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Review Article

Recent advances in animal model experimentation in autism research

Tania M, Khan MA, Xia K. Recent advances in animal model experimentation in autism research

Objective: Autism, a lifelong neuro-developmental disorder is a uniquely human condition. Animal models are not the perfect tools for the full understanding of human development and behavior, but they can be an important place to start. This review focused on the recent updates of animal model research in autism.
Methods: We have reviewed the publications over the last three decades, which are related to animal model study in autism.
Results: Animal models are important because they allow researchers to study the underlying neurobiology in a way that is not possible in humans. Improving the availability of better animal models will help the field to increase the development of medicines that can relieve disabling symptoms. Results from the therapeutic approaches are encouraging remarkably, since some behavioral alterations could be reversed even when treatment was performed on adult mice. Finding an animal model system with similar behavioral tendencies as humans is thus vital for understanding the brain mechanisms, supporting social motivation and attention, and the manner in which these mechanisms break down in autism. The ongoing studies should therefore increase the understanding of the biological alterations associated with autism as well as the development of knowledge-based treatments therapy for those struggling with autism.
Conclusion: In this review, we have presented recent advances in research based on animal models of autism, raising hope for understanding the disease biology for potential therapeutic intervention to improve the quality of life of autism individuals.

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Summations

- Autism is a neurobehavioural disease that is difficult to study in human subjects. Animal model experimentation can provide excellent support in autism research.
- Autistic model animals can be generated by certain drug treatments and mutagenesis.
- This is a review article that discusses the success, limitation and future direction of animal model experimentation in autism research.

Considerations

- Difficult to generate the autistic model of animals.
- Psychologically and physiologically, the animal brain differs from the human brain. Therefore, the animal model cannot give the exact study model.
- Clinical implication of autism research is very limited.

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Autism: a neurogenetic disorder

Autism is a highly heritable complex disorder of neural development characterised by impaired social interaction and communication, and by restricted and repetitive behaviour (1). The hallmark feature of autism is impaired social interaction (2). Although autism varies significantly in characteristics and severity, it occurs in all ethnic and socio-economic groups and affects every age group (3). The number of reported cases of autism has markedly increased since the 1990s and early 2000s, and the prevalence of autism is 10–20 per 10 000 (4,5). At present, there is no cure for autism (2). Therapies and behavioural interventions are designed to remedy specific symptoms that can cause substantial improvement (6). However, the treatment is expensive, and publicly supported programmes are often inadequate or inappropriate for a given child (7).

Although the exact aetiology of the condition is not known, family and twin studies strongly indicated genetic factors behind autism. Genome-wide scans suggest several susceptibility loci that may contain one or more predisposing genes. Moreover, it does not seem to be a single gene disorder (8). The large number of autistic individuals with unaffected family members may result from copy number variations, spontaneous deletions or duplications in genetic material during meiosis (9,10). Environmental factors such as exposure to certain chemicals including thalidomide, misoprostol and valproic acid (VPA) in early pregnancy are also believed to contribute to autism (11). Autism may result from the impairment of foetal brain development caused by the defects in genes that control brain growth and regulate brain cell communications, possibly because of the influence of environmental factors on gene function (12,13).

The brain mechanisms responsible for moderating social behaviour, the specific neuronal circuitry and the chemicals involved in these processes are relatively mysterious. This is mostly because of the difficulty in studying the fundamental neurophysiological processes directly in the human brain. Finding an animal model system with similar behavioural characteristics as human is thus vital for understanding the brain mechanisms in autism.

Why animal model of autism study is necessary

Recent autism research has changed focus from behavioural observations of autism to translating findings from animal models and genomic manipulation studies to pharmacological agents, with the aim to reverse the interior symptoms of autism (14). The brain mechanisms responsible for autism are not fully understood and the animal models, which parallel related emotional and cognitive impairments, may be helpful in sorting out these mechanisms (15). Although it is difficult to reflect human pathophysiology in animal models, some aspects of molecular pathways, brain anatomy, cognitive and behavioural phenotypes can be addressed. Some research groups have created animal models of autism, which are based on the human central nervous system. These mouse models display some brain anatomical and behavioural abnormalities, providing insight into human neuropsychiatric disorders that will contribute to the screening of novel drugs.

