



Invited review

Influence of social isolation in the rat on serotonergic function and memory – Relevance to models of schizophrenia and the role of 5-HT₆ receptors

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ABSTRACT

There is increasing awareness of the importance that early environmental factors have on brain development and their role in the neurobiology of neurodevelopmental disorders including schizophrenia. The isolation reared rat attempts to model adverse effects that human social isolation (absence of social contact) can have on normal brain development. The isolation reared rat also models aspects of schizophrenia including the development of persistent learning and memory deficits. This short review concentrates on the effects of isolation rearing on cognition, including deficits in novel object discrimination, and the neural mechanisms that may underlie this impairment. There is evidence that a key effect of social isolation may be loss of neuronal plasticity combined with change in the functional state of various cortical and hippocampal neurotransmitters, including glutamate and serotonin. Reduced glutamate function may underlie the deficits in novel object discrimination, which can be reversed by administration of a 5-HT₆ receptor antagonist. This suggests that the 5-HT₆ antagonists may act by reducing 5-HT₆ receptor mediated activation of GABA, resulting in glutamate disinhibition. Thus drugs acting at 5-HT₆ receptors may offer a novel approach to treat neurodevelopmental cognitive symptoms, including those seen in schizophrenia.

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1. Introduction

The approach to developing novel animal models of human psychiatric disorders, such as schizophrenia, has transferred attention from a purely pharmacological to a more causative methodology. This change follows advancement in our understanding of the importance of identifiable environmental fine factors, combined with certain genetic predispositions, in the development of such disorders (Karam et al., 2010). For example there is now a consensus view that certain early environmental factors, whether physiological (poor nutrition, obstetric complications and compromised foetal blood supply), pharmacological (maternal drug abuse and early use of drugs, such as cannabis) or psychological (maternal loss and separation, social isolation, sexual and physical abuse), play an essential role in the development of adult disorders like

schizophrenia (Morgan and Fisher, 2007; van Os et al., 2010). Particular interest has focused on the way in which these various factors may lead to changes in brain development that can help to explain the development of psychiatric difficulties in later life.

Various animal models have been used to explore the effects and the mechanisms by which early psychologically harmful events can alter the normal development of the brain. The models include rodent maternal separation (Heim and Nemeroff, 2001; Plotsky and Meaney, 1993; Slotten et al., 2006; Stevenson et al., 2008) and isolation rearing (Bellon et al., 2009; Fone and Porkess, 2008; Millan and Brocco, 2008; Neill et al., 2010), and the present short review will focus on the effects of isolation rearing on brain development and function in the rat, with particular attention being given to the role of the serotonergic system in memory dysfunction associated with early social isolation.

2. The isolation reared rat, general comment on the procedure

Rat pups reared in social isolation from weaning (usually between postnatal day 21 and day 26 depending on the strain)

Abbreviations: MPEP, 2-methyl-6-(phenylethynyl)-pyridine; CER, conditioned emotional response; PFC, prefrontal cortex; PPI, prepulse inhibition of acoustic startle.

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show a wide range of persistent behavioural effects combined with various neurochemical and structural changes within the brain (for a general review see Fone and Porkess, 2008; Jones et al., *in press*). The majority of isolation rearing studies use the same approach in that the pups are singly housed and compared with group-housed littermates (4–6/cage) with all the animals kept in the same room so they have visual auditory and olfactory contact with other rats but the singly housed rats are deprived of social contact and play, and their handling (cleaning etc) is also kept to a necessary minimum. It is important to note that the range of effects of isolation rearing are only observed when isolation starts at or very close to weaning and a clear distinction needs to be made between studies using isolation rearing and the isolation of adult rats as the results are not comparable. The key element in obtaining persistent and reproducible effects with isolation rearing is rigid control of the social environment (for example minimal contact with the experimenter and absence of any form of environmental enrichment in the cage) and studies have shown how variation in these factors can alter the behavioural effects (Weiss et al., 1999). There are also published data showing strain differences in the degree of certain behavioural effects of isolation rearing which is probably most extensively investigated in terms of the hyperactivity and reduced habituation to novelty seen in the isolates; an effect often considered as the most reliable and reproducible. For example, this response is more marked in Lister hooded than Sprague-Dawley rats (Geyer et al., 1993; Weiss et al., 2000). Duration of isolation is also another factor and most studies use a minimum of four weeks before starting behavioural testing, though periods of six weeks or longer may result in more robust behavioural changes. For example, hyperactivity appears after 2–3 weeks isolation (Bakshi and Geyer, 1999; Einon and Morgan, 1977) while at least four to five weeks are required before changes in prepulse inhibition (PPI) of acoustic startle (thought to reflect impaired sensorimotor gating) are observable in Sprague-Dawley rats (Varty et al., 1999a) and even longer in Lister hooded rats (Bakshi and Geyer, 1999).

