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Review Article

SOCIAL ISOLATION DURING PUBERTY AFFECTS SOCIAL BEHAVIOUR IN ADULT MICE

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Summary: Early social isolation can have profound consequences on different social behaviours due to alterations in brain structures or gene expressions, but its influence on social recognition or vasopressin (AVP) and oxytocin (OXT) expression has not been thoroughly investigated in mice. We examined social recognition in mice of both sexes that were individually housed from 30 days of age until testing at around day 80, individually housed from day 30 until day 60 and regrouped from day 60 until testing at day 80 and in control mice that were group housed throughout experiment. The ability to recognize familiar mouse was tested using standard social recognition test. Group housed mice showed strong social memory, whereas individually housed did not. Interestingly, mice reared in isolation for a limited period showed reduced social memory, suggesting that even isolation for a limited period can have lasting behavioural deficit, especially in female mice. Using immunohistochemistry we examined vasopressin and oxytocin expression in the brain. As expected, immunohystochemical detection of AVP in lateral septum (LS) revealed robust sex difference with males having much more AVP in fibers than females. However, there were no obvious differences in either vasopressin or oxytocin between groups in different housing regimes, suggesting that social isolation in mice has no effect on the expression of these two neurohormones.

Key words: mice; social stress; isolation; social behaviour; social recognition; vasopressin; oxytocin

Introduction

In the natural conditions, mouse *(Mus musculus)* is a social species living in large social groups establishing group territories (1)**.** The ability to recognize familiar conspecifics, social recognition memory, is critical for many forms of social interactions (2). But in laboratory conditions they are often individually housed to prevent intermale aggression or unwanted matings (1, 3). Many studies have shown that early social deprivation, not only in rodents but also in primates and humans, can induce different behavioural, brain structure and gene expression abnormalities (4, 5). It can cause hyperactivity, reduction in habituation and reduction in anxiety-like behaviour in the elevated plus maze (EPM) test, but an opposite effect in the dark-light (3) and staircase test (6), impairment in novel object recognition (7), aberrant self-manipulation, frequent chasing and biting of the tail (1) and higher levels of aggressive attacks in males (8).

Isolation in rats induces enlargements in different stress-sensitive brain regions (5), cytoskeletal microtubular alterations in the hippocampus (9) and reduction in the size of medial prefrontal cortex (10). It also alters peripheral vasopressin (AVP) and oxytocin (OXT) concentrations, and a lack of social stimuli adversely affects development of these two systems in rats (11).

Social isolation and social recognition

Social recognition in rodents is critical for the formation and maintenance of all social relationships. The influence of social isolation on performance in social recognition tests has not been thoroughly investigated. There are only two studies that reported impairments in social recognition in individually housed male (12) and female rats (11). Our

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study revealed that the strongest pattern of social recognition is present in socially housed males. Social recognition was also observed in socially female mice with much smaller reduction in sniffing time (lower habituation), but still with significant difference between last two trials (the last trial with a new unfamiliar female), suggesting that they could distinguish familiar from unfamiliar mouse. In contrast, both male and female mice that were isolated throughout the test did not show either habituation during the first 8 tests and neither social recognition as there was no significant difference between tests 8 and 9. In male mice isolated for a limited period the habituation was reduced, although social recognition was still present as evident by significant difference between tests 8 and 9. However, in female mice that were isolated for a limited period, there was no social recognition (although habituation was similar to social female mice), suggesting that even isolation for a limited period can have lasting effect on this behaviour (13).

Social isolation and expression of AVP and OXT

Social isolation has been reported to affect expression of hypothalamic OXT and AVP (11), which are important in modulating the social recognition and other social behaviours (reviewed in (14, 15). Lateral septum, medial amygdala (MeA), hippocampus, hypothalamus, olfactory bulbs and vomeronasal organ have all been demonstrated as regions critical for OXT and AVP effects on social recognition (16). Previous studies have shown that administration of AVP agonists into LS have improved (17), while AVP antagonists have blocked normal social recognition in rats (18). Post-weaning social isolation can decrease number of AVP cells in male or OXT in female rats in the paraventricular nucleus (PVN), what coincides with the impairment in social recognition in isolated rats (11) and with the suggestion that AVP is more important in male (14), and OXT in female behaviour (15).

In our study, immunoexpression of AVP in LS, which contains axons from the MeA and bed nucleus of the stria terminalis (BNST), and OXT in PVN was not altered by social isolation. However, since we only used immunocytochemistry that could only detect proteins stored in the nerve fibers, it is still possible that there are differences in either of these two peptides at the level of protein secretion or turnover, or even at the level of their receptors expression, therefore, we were not able to either confirm or reject the hypothesis that dysregulation of AVP and/or OXT system in the brain is responsible for alterations in social recognition behaviour in socially isolated mice (16).

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SOCIALNA OSAMITEV MED PUBERTETO VPLIVA NA SOCIALNO OBNAŠANJE PRI ODRASLIH MIŠIH

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Povzetek: Zgodnja socialna osamitev, ki povzroča spremembe tako v strukturi možganov kot tudi v izražanju genov, ima lahko pomemben vpliv na različna socialna obnašanja. Vpliv osamitve pri miših na socialno prepoznavanje ali izražanje vazopresina (AVP) in oksitocina (OXT) pa še ni bil raziskan. Proučevali smo socialno prepoznavanje miši obeh spolov, ki so bile nastanjene individualno vse od starosti 30 dni pa do testiranja pri starosti 80 dni, individualno nastanjene od 30. do 60. dneva in nato od 60. dneva ponovno skupinsko nastanjene in kontrolna skupina, ki je bila cel čas nastanjena skupinsko. S standardnim testom socialnega prepoznavanja smo ugotavljali sposobnost testnih miši ločiti znano miš od neznane. Skupinsko nastanjene miši so kazale neokrnjen, močan socialni spomin, medtem ko ga miši, nastanjene individualno, niso. Zanimivo je, da so individualno nastanjene miši za določeno časovno obdobje, kazale slabši socialni spomin, kar pomeni, da ima lahko tudi osamitev za določen čas trajne posledice pri socialnem obnašanju, še posebej pri mišjih samicah. Z imunohistokemično metodo smo ugotavljali izražanje vazopresina in oksitocina v možganih. Po pričakovanjih smo našli očitno spolno razliko v izražanju vazopresina v stranskem septumu (LS). Samci so imeli namreč več vazopresina v živčnih vlaknih kot samice. V izražanju tako vazopresina kot oksitocina glede na način nastanitve nismo našli razlik.

Ključne besede: miši; socialni stres, osamitev; socialno prepoznavanje; vazopresin; oksitocin