Mouse models are advantageous in many respects, primarily because they are genetically developed and appropriate for invasive studies. Knockout mouse variants, in which existing genes have been inactivated via genetic engineering, offer invaluable opportunities to test the functional and behavioural repercussions of manipulating a particular aspect of the nervous system (16). An ideal animal model of autism would exhibit face validity, in which the behaviour of the model is compromised in a manner that is consistent with autism; construct validity, similar to the underlying biological mechanisms of the disorder; and predictive validity, in which interventions effective in treating autism induce the expected response in the model (17). Similarly, the underlying causes of the disorder and predictive validity are nearly impossible to address in rodent models, as the underlying causes of autism are unknown and it is difficult to establish face validity (18).

Non-human primates provide an attractive, complementary model for autism owing to the complexity and dynamics of social structures, reliance on vision for social signalling and striking homology in the anatomy of neural circuits mediating social behaviour (16). The non-human primates have a large behavioural repertoire with a high degree of isomorphism to human behaviour (19). Neural manipulations in non-human primates that affect behaviour in a manner reminiscent of autism can thus be used as a tool for the study of the aetiology of autism, or as a model for testing therapeutic agents that ameliorate autism symptoms. However, translational research is needed to discover pharmacological targets and treatments of autism. Animal models with phenotypic relevance to diagnostic criteria offer clear experimental strategies to test the efficacy and safety of novel treatments (20).

Generation of animal models for autism research

Autism is characterised by impairments in reciprocal social communication and stereotyped verbal and

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Table 1. Strategies in generating autism model by drug treatment

Drugs	Effects of treatment	References
VPA	Prenatal exposure of VPA in rodents produces neuroanatomical and behavioural deficits and alters social behaviours. VPA exposure in rats lowers neurons and alters neuronal morphology, and produces an imbalance of oxidative homeostasis that facilitates susceptibility to autism	(22–30)
PPA	ICV injections of PPA results in brain and behavioural abnormalities in rats, generates neuroinflammatory response, increases oxidative stress, which are linked to autistic behaviour	(31–33)

ICV, intracerebroventricular; PPA, propionic acid; VPA, valproic acid.

Table 2. Strategies in generating autism model by mutagenesis

Target proteins	Effects of mutations	References
Neuroligin	Defects in sensory behaviours and sensory processing; hypersensitive to oxidative stress and mercury compounds; the grey matter structures, such as the hippocampus, the striatum and the thalamus are found to be smaller in the NL3 knockin mouse model; knockout of NL-3 and NL-4 in mice diminishes social behaviour and vocalisations	(35–39)
Neurexins	Neurexin-1alpha-deficient mice displays electrophysiological and behavioural changes consistent with cognitive impairments	(40)
Shanks	Motor functions are reduced in Shank1 null-mutant mice; Shank2-mutant mice shows a marked decrease in NMDA-receptor function; Shank3 (+/ΔC) mice shows behavioural deficits, suggestive of autism and reduces NMDA-receptor function	(44–46)
Mecp2	Mecp2 mutant mice displays social behaviour impairment	(47,48)
Foxps	Knockout of Foxp2 leads to reduced vocal behaviour and premature death	(38)
Cntnap2	Knockout of the *CNTNAP2* gene is associated with neurodevelopmental impairment	(52,53)
Ube3a	Cognitive and motor abnormalities	(54,55)
Tsc	Loss of Tsc1 in mouse cerebellar Purkinje cells results in abnormal social interaction, repetitive behaviour and vocalisations; the loss of Tsc2 causes a progressive increase in Purkinje cell size and subsequent death from apoptosis	(57–59)

NL, neuroligin; NMDA, *N*-methyl-D-aspartate.

non-verbal behaviours (21). A variety of features of autism can be simulated in rodents, including repetitive behaviours, deficits in social interaction and communication. Neuropathological and some characteristic neurochemical changes, which are frequently seen in autism, and alterations in the immune status in the brain and periphery are found in some of the models by drug treatment or mutagenesis (Tables 1 and 2).

