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Research report

The effects of isolated and enriched housing conditions on baseline and drug-induced behavioural responses in the male rat

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HIGHLIGHTS

- Rats housed in isolation consumed more food and were heavier than socially-housed counterparts.
- No housing effect on baseline locomotor activity or time spent immobile in the FST.
- Isolated rats had reduced percent open arm time in the EPM compared to standard-housed controls.
- Isolation enhanced, while social housing attenuated, desipramine and diazepam effects in the FST and EPM.
- Locomotor-stimulating effects of amphetamine were greater in socially-housed rats than in isolates.

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ABSTRACT

Environmental enrichment (EE) involves enhancing an animal's environment, with the goal of improving animal welfare. Though a well-established discipline, the consequences of EE on behavioural pharmacological tests have not been extensively examined. The purpose of this study was to examine the consequences of EE (or isolation) housing on a range of behavioural pharmacological tests in the rat. Male Sprague-Dawley rats were randomly assigned to the 3 housing conditions; IC (isolation) and SC (standard group-housed, 4/cage) were housed in standard cages (42 cm × 25.5 cm × 20 cm), while the EE group was housed in groups of 4 in larger cages (54 cm × 38 cm × 19 cm) enriched with a variety of wooden, cardboard and plastic toys/objects. After 4 weeks, housing effects were examined in the following pharmacological tests: diazepam (DZP) effects on anxiolytic behaviour in the elevated plus maze (EPM); desipramine (DMI) effects on immobility time in the forced swim test (FST) and amphetamine (AMP) effects on homecage activity. Dose–response assessments demonstrated that rats housed in EE showed reduced sensitivity to the behavioural effects of DZP and DMI but increased sensitivity to the locomotor-enhancing effects of AMP compared to SC and IC; while IC animals exhibited the clearest dose–response effects to increasing doses of DMI. It may be concluded that environmental manipulation can vary along a continuum and its intensity may be crucial to observable effects. Nonetheless, environmental factors can influence sensitivity to psychotropic drugs and should be considered when implementing EE protocols in such evaluations.

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1. Introduction

Environmental enrichment (EE) refers to the provision of physical and/or social stimulation to laboratory animals that is greater than they would receive under standard housing conditions [1]. EE can be classified into two types; physical enrichment and social enrichment. *Physical enrichment* involves physical modifications to the cage, including increased floor space and the inclusion of features such as supplementary bedding materials, plastic tunnels, wooden objects to gnaw, ropes, swings, running wheels, balls, ramps, ladders and other appropriately-sized animal toys. *Social enrichment* refers to housing social animals in groups wherever possible; cagemate(s) provide constant dynamic interaction and unpredictability. The most recent EU directive for the protection of animals used for scientific purposes in 2010 recommends that laboratory animals be housed in social groups where appropriate and provided with enrichment to promote exercise, foraging, manipulative and cognitive ability (Directive 2010/63/EU of the European Parliament).

There has been growing interest in the area of EE research during the past number of years due to findings that EE rearing can

Abbreviations: EE, environmental enrichment; SC, standard conditions; IC, isolated conditions; EP, Melevated plus maze; FST, forced swim test; NA, noradrenaline; 5HT, serotonin; PND, post-natal day; MWM, Morris water maze; NOR, novel object recognition; LTP, long term potentiation; SD, Sprague-Dawley; DZP, diazepam; DMI, desipramine; AMP, amphetamine; HCMA, homecage monitoring apparatus.

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promote neurogenesis, increase dendritic branching and increase neuronal cell size and improvements in learning and memory [2–4], which have implications for recovery in animal models of neurodegenerative disease, brain injury and psychiatric disorders [5–9]. When evaluating the impact of EE, it is initially important to consider the use of appropriate controls against which comparisons can be made. Rats are social animals and it is recommended that they are housed in standard social conditions (SC) however in experimental conditions where this is not possible, isolated housing conditions (IC) are permissible. In studies of EE, employing both SC and IC conditions as controls may be most suitable as housing conditions vary between laboratories. The provision of EE can influence the young rat's development. Pre-weaning (i.e. prior to PND 21) EE can enhance neural development in the somatosensory cortex [10] and auditory cortex [11], as well as reducing dominant play behaviours [12] and subsequent responsiveness to stress [13]. A number of protocols implement a period of EE just after weaning; post-weaning EE increases exploration and improves habituation to a novel arena [14,15] compared to rats housed in IC or SC conditions. The effects of post-weaning EE on anxiety-like behaviours in other tests are inconsistent, with some reports of increases [16,17], or no effect on [15] open arm entries and open arm time in the elevated plus maze (EPM) when compared to IC and SC controls. Similarly, EE during adolescence had no effect on latency to enter the bright side of the light/dark box in one study [18] but reduced latency to enter the bright side compared to SC and IC controls in another [19]. When compared to SC and IC, rats housed in EE from weaning have been shown to spend more time swimming and less time immobile in the forced swim test (FST) [15,20], which were correlated with neurochemical alterations; i.e. climbing and swimming behaviour correlated positively, while immobility time correlated negatively with noradrenaline (NA) and serotonin (5HT) levels in the hippocampus of EE rats [15]. This would suggest that EE housing helped to improve rats' coping skills and display a more active strategy (i.e. trying to escape) when faced with such a stressor as the FST [21].

