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REVIEW

Social isolation stress and neuroactive steroids

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Abstract Social isolation of rats immediately after weaning is associated to a reduction in the cerebrocortical and plasma concentrations of progesterone and its metabolites 3α,5α-TH PROG and 3α,5α-THDOC. Although we found that the basal plasma concentration of adrenocorticotropic hormone in isolated rats was slightly decreased compared with that in group-housed animals no other significant changes were found in the steroidogenic machinery (peripheral benzodiazepine receptors, steroidogenic regulatory protein (StAR)). However, the functional response of the hypothalamic-pituitary-adrenal axis HPA axis to an acute stressful stimulus (foot shock), or to an acute injection of ethanol or isoniazid is markedly increased in isolated rats. Behavioral studies have also indicated that the ability of ethanol to inhibit isoniazid-induced convulsions is greater in isolated rats than in group-housed animals and this effect of isolation is prevented by treatment with the 5α-reductase inhibitor finasteride. Social isolation modified the effects of ethanol on the amounts of StAR mRNA and protein in the brain suggesting an alteration in the mechanism of cholesterol transport in mithocondria. Moreover, the amounts of the α_4 and δ subunits of the $GABA_A$ receptor in the hippocampus were increased in isolated rats, and these effects were accompanied by an increase in $GABA_A$ receptor-mediated tonic inhibitory currents in granule cells of the dentate gyrus. Ethanol also increased the amplitude of $GABA_A$ receptor-mediated miniature inhibitory postsynaptic currents (mIPSC) recorded from CA1 pyramidal neurons with a greater potency in hippocampal slices prepared from socially isolated rats than in those from group-housed, an effect inhibited by finasteride.

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1. Introduction

Early life experiences are thought to have a profound impact on the development and maturation of the central nervous system. Rats deprived of social contact with other rats at a young age experience a form of prolonged stress that leads to long-lasting alterations in their behavioral profile (Einon and Morgan, 1977; Hall et al., 1998). Isolated rodents are aggressive, neophobic, and highly reactive to human handling. They display aggressive behavior-in particular, biting and boxing—when transferred to groups of animals (Wongwitdecha and Marsden, 1996), and they manifest increased exploratory and locomotor activity in response to novel situations (Hilakivi et al., 1989; Varty et al., 2000). Furthermore, in the elevated plus-maze test, light—dark test, and exploratory head-dipping test, social isolation is associated with high levels of fearlike behavior (Parker and Morinan, 1986; Hilakivi et al., 1989; Voikar et al., 2005). Social isolation markedly increases the hyponeophagic response of rats and reduces the punished consumption of water in the Vogel conflict test (Parker and Morinan, 1986; Serra et al., 2000). Social isolation is thus thought to be stressful for these normally gregarious animals, and their abnormal reactivity to environmental stimuli when reared under this condition is thought to be a product of prolonged stress. Although the underlying mechanisms remain poorly understood, similar social conditions are thought to contribute to the etiology of psychiatric disorders such as schizophrenia, depression, and anxiety in humans (Heim and Nemeroff, 2001).