Drug-induced autism model

VPA. Experiments on rodents have indicated that maternal VPA exposure has permanent adverse effects on neurological and behavioural development. The animal model induced by prenatal exposure of VPA has been proposed to study autism, as prenatal VPA exposure produces many neuroanatomical and behavioural deficits associated with autism (22,23). Several studies compared the effects of different time intervals of prenatal VPA exposure for inducing the altered social behaviours relevant to autism. Anatomically, there was a reduction in brain weight and cortical thickness along with decreased dendritic branching in the orbitofrontal cortex (OFC) and medial prefrontal cortex (mPFC) and decreased spine density in the mPFC, OFC and cerebellum (24–26). These studies reported that VPA-exposed rats showed significantly fewer neurons and significant alterations in neuronal morphology, and thus prenatal VPA exposure in rats appears to produce similar dysmorphology as reported in the autistic human brain. Kim et al. (27) reported that prenatal exposure of VPA in rat model shows social behaviour impairment, crooks tail phenotype, reduces expression of GABAergic neuronal marker GAD and increases the expression of glutamatergic neuronal marker vGluT1. Favre et al. (28) reported that rat offspring exposed to VPA leads to the neocortex and amygdala hyperreactive and hyperplastic because of hyper-connectivity between the neurons. They treated Wistar dams with a single intra-peritoneal injection of 500 mg/kg VPA on embryonic day E12.5 and found that offspring exposed to VPA show smaller brain mass on postnatal day 1 and 14, as well as abnormal nest-seeking behaviour at postnatal day 10 in the olfactory discrimination test and physical malformation. Go et al. (29) reported that prenatal exposure of VPA increases the neural progenitor cell pool and induces macrocephaly in rat brain via a mechanism involving the GSK-3β/β-catenin pathway. Zhang et al. (30) suggested that the upregulation of the Wnt/β-catenin signalling pathway induced by VPA administration during early pregnancy produces an imbalance in oxidative homeostasis that facilitates susceptibility to autism.

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Propionic acid (PPA). PPA is a dietary short-chain fatty acid produced in the body during normal cellular metabolism and a metabolic end-product of enteric bacteria. Shultz et al. (31) reported that intracerebroventricular (ICV) injection of PPA results in anatomical and behavioural abnormalities in rats similar to the humans suffering from autism. They administered ICV injection of PPA to Long-Evans hooded rats and showed marked impairment in the water maze task and beam task. MacFabe et al. (32) administered PPA to adolescent male rats and immunohistochemical analysis of the brain tissue from PPA rats revealed reactive astrogliosis and activated microglia, indicating an innate neuroinflammatory response. El-Ansary et al. (33) administered neurotoxic dose of PPA (250 mg/kg body weight/day) to Western albino male rats and they reported an impairment of social behaviour, typical cognitive disability, repetitive behaviour and object-directed behaviour coupled with the increasing oxidative stress markers, a decrease in glutathione level, decreased activity of glutathione peroxidase and catalase. Thus, the neurotoxicity induced by PPA might be an environmental factor that plays a central role in the aetiology of autistic biochemical features.

Mutagenesis in animal model

A number of mouse models based on the genetic variants have been developed that are associated with autism or autistic features. The genetic heterogeneity of autism poses a major challenge for identifying mechanism-based treatments. A number of rare mutations are associated with autism and it is unclear whether these result in common neuronal alterations (34). Mouse models have been generated that carry mutations similar to those identified in patients. These models offer the opportunity to investigate *in vivo* the physiological and behavioural consequences of the mutations in the genes coding for the proteins associated with autism, including neuroligin (NL), neurexin, shank, Mecp2, Foxp, Cntnap2, Ube3a and Tsc1/Tsc2.