In summary, isolation rearing in rats refers to a strictly limited environmental state involving minimal social contact of any form, however it is important to be aware that the detail of the effects, in particular behaviour, can be influenced by the rat strain used. At Nottingham over many years (Jones et al., 1992, *in press*) we have used Lister hooded rats for our studies on isolation rearing as we have found this strain to produce consistent and reproducible behavioural effects.

3. Behavioural effects of isolation rearing

Behavioural effects of isolation rearing have been extensively reviewed recently by Fone and Porkess (2008) and Jones et al. (*in press*) it is only intended here to highlight certain behaviours relevant to the later discussion of the serotonergic changes seen in the isolates and the possible use of serotonergic drugs to reverse cognitive deficits.

As already mentioned isolates show hyperactivity and increased reactivity, combined with reduced habituation, to a novel environment and as this appears early after isolation it is often used as a marker of successful isolation rearing. Isolates also show deficits in PPI (Varty et al., 1999a,b; Varty and Geyer, 1998; Varty and Higgins, 1995) which has attracted considerable interest as these deficits are also a feature of schizophrenia as well as other psychiatric disorders (Swerdlow et al., 2000) and the deficits in the isolates can be reversed by several atypical antipsychotics (Cilia et al., 2001; Varty and Higgins, 1995) but not all (Barr et al., 2006). A recent study has shown that not only is the PPI response reduced in isolates but also the enhancement in PPI induced by auditory fear conditioning is lower than that seen in socially reared rats (Li et al., 2008). The effect

of auditory fear conditioning on PPI is blocked by administration of the selective metabotropic glutamate receptor subtype 5 (mGluR5) antagonist, 2-methyl-6-(phenylethynyl)-pyridine (MPEP) (Li et al., 2008), indicating glutamatergic involvement. In the case of response to rewarding stimuli isolates show an enhanced incentive motivational response (Hall et al., 1997) but, interestingly, a reduced response to reward-producing drugs measured either by self-administration (Phillips et al., 1994) or conditioned place preference (Wongwitdecha and Marsden, 1996).

The disruptions in PPI and rewarding stimuli in the isolates most likely relate to the increase in pre-synaptic dopaminergic function in the nucleus accumbens seen following activation, although basal (tonic) levels of dopaminergic function are unaltered in this area (Fulford and Marsden, 1998b; Jones et al., 1992) combined with a dysfunctional post-synaptic responsiveness to dopamine release. This dysfunctionality may involve dopamine D₂ receptor down-regulation in the nucleus accumbens (Hall et al., 1998) as well as disrupted GABA and glutamate function as indicated by the results using MPEP (Li et al., 2008) and further discussed later. Interestingly increased expression of reelin (an extracellular matrix protein secreted by cortical GABAergic neurones thought regulate synaptic formation and plasticity) occurs in layer 1 prefrontal cortex (PFC) cells at the same time, ~PND60, as the emergence of PPI deficits in isolates (Cassidy et al., 2010a) which may thus also be linked with synaptic remodelling in this area.

Isolation rearing also has marked effects on aversive conditioned and cognitive behaviours which cannot so readily be ascribed to changes in dopaminergic function but may involve altered serotonin and other neurotransmitter release. One of the most consistent findings is that isolation reared rats, while showing no impairment in acquisition, often show impairment in the ability to alter the strategy or rule required to achieve a task (Jones et al., 1991; Morgan, 1973). In more recent years the use of an attentional set-shifting task (Birrell and Brown, 2000), that measures learning flexibility, has underscored the cognitive rigidity shown by isolation reared rats as they show both impairments in reversal learning (Schrijver et al., 2004) and extra-dimensional (attentional) shifting (Schrijver and Wurbel, 2001) using a radial arm maze for the test in comparison to the digging based version described by Birrell and Brown (2000). This is of wider interest as similar impairments occur in human schizophrenics when this ability is measured using an analogous task, such as the Wisconsin Card Sort Test (Bozikas et al., 2006; Elliott et al., 1995). Furthermore, this form of reversal learning involves the pathway between the PFC and the striatum which, as will be discussed later, shows abnormal function in the isolation reared rat as well as being implicated in disorders such as schizophrenia (Chudasama and Robbins, 2004).

Schizophrenics also show impairments in episodic and visual memories (McClure et al., 2007; Nestor et al., 2007) and in the rodent this type of memory can be modelled by the novel object discrimination task, developed by Ennaceur and Delacour (1988) in the rat and later reproduced in the mouse (Hammond et al., 2004). In the simplest non-spatial form of this test rodents are given two unknown but identical objects to explore for a defined short period and then after a suitable inter-trial period the rats are returned to the same test environment but one of the familiar objects is replaced by a novel object. The normal behaviour is for rats in the second trial to spend more time exploring the novel rather than the remembered familiar object. Isolation reared rats however show an impairment and fail to discriminate between the novel and the familiar object with relatively short inter-trial intervals, such as 2 h (Bianchi et al., 2006; Jones et al., 2011; King et al., 2007a), while group-housed rats show discrimination. A similar deficit in novel object recognition is observed in female rats reared in social isolation as these animals can only discriminate between the novel

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