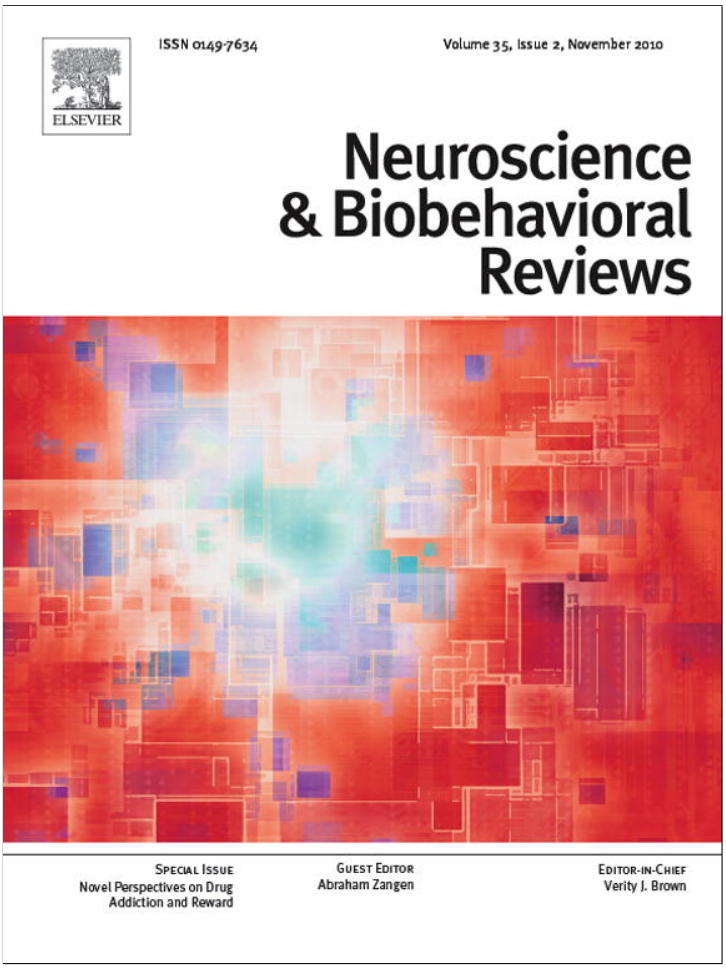

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Review

The role of dehydroepiandrosterone (DHEA) in drug-seeking behavior

Gal Yadid[a,*], Einav Sudai[a], Rachel Maayan[b], Iris Gispan[a], Abraham Weizman[b,c]

[a] The Mina & Everard Goodman Faculty of Life Sciences, The Leslie Susan Gonda (Goldschmied) Multidisciplinary Brain Research Center, Bar-Ilan University, Ramat Gan, Israel
[b] Felsenstein Medical Research Center, Rabin Medical Center, Beilinson Campus and the Sackler Faculty of Medicine, Tel Aviv University, Israel
[c] Geha Mental Health Center, Petah Tikva, Israel

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ABSTRACT

Conventional substance-abuse treatments have only had limited success especially for drugs such as cocaine, methamphetamine and nicotine. Newer data have begun to shed light on the complexity of the addictive process and new treatment approaches, including interference with brain neurosteroids, to attenuate drug-seeking behavior, are in advanced stages of development. Neurosteroids are synthesized in the brain and peripheral tissues, from cholesterol or steroidal precursors imported from peripheral sources. The most abundant neurosteroids in the human body are DHEA and its sulfate ester, DHEAS. These neurosteroids can act as modulators of neurotransmitter receptors, such as γ-aminobutyric-acid-type A ($GABA_A$), NMDA, and sigma-1 receptors which may contribute to apparent enduring behavioral manifestations facilitated by substances of abuse. Neurosteroid concentrations respond to environmental and behavioral circumstances, such as stress and mood, both which are involved in the progression of substance use that advance substance addiction.

This article reviews the current literature pertaining to neurosteroids and substances of abuse, focusing on DHEA, and discusses its role in drug-seeking behavior as suggested by preclinical observations.

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* Corresponding author. Tel.: +972 3 531 8123; fax: +972 3 635 4965.
E-mail address: yadidg@mail.biu.ac.il (G. Yadid).

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1. Introduction

Drug addiction is characterized by long-lasting motivational disturbances such as compulsive drug seeking and episodes of intense drug craving. The neurobiological mechanisms that underlie the persistence of such behavior remain poorly understood.

Effects of steroid hormones on the nervous system are not limited to transcriptional regulation through interaction with nuclear receptors. Rapid, nongenomic and stereospecific steroid actions are also transmitted via specific membrane receptors, such as γ-aminobutyric-acid-type A ($GABA_A$), ionotrophic glutamate, and sigma receptors. This type of rapid neuronal regulation is due to both the action of gonadal steroids on the brain and synthesis of neurosteroids within the nervous system (Falkenstein et al., 2000; Jung-Testas et al., 1989), which are synthesized from cholesterol.