NL. NL is a member of the class of cell adhesion proteins that mediate synapse development and have been implicated in autism (35). NL mutants are defective in a subset of sensory behaviours and sensory processing, and are hypersensitive to oxidative stress and mercury compounds; the behavioural deficits are strikingly similar to traits frequently associated with autism (36). In one study, Ellegood et al. (37) reported that the NL-3 knockin mouse model has marked volume differences in many different structures in the brain: grey matter structures, such as the hippocampus, the striatum and the thalamus, were all found to be smaller in the NL-3 knockin. In addition, knockout of NL-3 and NL-4 in mice diminishes social behaviour and vocalisations (38). NL-3 and NL-4 knockout mice represent a useful animal model for understanding pathophysiological events in autism and for developing novel treatment strategies in this devastating disorder (39).

Neurexins. Neurexins are presynaptic membrane proteins that bind to postsynaptic cell adhesion proteins, NLs (36). Etherton et al. (40) reported that neurexin-1alpha-deficient mice display a decrease in prepulse inhibition, an increase in grooming behaviours, an impairment in nest-building activity and an improvement in motor learning. Their report indicated that deletion of neurexin-1-alpha is correlated to the electrophysiological and behavioural changes in mice, which is consistent with cognitive impairments observed in human patients (40).

Shanks. *SHANK* genes encode a family of synaptic scaffolding proteins located postsynaptically on excitatory synapses and mutations in *SHANK* genes have been detected in several autistic individuals. Silverman et al. (41) reported that adult Shank1-null mice are on standardised measures of gen health, neurological reflexes and sensory skills; however, their motor functions are reduced, suggesting that Shank1 has a role in motor functions, although Shank1-null mice do not show autism-relevant social interaction problem directly (41). Won et al. (42) showed that Shank2-mutant mice, carrying a mutation identical to the autism-associated micro-deletion in the human *SHANK2* gene, exhibit autism-like behaviours including reduced social interaction and reduced social communication. These mice showed a marked decrease in *N*-methyl-D-aspartate (NMDA) glutamate receptor (NMDAR) function (42). The protein complex ProSAPs/Shanks at the excitatory synapses organises the complex protein machinery of the postsynaptic density. Genetic deletion of ProSAP1/Shank2 upregulates ionotropic glutamate receptors at the synapse in a brain region-specific manner (43). These mutants were found to display autistic-like behavioural alterations such as repetitive grooming as well as abnormalities in vocal and social behaviours. Bangash et al. (44) created a mouse genetic model associated with autism that mimics a human mutation of Shank3, which deletes the C terminus. Shank3 (+/ΔC) mice showed behavioural deficits

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suggestive of autism and reduced NMDA receptor function. Direct stimulation of NMDARs with D-cycloserine (a partial agonist of NMDARs) or treatment with a positive allosteric modulator of metabotropic glutamate receptor 5 normalises NMDAR function and improves social interaction in Shank-mutant mice (42,45). Peca et al. (46) generated Shank3-mutant mice displaying different levels of severity in synaptic defects and phenotypes in Shank3-related autism. They showed that mice with *SHANK3* gene deletions could lead to varying degrees of functional defects such as self-injurious repetitive grooming and deficits in social interaction, which may contribute to the genesis of autistic-like behaviours in mice.

Mecp2. Mouse models of autism with targeted mutations in the *MECP2* gene (encodes a methyl-CpG-binding protein) show a high degree of phenotypic consistency with the clinical syndrome. A variety of studies have demonstrated that Mecp2-mutant mice display impaired social behaviour (47). Derecki et al. (48) transplanted wild-type bone marrow into irradiation-conditioned Mecp2-null murine model and reported that wild-type Mecp2-expressing microglia within the context of a Mecp2-null mouse arrested disease development and improved locomotor activity. In this study, they suggested bone marrow transplantation as a possible therapeutic approach for autism (48). However, Pearson et al. (49) performed a series of classic and refined social behaviour tasks in hypomorphic Mecp2 (308/Y) mutant mice, and they suggested that mutations in the Mecp2 are not associated with autism-relevant social impairment in mice (49).

