/SvImJ (129S) mice (Gould et al. 2014). It is thought to be associated with increased density and binding to $5HT_{1A}$ and CB1 receptors in the hippocampus of BTBR mice (Gould et al. 2014).

5.2. Immune system

BTBR mice display aberrant immune responses (for review see Careaga et al. 2015). Heo and colleagues (Heo et al. 2011) found that the basal levels of plasma IgG, IgE and anti-brain antibodies (Abs) were increased in BTBR as compared with B6 mice. BTBR mice also had a higher number of mast cells, an increased proportion of MHC class II-expressing microglial cells and more IgG and IgE deposited in the brain itself, suggesting an ongoing neuroinflammation. The BTBR mice also displayed elevated levels of proinflammatory cytokines such as IL-33, IL-18 and IL-1b and seemed to have an upregulated humoral response to environmental insults. The cellular response, however, was weaker (as compared with B6 mice), despite the basal increased level of $CD8^{+}$T cells in the mesenteric lymph nodes. BTBR mice also displayed lower levels of Foxp3+ and higher levels of RORγt+, T-bet+, and GATA-3+ production, as well as higher levels of C-C chemokine receptor (CCR) and C-X-C motif chemokine receptor (CXCR) production and expression in CD4+ T cells (Bakheet et al. 2016a and b). This phenotype, as well as the increased level of IL-17 (mRNA

and protein) in spleen and brain, was reversed by reservatrol treatment (Bakheet et al. 2016a and b). Reservatrol reduced, in a dose-dependent way, the excessive grooming displayed by BTBR mice (Bakheet et al. 2016a). A more detailed analysis of the overexpression of serum and cultured bone marrow IgGs in BTBR mice showed a higher IgG_1:IgG_{2a} ratio in BTBR mice than in FVB mice. Abs were found to be elevated in the striatum and substantia nigra regions, while increased deposition of IgG_1 was found in the cerebellum, cortex, hippocampus and striatum (Kim et al. 2016). Hwang and colleagues (Hwang et al. 2015) looked at levels of IgG isotypes deposited in fetal brain of BTBR mice. All but IgG_1 were elevated in comparison to FVB fetal brains. Despite the obvious neuroinflammatory profile, BTBR mice (and ASD patients) seem to have intact NF-κB signaling (Malik et al. 2011).

Onore and colleagues (Onore et al. 2013) found that BTBR bone marrow derived macrophages react with elevated production of IL-6, MCP-1, and MIP-1α and a lower level of IL-10 (as compared with B6) to LPS activation alone, and less IL-10 and more IL-12p40 to IL-4/LPS treatment. BTBR also responded with higher IL-12(p70) production to IFNγ/LPS stimulation, an immune response very similar to that observed in ASD patients. Moreover, the cytokine profile correlated with the severity of repetitive grooming (Onore et al. 2013). Inhibition of IL-6 trans-signaling (with 1.5μg of 130Fc protein infused to the right lateral ventricle over the course of 14 days) resulted in an increase in social approach and a trend towards a decrease in grooming behavior (Wei et al. 2016c).

Maternal immune status was also found important for the development of an autism-like phenotype. Infection with a viral mimic polyinosinic-polycytidylic acid (polyI:C) during gestation produced impairments in pre-pulse inhibition in the acoustic startle response as well as aberrant social interactions in adults and ultrasonic vocalization in B6 pups (Shi et al. 2003, Malkova et al. 2012). In BTBR mice, maternal immune activation (MIA) resulted in an increase in the number of ultrasonic calls in pups (postnatal days 8 and 10) but no change in social approach at 10 weeks of age. It also increased grooming (only in males) and marble burying behaviors (Schwartzer et al. 2013). In this context it was interesting that BTBR embryo transplantation to healthy B6 dams improves social behavior displayed by BTBR pups (Zhang et al. 2013). Conversely, embryo transfer of B6 fetuses to BTBR dams, as well as gestational injection of purified IgG from sera of BTBR mice to B6 fetuses in B6 dams produced sociability impairment of the resulting pups (Zhang et al. 2013).

Intracerebroventricular transplantation of human mesenchymal stem cells (MSC: Segal-Gavish et al. 2016) resulted in increased sociability of BTBR mice, including improved social approach and increased social novelty preference in the three-chambered apparatus as well as increased social sniffing in reciprocal dyadic interactions, it also reduced stereotypic digging behavior and excessive grooming as compared with sham-operated mice. Given the choice of running in a jammed wheel and interacting with a stranger mouse, MSC treated BTBR mice also showed greater preference for social interaction than the sham-operated mice, as well as reduced cognitive rigidity in a water t-maze task. Transplantation of allogeneic (B6) bone marrow, but not syngeneic (BTBR) bone marrow, increased three-chamber social approach and total time spent social sniffing in BTBR mice without affecting the grooming behavior (Schwartzer et al. 2016). The reverse transplant (allogeneic BTBR bone marrow to B6 mice) resulted in an increase in grooming.