2. Social isolation and neuroactive steroids

Several lines of evidence support the notion that neuroactive steroids are of major importance for the maintenance of plasticity and homeostasis in the central nervous system, and that dysregulation of the synthesis and secretion of these endogenous compounds is a determinant of some affective disorders (Biggio and Purdy, 2001; Smith, 2004). Indeed, progesterone metabolites such as 3α-hydroxy-5α-pregnan-20-one (allopregnanolone, or 3α,5α-TH PROG) and 3α,5α-tetrahydrodeoxycorticosterone (3α,5α-TH DOC) are among the most potent positive allosteric modulators of the function of type A receptors for-aminobutyric acid (GABA) (Majewska et al., 1986), and their administration in pharmacological doses elicits anxiolytic, anticonvulsant, and sedative-hypnotic effects in rodents (Majewska, 1992). We have shown that social isolation of rats for 30 days immediately after weaning, in the absence of any additional stressor, induced marked reductions in the basal cerebrocortical and plasma concentrations of progesterone (25% and 61%, respectively), 3α,5α-TH PROG (42% and 34%, respectively), and 3α,5α-TH DOC (39% and 37%, respectively), compared with the corresponding values for group-housed animals (Serra et al., 2000). In mice, social isolation also reduced the brain content of 3α,5α-TH PROG and its precursor 3α-dihydroprogesterone (3α-DHP) but did not affect that of progesterone or pregnenolone (Matsumoto et al., 1999; Dong et al., 2001). The effects of social isolation on the activity or expression of enzymes involved in the synthesis of certain neuroactive steroids may thus be species specific. The molecular mechanisms that underlie the persistent decrease in the abundance of neuroactive steroids induced by social isolation in rats remain unclear.

Given that adrenal steroidogenesis plays an important role in maintaining the concentrations of neuroactive steroids in both plasma and the brain, as revealed by the observation that adrenalectomy results in a marked reduction in these concentrations (Purdy et al., 1991; Barbaccia et al., 1997), a reduced activity of the hypothalamic-pituitary-adrenal (HPA) axis may be responsible for the down-regulation of these steroids apparent in isolated animals. Changes in the activity of the HPA axis accompany various types of chronic stress, including isolation rearing. However, the effects of social isolation on the HPA axis are not consistent among studies, with differences in the duration of isolation or in animal age at its onset possibly accounting for the increase (Gamallo et al., 1986), no change (Holson et al., 1991), or decrease (Mar Sánchez et al., 1998) in axis function described in these studies.

We found that the basal plasma concentration of adrenocorticotropic hormone (ACTH) in isolated rats (1023 ± 148 pg/ml, mean ± SE) was decreased compared with that in group-housed animals (1495 ± 210 pg/ml) (Serra et al., 2000). However, this relatively small difference in the plasma concentration of ACTH, although significant ($P < 0.05$), is likely not entirely responsible for the decrease in the cerebrocortical and plasma concentrations of progesterone, 3α,5α-TH PROG, and 3α,5α-TH DOC induced by social isolation.

The biosynthesis of steroids begins with the conversion of the precursor cholesterol to pregnenolone, the rate-limiting step of which is the transport of cholesterol from cellular stores across the intramembrane space of mitochondria to the inner mitochondrial membrane. Steroidogenic acute regulatory protein (StAR) and the peripheral-type benzodiazepine receptor (PBR) function in a coordinated manner to mediate this transport of cholesterol (Krueger and Papadopoulos, 1990; Stocco, 2000; Casellas et al., 2002; Hauet et al., 2005). The 37-kDa precursor form of StAR is produced in the cytoplasm and is converted to a 32-kDa form during its incorporation into the inner mitochondrial membrane (Lin et al., 1995). We have found that the amounts of both StAR mRNA and the two forms of the protein (37 and 32 kDa) in the cerebral cortex or hippocampus did not differ between isolated and group-housed rats under basal conditions (data not shown), suggesting that changes in the expression of StAR are not responsible for the reduction in the basal levels of neuroactive steroids observed after social isolation. Kinetic analysis of the binding of the specific PBR ligand [^{3}H]PK 11195 to membranes prepared from the cerebral cortex, adrenal gland, or testis of rats revealed that social isolation induced an increase in receptor density (B_{max}) in each tissue (cerebral cortex, +16%; adrenal gland, +30%; testis, +24%), although these effects did not achieve statistical significance and binding affinity (K_d) was unaffected (Serra et al., 2004). These results suggested that this small increase in the number of PBRs in the brain and peripheral organs of isolated rats may reflect a coping mechanism to counteract the protracted decrease in the levels of neuroactive steroids induced by social isolation. Consistent with this notion, during pregnancy, a condition in which the plasma and brain concentrations of neuroactive steroids are greatly increased