Post-weaning EE has also improved performance in tests of learning and memory, with reduced latencies to locate the platform in the Morris water maze (MWM) compared to SC controls [19,22], significantly greater preference for the novel object in the novel object recognition (NOR) test compared to SC [23] and greater recognition of spatial displacement of an object compared to IC controls [19]. These results reflect improvements in brain plasticity due to the stimulation provided by EE rearing [6]. EE and SC rearing from weaning resulted in greater long term potentiation (LTP) induction in the CA1 area of the hippocampus [24], increased newborn cells in the sub-granule cell layer of dentate gyrus and evidence of superior memory skills in the MWM [24,25] when compared to IC controls. Furthermore, increased spine density of parietal neurons due to EE housing was associated with superior problem-solving skills in the radial arm maze and memory in the MWM compared to IC and SC controls [26]. Thus EE conditions can enhance plasticity in the rat brain and improve cognitive functioning when compared to rats reared in an impoverished environment. The behavioural and neuronal changes observed after EE rearing are not confined to young animals. EE has been shown to enhance cortical structure from prenatally developing rats to those over 2 years of age [27,28] and the ability of EE to promote plasticity in the brain prompted investigation of the ability of EE to attenuate cognitive decline associated with age-related deficits.

Similar to its effects when provided post-weaning, EE in adulthood has been shown to reduce anxiety-like behaviour in the EPM and defensive burying tests compared to SC controls [29], and reduced latencies in the MWM compared to IC controls [30,31], coupled with increased neurotrophic factor concentration in various brain regions [30] and hippocampal neurogenesis [29]. EE implementation immediately post-weaning has reduced immobility time compared to IC and SC controls [15,32] in the FST. However, few studies have investigated the effects of early adulthood EE on male rats' behaviour in the FST, and those which have report somewhat inconsistent results. Long Evans and Sprague-Dawley (SD) rats (housed in EE conditions for 6 weeks from approximately. 3 months of age) displayed significantly more climbing and swimming behaviours in the FST compared to SC controls [33]. However Wistar rats aged 2–2.5 months old showed no effect of EE or SC housing on activity in the FST [34]. Furthermore, few studies of early adulthood housing effects employ SC and IC control groups to account for any effects of social enrichment alone on behaviour.

The aim of the present study was to investigate the effects of EE and IC housing during early adulthood on baseline behaviours and in dose–response assessments, compared to SC controls. The behavioural assays and drug challenges selected were based on previous studies in this laboratory; moreover, they are validated and well-characterised in behavioural pharmacology literature.

2. Materials and methods

2.1. Animals

Seventy-two male SD rats (150–170 g/approximately 6 weeks old on arrival, Charles River, U.K.) were housed in groups of 4 for four days acclimatisation, then randomly assigned to one of three housing conditions; IC, SC or EE. Rats were housed in plastic-bottomed cages with sawdust bedding and all rats were provided continuous access to rat chow pellets and tap water. They were maintained on a 12 h light:dark cycle (lights on 08:00) in a temperature controlled room ($20 \pm 2\,^{\circ}C$), with relative humidity of 45–70%. All rats were handled and weighed weekly; bedding was changed once weekly for singly-housed and 3 times weekly for group-housed animals. Food and water were replenished as necessary. The same rats were employed in all behavioural tests, a washout period of up to 7 days was allowed between test and drug exposures.

2.1.1. Housing conditions

Rats housed in SC and EE were housed in same sex groups of 4, the IC group were singly housed. Those housed in SC and IC were maintained in the standard sized cages (42 cm × 25.5 cm × 20 cm), while rats in EE were kept in larger cages (54 cm × 38 cm × 20 cm) with enrichment objects and toys (Table 1).

In addition to the regular rat chow, rats housed in EE were also provided with supplementary food treats such as coco pops (Kelloggs®), pop corn (Tayto®) and dried fruit and nuts. The provision of such palatable foods is frequently employed as an additive to EE [35]. Environmental enrichment objects were provided and changed at least twice weekly. Objects and toys were thus rotated between the EE cages and a record was kept of the objects received by each group. In this way all groups were exposed to all objects and the combinations of objects were varied to enhance their novelty value. All animals were maintained in their respective housing conditions for four weeks before behavioural testing began and throughout the test period (total 9 weeks, see Fig. 1) and all rats were weighed weekly.

2.2. Drugs

Diazepam (DZP; Actavis, Iceland) was administered at 1.25, 2.5 or 5 mg kg^{-1} (i.p.) doses 30 min prior to EPM testing. The tricyclic antidepressant desipramine (DMI; Sigma, D3900) was administered at 2.5, 5 or 10 mg kg^{-1} (i.p.) 24, 5 and 1 h prior to the FST. The psychomotor stimulant amphetamine (AMP; Sigma, A5880) was administered at 0.75, 1.5, 3, or 3.75 mg kg^{-1} (s.c.) immediately prior to homecage monitoring. DZP and AMP were administered in a dose volume of 1 ml kg^{-1}, while

Table 1
Enrichment objects.

Bamboo tunnel (Critter's Choice, U.K.)
Baguette hamster house hideaway
Super Pet Igloo small animal shelter
Living World Dome small animal shelter
Wooden shelters (Happy Pet Products Ltd, U.K.)
Super Pet Hide and See T.V. pet toy
Just 4 Pets Roll 'N' chew
Plastic Tunnels
Cat toys with bell and with rattle
Super Pet Grassy Tunnels
Ka-Bob wooden chew sticks and balls
Burgess gnaw sticks
Nestledown bedding

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