Foxps and Cntnap2. There is emerging evidence that the *FOXP* family of genes is strongly linked to autism. The *FOXP* family of genes includes three genes expressed in the central nervous system: *FOXP1*, *FOXP2* and *FOXP4* (50). According to the report of Fischer and Hammerschmidt (38), knockout of FoxP2 leads to reduced vocal behaviour and eventually premature death. They suggested that the introduction of human variant of FoxP2 protein in mice might result in shifts in the frequency and modulation of pup ultrasonic vocalisations. Fujita et al. (51) showed a genetic connection between *FOXP2* and *CNTNAP2* and reported that Cntnap2 mRNA level is significantly increased in the cerebellum of Foxp2 (R552H) knockin pups. Cntnap2 and CtBP (co-repressor of Foxp2) are ubiquitously expressed, whereas Foxp2 co-localised with CtBP only in Purkinje cells (51). Peñagarikano et al. (52) characterised a mouse knockout of the *CNTNAP2* gene, which is strongly associated with autism and related neurodevelopmental disorders. There are some other strong neurobiological, genetic and imaging evidence that the *CNTNAP2* gene is a risk factor for autism spectrum disease, which has been reviewed in detail by Peñagarikano and Geschwind (53).

Ube3a. The most widely used model for autism is the *UBE3A*-maternal-deficient mouse that recapitulates most of the essential features of autism, including cognitive and motor abnormalities (54). Jiang et al. (55) generated mutant mice with a 1.6-Mb chromosomal deletion from *UBE3A* and *GABRB3* genes, and suggested that mutant mice with this maternal deletion provide an autistic mouse model that is more similar to the contiguous gene deletion form of autism in humans in molecular biological aspect (55).

Tuberous sclerosis complex (TSC). Mutation in TSC is an intriguing model to investigate the cerebellar contribution to the underlying pathogenesis of autism (56). Tsai et al. (57) showed that both heterozygous and homozygous loss of Tsc1 in mouse cerebellar Purkinje cells resulted in autistic-like behaviours, including abnormal social interaction, repetitive behaviour and vocalisations, in addition to decreased Purkinje cell excitability (55). Zeng et al. (58) characterised a novel mouse model involving conditional inactivation of the *TSC2* gene in glial-fibrillary acidic protein (GFAP)-positive cells [Tsc2(GFAP1)C knockout mice]. Carson et al. (59) reported that Tsc1 conditional knockout animals die by 25 days of life; their brains have increased size and contain prominent large cells within the cerebral cortex that have considerably increased mTORC1 signalling and decreased mTORC2 signalling (59). These findings define a molecular basis for a cerebellar contribution to autism.

Future research

The aetiology of autism is not fully known, and there are very few drugs for ameliorating the basal symptoms of this disease. The introduction of efficient neuroprotective drugs, which might ameliorate secondary neuronal cell damage in various brain regions to the therapy, is the main objective of numerous experimental studies (60). Genetic evidence of the involvement of multiple susceptibility genes in autism will enable future

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studies to move from single-gene models to models with multiple modified loci, with the promise of better representing the complexity of autism (61). Transplantations of transfected cells capable of producing neurotrophic factors or stem cells to the brain might be an efficient method for improving brain function in the future (61). If the validity of this animal model is confirmed by future research, translational studies focusing on the interaction between early experience and opioid neurotransmission may provide useful insights for identifying endophenotypes of autism (62). In future, these animal models will be invaluable preclinical tools for the development of highly specific and efficacious treatments for children affected with autism (63).

Conclusions

Autism is a common socially devastating disorder. The brain mechanisms responsible for autism are not understood properly and animal models paralleling related emotional and cognitive impairments may prove helpful in unravelling them. Better animal models may play a critical role in understanding the aetiology of autism and develop more effective therapies. Through careful behavioural analyses, most of the core characteristics of autism, that is, impairments in social interaction, difficulty with language, and repetitive and stereotyped motor behaviours can be modelled in mice. Integrating clinical studies on humans, genetic manipulations in mice and neural system studies on non-human primates will offer the most promising approach for understanding the biology and allowing the development and testing of therapeutic agents. Finally, the use of intelligent animals in any research programme demands close scrutiny and ethical concerns, and associated financial and social supports.

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Conflict of Interest

The authors report no conflicts of interest.

