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Research report

A behavioural test battery to investigate tic-like symptoms, stereotypies, attentional capabilities, and spontaneous locomotion in different mouse strains

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HIGHLIGHTS

- Different mouse strains exhibit differential levels of spontaneous locomotion and perseverative responding.
- Different mouse strains show a differential response to DOI-induced tic-like behaviours.
- SJL and ABH mice exhibit selective variations in isolated drug-induced behavioural parameters.
- CD1 and C57 mice exhibit generalized variations in several behavioural parameters.

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ABSTRACT

The preclinical study of human disorders associated with comorbidities and for which the aetiology is still unclear may substantially benefit from multi-strain studies conducted in mice. The latter can help isolating experimental populations (strains) exhibiting distinct facets in the parameters isomorphic to the symptoms of a given disorder. Through a reverse-translation approach, multi-strain studies can inform both natural predisposing factors and environmental modulators. Thus, mouse strains selected for a particular trait may be leveraged to generate hypothesis-driven studies aimed at clarifying the potential role played by the environment in modulating the exhibition of the symptoms of interest. Tourette's syndrome (TS) constitutes a paradigmatic example whereby: it is characterized by a core symptom (tics) often associated with comorbidities (attention-deficit-hyperactivity and obsessive–compulsive symptoms); it has a clear genetic origin though specific genes are, as yet, unidentified; its course (exacerbations and remissions) is under the influence of environmental factors. Based on these considerations, we tested four mouse strains (ABH, C57, CD1, and SJL) – varying along a plethora of behavioural, neurochemical, and immunological parameters – on a test battery tailored to address the following domains: tics (through the i.p. administration of the selective 5-HT2 receptor agonist DOI, 5 mg/kg); locomotion (spontaneous locomotion in the home-cage); perseverative responding in an attentional set shifting task; and behavioural stereotypies in response to a single amphetamine (10 mg/kg, i.p.) injection. Present data demonstrate that while ABH and SJL mice respectively exhibit selective increments in amphetamine-induced sniffing behaviour and DOI-induced tic-like behaviours, C57 and CD1 mice show a distinct phenotype, compared to other strains, in several parameters.

1. Introduction

Animal models recapitulating the symptoms of a given human disease often rest upon targeted manipulations, genetic and/or environmental, performed on a specific mouse strain. This approach, theoretically independent of the specific strain selected, holds promise to highlight the influence of the given manipulation on the onset, exacerbation, and course of the disease of interest. The selection of the appropriate mouse strain thus constitutes a fundamental cornerstone, potentially dictating the success or failure of the endeavour (see *e.g.* [1]). Specifically, a mouse strain overly sensitive or resilient to the determinant manipulation may mask the consequences of the manipulation itself and ultimately hamper animal model development (see [2] for a discussion). Therefore,

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before venturing in the development of a disease mouse model, it is crucial to systematically evaluate whether different strains display diverse phenotypes on the test-battery selected to mimic the characteristic symptoms of the disease.

Recent evidence indicates that distinct mental disorders may share common behavioural alterations and, in turn, neurobiological substrates [3,4]. The 2008 NIMH strategic plan [5] emphasized the need to approach mental disorders from an integrated perspective capable of combining behavioural, physiological and neurobiological indices. Within this framework, psychiatric disturbances are not to be regarded as rigid units characterized by a single determinant cause associated with an invariant outcome, but rather as a constellation of malleable symptoms. Such theoretical shift may have substantial repercussions in terms of animal models, whereby it entails two fundamental considerations: mental disturbances for which the genetic and environmental predispositions are multifactorial or unidentified may not be adequately modelled by a candidate-gene approach; a multi-strain approach in which the constellation of symptoms is first observed and then reversely associated with a common neurobiological function may serve as a valuable complement in dissecting the fundamental mechanisms of distinct mental disorders sharing common substrates.

Tourette's syndrome (TS), a paediatric disorder characterized by the presence of recurrent motor and phonic tics lasting for more than 1 year [6], constitutes a paradigmatic example of a disturbance characterized by a distinct nosography often associated with several comorbidities [7]. Specifically, TS is often comorbid with attention-deficit-hyperactivity-disorder (ADHD,) and obsessive–compulsive disorder (OCD, [7]). Additionally, tics are generally anticipated by premonitory urges [8] that have been associated with impaired sensorimotor gating, also prevalent in schizophrenia [9]. These disorders have been proposed to share common neurobiological substrates affecting inhibitory systems. In particular, TS and its comorbidities have been associated with alterations at the level of the cortico-striatal-thalamo-cortical circuit and its neurotransmitters: GABA, glutamate, dopamine and serotonin [10].