6. Future directions

The BTBR mouse continues to intrigue researchers with its complex genetic, molecular and physiological background, a complexity that supports the BTBR mouse as a model for the idiopathic form of autism. The difficulty of modeling autism spectrum disorder lies in the obscurity of the mechanisms involved. Since the ASD diagnosis in humans is based entirely on behavioral measures, the ASD population by definition is very likely to be heterogeneous.

The ultimate goal of ASD research is then to find the common denominator, for at least some portion of that population, which could serve as an anchor for development of therapeutic strategies. The character of that common factor remains elusive, but each study describing new developments in the field brings us closer to that discovery.

While studies conducted on ASD patients often address only one signaling pathway or one physiological system at a time, the BTBR mouse provides a unique opportunity to study multiple aberrations found throughout the ASD population in one animal. Pharmacological studies reviewed here prove the necessity of such multi-pathway or even multi-level approach as several of the drugs tested in the BTBR mouse improved only one of the clusters of ASD-like symptoms (social impairments or repetitive behavior). A successful pharmacotherapy regime might in such case require preclinical screening of multi-drug treatments. BTBR mice offer a possibility of testing the interaction of such drugs. Moreover, the success of pharmacotherapy may be hindered by additional factors, such as social anxiety displayed by ASD patients. Thus the innate, baseline high corticosterone level of the BTBR mice provides a relevant background for testing of new pharmacological interventions. Such screening for possible adverse reactions would not be possible if the drug was tested on a less anxious/HPA normative strain.

Future research should also attempt to integrate neuroanatomical and gene expression data in search for different brain regions playing a role in the development of autism-like behaviors in the BTBR mouse. So far, several studies focused on gene and protein expression in the hippocampi of these animals, even though BTBR mice do not display spatial memory impairment or disruption in memory formation within that region (MacPherson et al. 2008). They do, however, have deficient BDNF signaling (Scattoni et al. 2013) and reduced neurogenesis in that region (Stephenson et al. 2011). The results of these genomic and proteomic studies confirmed aberration in several signaling pathways as well as axon guidance, neurogenesis and regulation of changes in the cytoskeleton observed in the brains of these mice. These changes, however, are not restricted to hippocampi alone. The amygdalar complex seems to be an alternative region of interest. Its morphology is altered in the BTBR mice (Mercier et al. 2012). Amygdala-dependent fear learning is impaired, both in the classic conditioning paradigm (MacPherson et al. 2008) and during social co-learning of fear responses (Lipina and Roder, 2013). The activation of several nuclei of amygdala was also dampened, as compared with B6 mice, in response to emotional information transfer from a conspecific (Meyza et al. 2015). Central amygdala function was also implicated in appetitive learning and cognitive rigidity (Knapska et al. 2013, Pusścian et al. 2014). It is therefore crucial to verify the functionality of synaptic connections in this region and their

possible role in the excess of stereotypic behaviors displayed by BTBR mice. Whether the increased corticosterone tone in BTBR mice is related to the aberrant function of the amygdala also remains to be studied.

In sum, BTBR mice, with their complex molecular phenotype require further scientific attention in order to establish the role of the affected pathways in the development of ASD-like behavior. At the same time they provide a unique source of information about multiple system realignment, which might be evoked by factors acting at early developmental stages. Further studies are required in order to understand how early in the development these changes occur.

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Highlights

- BTBR mice display autism-relevant behaviors
- Several manipulations ameliorate their social impairments and/or the excess of repetitive behaviors
- Multiple signaling pathways are affected
- BTBR mice share neuroanatomical features with a subgroup of ASD patients

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Table 1

Pharmacological manipulations affecting social and repetitive behavior in the BTBR $T^{+}Itpr3^{tf}$/J mouse.