References

1. Klauck SM. Genetics of autism spectrum disorder. Eur J Hum Genet 2006;**14**:714–720.
2. Myers SM, Johnson CP. Council on Children with Disabilities. Management of children with autism spectrum disorders. Pediatrics 2007;**120**:1162–1182.
3. Newschaffer CJ, Croen LA, Daniels J et al. The epidemiology of autism spectrum disorders. Annu Rev Public Health 2007;**28**:235–258.
4. Wing L, Potter D. The epidemiology of autistic spectrum disorders: is the prevalence rising? Ment Retard Dev Disabil Res Rev 2002;**8**:151–161.
5. Fombonne E. Epidemiology of pervasive developmental disorders. Pediatr Res 2009;**65**:591–598.
6. Howlin P. Practitioner review: psychological and educational treatments for autism. J Child Psychol Psychiatry 1998;**39**:307–322.
7. Montes G, Halterman JS. Child care problems and employment among families with preschool-aged children with autism in the United States. Pediatrics 2008;**122**: e202–e208.
8. Shastry BS. Molecular genetics of autism spectrum disorders. J Hum Genet 2003;**48**:495–501.
9. Nomura J, Takumi T. Animal models of psychiatric disorders that reflect human copy number variation. Neural Plast 2012;**2012**:589524.
10. Cook EH, Scherer SW. Copy-number variations associated with neuropsychiatric conditions. Nature 2008;**455**:919–923.
11. Landrigan PJ. What causes autism? Exploring the environmental contribution. Curr Opin Pediatr 2010;**22**: 219–225.
12. Courchesne E, Pierce K, Schumann CM et al. Mapping early brain development in autism. Neuron 2007;**56**: 399–413.
13. Chomiak T, Hu B. Alterations of neocortical development and maturation in autism: insight from valproic acid exposure and animal models of autism. Neurotoxicol Teratol 2013;**36**:57–66.
14. Smile S, Anagnostou E. New models for considering the role of medication in the treatment and elucidation of the etiology of autism. Curr Psychiatry Rep 2012;**14**:726–731.
15. Meyza KZ, Defensor EB, Jensen AL et al. The BTBR T(+)tf/J mouse model for autism spectrum disorders-in search of biomarkers. Behav Brain Res 2013;**251**:25–34.
16. Watson KK, Platt ML. Of mice and monkeys: using non-human primate models to bridge mouse- and human-based investigations of autism spectrum disorders. J Neurodev Disord 2012;**4**:21.
17. Crawley JN. Designing mouse behavioral tasks relevant to autistic-like behaviors. Ment Retard Dev Disabil Res Rev 2004;**10**:248–258.
18. Nestler EJ, Hyman SE. Animal models of neuropsychiatric disorders. Nat Neurosci 2010;**3**:1161–1169.
19. Dantzer R, Kelley KW. Autistic children: a neuroimmune perspective. Brain Behav Immun 2008;**22**:804–805.
20. Silverman JL, Babineau BA, Oliver CF, Karras MN, Crawley JN. Influence of stimulant-induced hyperactivity on social approach in the BTBR mouse model of autism. Neuropharmacology 2013;**68**:210–222.
21. Ey E, Leblond CS, Bourgeron T. Behavioral profiles of mouse models for autism spectrum disorders. Autism Res 2011;**4**:5–16.
22. Roullet FI, Wollaston L, Decatanzaro D, Foster JA. Behavioral and molecular changes in the mouse in response to prenatal exposure to the anti-epileptic drug valproic acid. Neuroscience 2010;**170**:514–522.

https://doi.org/10.1017/neu.2013.58 Published online by Cambridge University Press