In the light of these considerations, in the present study, we devised a test battery mimicking TS-like symptoms and its comorbidities and administered it to four mouse strains selected on the basis of a preliminary literature survey. Such preliminary screening aimed at identifying candidate mouse strains that naturally display elevated scores on a series of tests and neurochemical assays of relevance to TS and its comorbidities. Beside focusing on the status of several neurotransmitters, the literature survey thus rested on the following domains: perceptual (sensorimotor gating), activational (impulse control), locomotor (behavioural stereotypies) and switching (perseverative responding). Based on multi-strain studies, we selected: CD1 as they display spontaneous stereotypies at an elevated rate [11,12]; C57BL/6J in the light of their remarkably elevated dopamine levels [13], poor attentional set-shifting capabilities [14], and poor pre-pulse-inhibitory capabilities [15,16]. Additionally, previous studies leveraged the SJL strain to design and develop a mouse model of TS based on an autoimmune hypothesis [17,18]. Specifically, Hoffman et al. [17] and Yaddanapudi et al. [18] immunized and repeatedly boosted SJL mice using Group A Beta Haemolytic *Streptococcus* homogenate. Such experimental strategy was aimed at mimicking the etiological bases of paediatric autoimmune neuropsychiatric disorders associated with *Streptococcus* (PANDAS [19,20]). Several TS cases have been proposed to fall within the category of PANDAS [19]. Such model has generated remarkable experimental and theoretical advancements, whereby it showed that the experimental immunization resulted in motor alterations associated with the presence of autoantibodies targeting striatum, deep cerebellar nuclei, and hippocampus [17,18]. We thus included SJL mice in the study. This inbred albino mouse strain is characterized by an elevated sensitivity of the immune system; to control for this aspect, we also included in the study ABH-Biozzi (hereafter ABH) mice, which are also characterized by elevated immune response [21,22].

In the aforementioned mouse strains we investigated a series of behavioural parameters that are dependent upon neurobiological systems involved in the aetiology of several diseases (Tourette's syndrome, autism, schizophrenia, and OCD): *head twitch* and *body jerk* responses to the administration of the selective 5-HT2 agonist (2,5-dimethoxy-4-iodoamphetamine, DOI), as an indicator of tic behaviours [23]; locomotor activity and behavioural stereotypies in response to amphetamine injection as an index of the behavioural reactivity in response to the stimulation of the dopaminergic system; attentional set-shifting abilities in a binary choice test [2,24,25] as a direct indicator of perseverative responses mediated by the prefrontal cortex [24,26]; and general locomotion in the home cage.

2. Materials and methods

2.1. Mice and rearing conditions

Adult male mice from four different strains ($N = 20$ per strain), ABH, SJL/J (hereafter SJL), C57BL/6 (hereafter C57) and CD1, were purchased from Charles River, Italy (Calco, LC). Upon arrival, ten mice of each strain were housed in pairs while the other half were housed individually in standard polycarbonate cages (33.0 cm × 13.0 cm × 14.0 cm) with sawdust bedding and water and food *ad libitum* (Mucedola, Settimo Milanese, Italy). Differential housing was due to the fact that some investigations (spontaneous locomotion and attentional set-shifting task) required mice to be housed individually. Specifically, the sensors measuring spontaneous locomotion do not distinguish individual subjects housed in the same cages. Therefore, in order to identify each individual subject, mice have been housed in isolation. Additionally, the attentional set-shifting protocol requires mice to be food deprived and granted limited access to food. Food restriction needs to be tailored to each individual mouse thereby resulting unsuited to grouped subjects. Mice of each strain were randomly distributed on the rows and columns of the rack. They were maintained in a controlled environment with temperature at 21 ± 1 °C and relative humidity of 60 ± 10% under a reversed 12:12 h light:dark cycle (lights on at 19.00 h). All experimental procedures were performed in accordance with European Communities guidelines (EC Council Directive 86/609), Italian legislation on animal experimentation (Decreto L.vo 116/92) and NIH guide for the care and use of laboratory animals. The study has been authorized by the Italian Ministry of Health (Decree Nr. 217/2010-B).

2.2. Drugs

D-Amphetamine (AMPH, 10 mg/kg, Sigma–Aldrich, St. Louis, MO, USA) was dissolved in saline (NaCl, 0.9%) and injected i.p. at a volume of 1 ml/100 g body weight. Doses have been chosen according to previous studies to maximize the observation of stereotypies [27].

The serotoninergic agonist 2,5-dimethoxy-4-iodoamphetamine (DOI, 5 mg/kg, Sigma–Aldrich, St. Louis, MO, USA) was dissolved in saline (NaCl, 0.9%) and administered i.p. at a volume of 1 ml/100 g body weight [28] to induce *head twitch* and *body jerk* responses [23].

2.3. Locomotor activity: apparatus for circadian cycle

Mice housed individually ($n = 40$; N(ABH) = 10, N(SJL) = 10, N(C57) = 10, N(CD1) = 10) were monitored for spontaneous locomotion ten days after their arrival. Locomotor activity was monitored