	Manipulation	Mechanism	Social interaction	Self-grooming	Marble burying	Other tests	Reference
Excitatory/Inhibitory imbalance	**2-Methyl-6-(phenylethynyl) pyridine (MPEP)**	selective mGluR5 antagonist	=	↓			Silverman et al. 2010a
				↓			Burket et al 2011
						Object location memory ↑	Seese et al. 2014
						MWM ↑ Rotarod ↑	Yang et al. 2015
	GRN-529	selective negative allosteric modulator of the mGluR5 receptor	↑ soc sniffing ↑ soc appr	↓			Silverman et al. 2012
	D-cycloserine	partial glycineB site agonist targeting NMDAR	↑	↓		Rearing ↓	Burket et al. 2013
	CX1837, CX1739 and CX546	AMPAKINEs	↑ soc sniffing	=		OF = (except for CX546, which caused sedation) CX1837 ↑ novel object recognition	Silverman et al. 2013
	CX929	AMPAKINE				Object location memory =	Seese et al. 2014
	Diazepam	positive allosteric modulator of GABAA receptors	↑ soc appr				Pobbe et al. 2011
			↓ under				Defensor et al 2011
						EPM arm entries ↑	Kazdoba et al. 2016
	Diazepam at P15–28					Multi-sensory integration ↑	Gogolla et al. 2014
	Clonazepam		↑ soc appr			Circling ↓ OF, EPM activity = Fear memory ↑	Han et al. 2014
	Allopregnanolone					EPM arm entries ↑	Kazdoba et al. 2016
	Ganaxolone		↑ soc sniffing ↑ soc appr	=	=	OF, EPM activity ↑	
	L-838,417	α2,3 subunit-selective positive allosteric modulator of GABAA receptors	↑ soc appr			Fear memory (short and long term) ↑	Han et al. 2014
	Zolpidem	α_1 subunit-selective positive GABAA modulator	↓ soc appr at a high dose			Fear memory (only short term) ↑	
	R-baclofen	selective GABAB receptor agonist	↑ soc appr	↓	↓		Silverman et al. 2015
monoaminergic	**Risperidone**	Qualitatively atypical antipsychotic ($5HT_{1A,B,D,5A,6,7}$ antagonist, $5HT_{2A,B,C}$ inverse agonist, $D_{1,2,4,5}$ antagonist, D_3 inverse agonist, $\alpha_{1A,B,\ 2A,B}$ antagonist, $H_{1,2}$ inverse agonist)	=		↓		Gould et al. 2011
			=			EPM =	Chadman 2011
						Probabilistic learning ↑	Amodeo et al. 2014
	Fluoxetine	SERT blocker	↑ soc appr		=		Gould et al. 2011

	Manipulation	Mechanism	Social interaction	Self-grooming	Marble burying	Other tests	Reference
			↑ soc appr			EPM =	Chadman 2011
	Buspirone	$5HT_{1A}$ receptor partial-agonist	↑ soc appr		=		Gould et al. 2011
	M100907	$5HT_{2A}$ antagonist				Probabilistic learning ↑	Amodeo et al. 2014
				↓			Amodeo et al. 2016a and b
	Citalopram	selective serotonin reuptake inhibitor (SSRI)				Tail suspension ↑	Crowley et al. 2005
	Dietary tryptophan	5HT precursor	↑ soc appr but not soc novelty	=	=		Zhang et al. 2015
	D-amphetamine	Psychostimulant, acting via DA-ergic enhancement in the mesolimbic circuit	↑ ↓ duration of soc sniffing	↓			Silverman et al. 2013
	3,4-Methylenedioxym ethamphetamine (MDMA, ecstasy)	Psychostimulant, presynaptic releasing agent of serotonin, norepinephrine, and dopamine				Locomotor activity =	Onaivi et al. 2011
	metamphetamine	Psychostimulant, full agonist of trace amine-associated receptor 1 (TAAR1)					
	1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)	Neurotoxin destroying dopaminergic neurons					
	(−)-*trans*-Δ^9-tetrahydrocannabi nol	partial agonist activity at the cannabinoid receptor CB1				Spontaneous wheel running ↓	
	Acetaminophen (paracetamol)	cannabinoid CB(1) receptor-mediated inhibition of serotonin (5-HT) transmission in the frontal cortex, 5HT agonism	↑ soc appr		=		Gould et al. 2012
	Atomoxetine	noradrenergic reuptake inhibitor				Fear memory ↑	Stapley et al. 2013
cholinergic	**Oxotremorine**	Muscarinic acetylcholine receptor (mAChR) agonist		↓	↓		Amodeo et al. 2014
	Nicotine	nicotinic acetylcholine receptor (nAChR) agonist	↑ soc appr at low doses	↓ at high doses		OF activity ↓	Wang L et al. 2015
	Donepezil	(AchEI) Acetylocholinester ase inhibitor	↑ soc appr and novelty ↑ soc sniffing			Rigidity in T-maze and jammed running wheel ↓	Karvat and Kimchi 2014
other pathways	**Chronic intranasal oxytocin**	Neuropeptide, OXTR agonist	= ↑ soc sniffing in females	=		Juvenile social interaction = Fear memory =	Bales et al. 2014
	Rapamycin	mTORC1 inhibitor	↑ soc appr ↑ soc sniffing	=			Burket et al. 2014
	histidine, lysine, threonine diet	mTORc1 inhibition	=	↓			Wu et al. 2016
	Sodium butyrate	HDAC inhibitor	↑ soc novelty at low doses	=	↓		Kratsman et al. 2016
	SR1078	retinoic acid receptor-related orphan receptor α (RORα) agonist		↓	↓		Wang et al 2016
	GW7647	Peroxisome proliferator-activated receptor agonist		↓	↓		D'Agostino et al. 2015
	sgp130Fc	IL-6 trans-signaling blocker	↑ soc appr	↓=			Wei et al. 2016c

soc appr – social approach in the three chambered apparatus

soc novelty – preference for novel mouse in the third phase of three chambered apparatus social approach test

soc sniffing – either during social approach test in the three chambered apparatus or in close dyadic interaction

MWM – Morris Water Maze

OF – Open Field test

EPM – Elevated Plus Maze