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BRAIN RESEARCH REVIEWS

Review

Changes in neuroactive steroid content during social isolation stress modulate $GABA_A$ receptor plasticity and function

Mariangela Serra[a,b,*], *Maria Giuseppina Pisu*[b], *Maria Cristina Mostallino*[b], *Enrico Sanna*[a], *Giovanni Biggio*[a,b]

[a]*Department of Experimental Biology, Center of Excellence for the Neurobiology of Dependence, University of Cagliari, Cagliari, Italy*
[b]*C.N.R. Institute of Neuroscience, Italy*

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ABSTRACT

Rats deprived of social contact with other rats at a young age experience a form of prolonged stress that leads to long-lasting alteration in their behavior profile. This chronic stress paradigm is thus thought to be anxiogenic 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. Neurochemical, molecular, and electrophysiological evidences demonstrate that social isolation is associated with alteration in the structure and function of $GABA_A$ receptors and suggest that endogenous content of the progesterone metabolite 3α,5α-TH PROG may be an important determinant in regulating brain excitability and sensitivity to stimuli and point out its possible role in psychiatric and neurological disorder.

Contents

* *Corresponding author*. Department of Experimental Biology, Chair of Pharmacology, University of Cagliari, Cagliari 09100, Italy. Fax: +39 070 675 4166.
E-mail address: mserra@unica.it (M. Serra).

Abbreviations: ACTH, adrenocorticotropic hormone; CRF, corticotropin-releasing factor; GABA, γ-aminobutyric acid; GHB, γ-hydroxybutyrate; HPA, hypothalamic–pituitary–adrenal; IPSC, inhibitory postsynaptic current; mIPSC, miniature IPSC; PBR, peripheral benzodiazepine receptor; StAR, steroidogenic acute regulatory protein; 3α,5α-TH DOC, 3α,21-dihydroxy-5α-pregnane-20-one; 3α,5α-TH PROG, 3α-hydroxy-5α-pregnane-20-one

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1. Introduction

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 γ-aminobutyric acid (GABA) (Majewska et al., 1989), and their administration in pharmacological doses elicits anxiolytic, anticonvulsant, and sedative-hypnotic effects in rodents (Majewska, 1992). $GABA_A$ receptors are heteromeric complexes formed by the assembly of five subunits that belong to various subunit classes (α_1 to α_6, β_1 to β_4, γ_1 to γ_3, δ, ε, π, θ, ρ_1 to ρ_3) (Barnard et al., 1998; Whiting et al., 1999; Kumar et al., 2002). Brain region-specific distribution and ontogeny-dependent expression of $GABA_A$ receptor subunit isoforms are responsible for the generation of a relatively large number of $GABA_A$ receptor subtypes, which differ not only in their subunit composition but also in their physiological and pharmacological properties (Kumar et al., 2002; Sieghart, 1995; Whiting et al., 1999).

Many studies have established that physiological and pharmacological fluctuations in the synaptic concentration of 3α,5α-TH PROG can affect expression of $GABA_A$ receptor subunit genes, and might therefore contribute to regulation of $GABA_A$ receptor-mediated synaptic activity (Concas et al., 1998; Biggio et al., 2000, 2001; Cagetti et al., 2003; Mostallino et al., 2006; Biggio et al., 2006; Maguire and Mody, 2007). Thus, emotional states associated to conditions such as stress, pregnancy, the menstrual cycle (Barbaccia et al., 1996a,b; Concas et al., 1998), as well as to pathological conditions such as major depression, premenstrual syndrome, panic disorder, anxiety, and mood disorders (Rapkin et al., 1997; Romeo et al., 1998, Uzunova et al., 1998; Strohle et al., 2003; Pisu and Serra, 2004) are modified by drugs that activate $GABA_A$ receptors or increase the brain content of neurosteroids.

In this chapter, we have reported some of the most recent data obtained using a rodent model of mild chronic stress, the socially isolated rat, showing that chronic stress, by altering brain content of neuroactive steroids, may modify $GABA_A$ receptor plasticity and function in specific brain areas and the subsequent responses to stress and ethanol.

2. Socially isolated rats

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 when transferred to groups of animals (Wongwitdecha and Marsden, 1996), and more responsive to novelty relative to rats housed socially (Hall et al., 1998; Hilakivi et al., 1989; Varty et al., 2000), as indexed by increased locomotors activity (Einon and Morgan, 1977; Gentsch et al., 1982) and enhanced preference for novel environments (Sahakian and Robbins, 1977). Furthermore, in the light–dark test, elevated plus-maze test, and exploratory head-dipping test, social isolation is associated with high levels of fear-like behavior (Parker and Morinan, 1986; Hilakivi et al., 1989; Voikar et al., 2005). Social isolation also 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.

2.1. *Neuroactive steroids*

Mild chronic stress due to 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). 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 HPA axis may be responsible for the down-regulation of these steroids apparent in isolated animals. Changes in the activity of the HPA axis are associated with various types of chronic stress, including isolation rearing. However, the effects of social isolation on the HPA axis in rats 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 HPA axis function described in these studies. We found that the basal plasma concentration of ACTH in isolated rats (1023±148 pg/ml, mean±SEM) was decreased compared with that in group-housed animals (1495±210 pg/ml) (Serra et al., 2005). A decrease in the plasma level of ACTH, despite the continuous presence of the stressor, has also been described for animals exposed to various chronic stressful stimuli, and several mechanisms for this effect, in addition to a reduction in pituitary responsiveness to modulators of ACTH secretion (CRF, arginine vasopressin), have been proposed (Keller-Wood and Dallman, 1984; Rivier and Vale, 1987; Hauger et al., 1990). Rivier and Vale (1987)