23. Lukose R, Schmidt E, Wolski TP Jr, Murawski NJ, Kulesza RJ Jr. Malformation of the superior olivary complex in an animal model of autism. Brain Res 2011;**398**:102–112.
24. Bambini-Junior V, Rodrigues L, Behr GA, Moreira JC, Riesgo R, Gottfried C. Animal model of autism induced by prenatal exposure to valproate: behavioral changes and liver parameters. Brain Res 2011;**1408**:8–16.
25. Kim KC, Kim P, Go HS et al. The critical period of valproate exposure to induce autistic symptoms in Sprague-Dawley rats. Toxicol Lett 2011;**201**:137–142.
26. Mychasiuk R, Richards S, Nakahashi A, Kolb B, Gibb R. Effects of rat prenatal exposure to valproic acid on behaviour and neuro-anatomy. Dev Neurosci 2012;**34**: 268–276.
27. Kim KC, Kim P, Go HS et al. Male-specific alteration in excitatory post-synaptic development and social interaction in pre-natal valproic acid exposure model of autism spectrum disorder. J Neurochem 2013;**124**:832–843.
28. Favre MR, Barkat TR, Lamendola D, Khazen G, Markram H, Markram K. General developmental health in the VPA-rat model of autism. Front Behav Neurosci 2013;**7**:88.
29. Go HS, Kim KC, Choi CS et al. Prenatal exposure to valproic acid increases the neural progenitor cell pool and induces macrocephaly in rat brain via a mechanism involving the GSK-3β/β-catenin pathway. Neuropharmacology 2012;**63**:1028–1041.
30. Zhang Y, Sun Y, Wang F, Wang Z, Peng Y, Li R. Downregulating the canonical Wnt/β-catenin signaling pathway attenuates the susceptibility to autism-like phenotypes by decreasing oxidative stress. Neurochem Res 2012;**37**:1409–1419.
31. Shultz SR, Macfabe DF, Martin S et al. Intracerebroventricular injections of the enteric bacterial metabolic product propionic acid impairs cognition and sensorimotor ability in the Long-Evans rat: further development of a rodent model of autism. Behav Brain Res 2009;**200**:33–41.
32. MacFabe DF, Cain NE, Boon F, Ossenkopp KP, Cain DP. Effects of the enteric bacterial metabolic product propionic acid on object-directed behavior, social behavior, cognition, and neuroinflammation in adolescent rats: relevance to autism spectrum disorder. Behav Brain Res 2011;**217**: 47–54.
33. El-Ansary AK, Ben Bacha A, Kotb M. Etiology of autistic features: the persisting neurotoxic effects of propionic acid. J Neuroinflam 2012;**9**:74.
34. Baudouin SJ, Gaudias J, Gerharz S et al. Shared synaptic pathophysiology in syndromic and non-syndromic rodent models of autism. Science 2012;**338**: 128–132.
35. Chadman KK, Gong S, Scattoni ML et al. Minimal aberrant behavioral phenotypes of neuroligin-3 R451C knockin mice. Autism Res 2008;**1**:147–158.
36. Hunter JW, Mullen GP, McManus JR, Heatherly JM, Duke A, Rand JB. Neuroligin-deficient mutants of C. elegans have sensory processing deficits and are hypersensitive to oxidative stress and mercury toxicity. Dis Model Mech 2010;**3**:366–376.
37. Ellegood J, Lerch JP, Henkelman RM. Brain abnormalities in a neuroligin3 R451C knockin mouse model associated with autism. Autism Res 2011;**4**:368–376.
38. Fischer J, Hammerschmidt K. Ultrasonic vocalizations in mouse models for speech and socio-cognitive disorders: insights into the evolution of vocal communication. Genes Brain Behav 2011;**10**:17–27.
39. Radyushkin K, Hammerschmidt K, Boretius S et al. Neuroligin-3-deficient mice: model of a monogenic heritable form of autism with an olfactory deficit. Genes Brain Behav 2009;**8**:416–425.
40. Etherton MR, Blaiss CA, Powell CM, Südhof TC. Mouse neurexin-1alpha deletion causes correlated electrophysiological and behavioral changes consistent with cognitive impairments. Proc Natl Acad Sci USA 2009;**106**:17 998–18 003.
41. Silverman JL, Turner SM, Barkan CL et al. Sociability and motor functions in Shank1 mutant mice. Brain Res 2011;**1380**:120–137.
42. Won H, Lee HR, Gee HY et al. Autistic-like social behaviour in Shank2-mutant mice improved by restoring NMDA receptor function. Nature 2012;**486**:261–265.
43. Schmeisser MJ, Ey E, Wegener S et al. Autistic-like behaviours and hyperactivity in mice lacking ProSAP1/ Shank2. Nature 2012;**486**:255–260.
44. Bangash MA, Park JM, Melnikova T et al. Enhanced polyubiquitination of Shank3 and NMDA receptor in a mouse model of autism. Cell 2011;**145**:758–772.
45. Deutsch SI, Pepe GJ, Burket JA, Winebarger EE, Herndon AL, Benson AD. D-cycloserine improves sociability and spontaneous stereotypic behaviors in 4-week old mice. Brain Res 2012;**1439**:96–107.
46. Peca J, Feliciano C, Ting JT et al. Shank3 mutant mice display autistic-like behaviours and striatal dysfunction. Nature 2011;**472**:437–442.
47. Johnson RA, Lam M, Punzo AM et al. 7,8-dihydroxyflavone exhibits therapeutic efficacy in a mouse model of Rett syndrome. J Appl Physiol 2012;**112**:704–710.
48. Derecki NC, Cronk JC, Lu Z et al. Wild-type microglia arrest pathology in a mouse model of Rett syndrome. Nature 2012;**484**:105–109.
49. Pearson BL, Defensor EB, Pobbe RL et al. Mecp2 truncation in male mice promotes affiliative social behavior. Behav Genet 2012;**2**:299–312.
50. Bowers JM, Konopka G. The role of the FOXP family of transcription factors in ASD. Dis Markers 2012;**33**:251–260.
51. Fujita E, Tanabe Y, Momoi MY, Momoi T. Cntnap2 expression in the cerebellum of Foxp2 (R552H) mice, with a mutation related to speech-language disorder. Neurosci Lett 2012;**6**:277–280.
52. Peñagarikano O, Abrahams BS, Herman EI. Absence of CNTNAP2 leads to epilepsy, neuronal migration abnormalities, and core autism-related deficits. Cell 2011;**147**:235–246.
53. Peñagarikano O, Geschwind DH. What does CNTNAP2 reveal about autism spectrum disorder? Trends Mol Med 2012;**18**:156–163.
54. Jana NR. Understanding the pathogenesis of Angelman syndrome through animal models. Neural Plast 2012;**2012**: 710943.
55. Jiang YH, Pan Y, Zhu L et al. Altered ultrasonic vocalization and impaired learning and memory in Angelman syndrome mouse model with a large maternal deletion from Ube3a to Gabrb3. PLoS One 2010;**5**:e12278.
56. Reith RM, Way S, McKenna J 3rd, Haines K, Gambello MJ. Loss of the tuberous sclerosis complex protein tuberin causes Purkinje cell degeneration. Neurobiol Dis 2011; **43**:113–222.

https://doi.org/10.1017/neu.2013.58 Published online by Cambridge University Press

57. Tsai PT, Hull C, Chu Y et al. Autistic-like behaviour and cerebellar dysfunction in Purkinje cell Tsc1 mutant mice. Nature 2012;**488**:647–651.
58. Zeng LH, Rensing NR, Zhang B, Gutmann DH, Gambello MJ, Wong M. Tsc2 gene inactivation causes a more severe epilepsy phenotype than Tsc1 inactivation in a mouse model of tuberous sclerosis complex. Hum Mol Genet 2011;**20**:445–454.
59. Carson RP, Van Nielen DL, Winzenburger PA, Ess KC. Neuronal and glia abnormalities in Tsc1-deficient forebrain and partial rescue by rapamycin. Neurobiol Dis 2012; **45**:369–380.
60. Budziszewska B, Lasoń W, Steczkowska M, Gergont A. Value of the experiment for developmental neurology. Przegl Lek 2009;**66**:958–962.
61. Flint J, Shifman S. Animal models of psychiatric disease. Curr Opin Genet Dev 2008;**18**:235–240.
62. Cinque C, Pondiki S, Oddi D et al. Modeling socially anhedonic syndromes: genetic and pharmacological manipulation of opioid neurotransmission in mice. Transl Psychiatry 2012;**2**:e155.
63. Piedimonte LR, Wailes IK, Weiner HL. Tuberous sclerosis complex: molecular pathogenesis and animal models. Neurosurg Focus 2006;**20**:E4.

https://doi.org/10.1017/neu.2013.58 Published online by Cambridge University Press