Lingering neuroendocrine perturbations were suggested to persist after discontinuation of drug usage use in addicts. DHEA and its sulfate ester, DHEAS, represent the most abundant steroid hormones in the body. In humans, levels of DHEA and DHEAS were shown to be altered during addiction to substances of abuse (Buydens-Branchey et al., 2002). Also, significantly lower levels of DHEAS were observed in abusers that relapsed (Shoptaw et al., 2004; Wilkins et al., 1996). A connection between levels of DHEAS and profile of mood states suggests that increased circulating DHEAS levels may provide enhanced CNS resiliency during withdrawal by lowering distressed mood levels (Maayan et al., 2008; Wilkins et al., 2005). The effects of DHEA on cocaine intake and reinstatement in controlled experimental studies using the animal models of addiction also confirmed the clinical observations (Doron et al., 2006a).

This article reviewed the current literature pertaining to neurosteroids and substance of abuse, focusing on DHEA, and discussed its possible role in attenuating drug-seeking behavior.

2. The complexity of the drug-addiction process

Drug addiction is a chronic brain disorder, characterized by loss of control over drug consumption (Leshner, 1997; O'Brien, 1998). It is generally believed that abuse of drugs activates the reward neuronal circuitry in the brain. It seems that addiction is initially a dopamine (DA)-dependent disorder, in which the positive reinforcing value of the drug and its reward is mediated through the activation of the mesolimbic DA system (Di Chiara, 1999). This system comprises DA neurons with cell bodies in the ventral tegmental area (VTA) of the midbrain and projection areas of these neurons in the limbic forebrain and in particular the nucleus accumbens (NAC). This VTA-NAC circuit is a key detector of the reward stimulus; drug-induced changes in these regions may modulate the sensitivity to the reward of drug exposure (for review see Self, 2004). In addition, other relevant brain regions were studied: the hippocampus which is crucial for the memory of the context of drug exposure and withdrawal. The hypothalamus is important in mediating effects of drugs on the body's physiological state. Also essential are the frontal regions of the cerebral cortex, often severely deregulated in addicts, which provide executive control over drug use. Neurons in the striatum (St) play a role in the expectation and detection of reward. All these regions do not function separately, but are part of a complex and highly integrated circuit network that is profoundly altered as a result of chronic exposure to drugs (Chao and Nestler, 2004; Martin-Soelch et al., 2001; Nestler and Malenka, 2004). All addictive drugs facilitate dopamine transmission. Therefore, determining the role of dopamine has been the predominant focus of research in addiction for about two decades.

2.1. The contribution of the glutamatergic system to drug addiction

Newer data have begun to shift our focus to the involvement of the glutamatergic system (Kalivas, 2004). Glutamate influences the level of DA in the NAC, while fluctuation of DA levels brings about the euphoria of the initial drug use and contributes to other aspects of substance abuse and addiction. Sutton et al. (2003) and Baker et al. (2003) reported that self-administration of cocaine causes a marked increase in glutamate concentration in the extracellular fluid in rat NAC that decreased after forced abstinence; restoration of glutamate level inhibits the recurrence of drug-seeking behavior. Antagonizing AMPA/kainate receptors in the anterior VTA blocked the rewarding effects of opiates (Shabat-Simon et al., 2008). Glutamate receptor 2 (GluR2) endocytosis results in synaptic depression in ventral medial prefrontal cortex (mPFC) that seems crucial for cue-induced relapse to heroin-seeking (Van den Oever et al., 2008).

Similar glutamatergic neuroadaptations arise after self-administration of cocaine, heroin, nicotine, and alcohol. For example, reinstatement to cocaine, nicotine, and alcohol can be prevented both by the stimulation of group II metabotropic glutamate receptors (mGluR II) and by the blockade of group I mGluR receptors (Conrad et al., 2008; Knackstedt and Kalivas, 2009; Self and Choi, 2004; Van den Oever et al., 2008). A failure of the prefrontal cortex to control drug-seeking behavior was postulated to be linked to an enduring imbalance between synaptic and extra-synaptic glutamate, and that was termed glutamate homeostasis (Kalivas, 2009).

2.2. Sigma-1 receptors and addiction

In addition to the involvement of glutamate, the importance of the σ1 receptor (σ1R) in the neurobiology processes underlying drug abuse and addiction has been highlighted. The σ1R is an intracellular protein present on the endoplasmic reticulum membrane that can be translocated after activation (Maurice, 2004; Maurice and Romieu, 2004), resulting in calcium mobilization and modulation of several neurotransmitter responses. Its activity is involved in DA release in the limbic regions, known to be implicated in the brain plasticity following drugs seeking behavior. It has been suggested that σ1R is a signal transduction activator (Hayashi and Su, 2003; Su and Hayashi, 2003) that facilitates DA neurotransmission. Repetitive treatment with cocaine during conditioning increases σ1R mRNA expression in the NAC, but not in the striatum, PFC or cerebellum. σ1R is involved in the acquisition of cocaine-induced reward properties (Romieu et al., 2003, 2006). Activation of this receptor is a key event in the relapse to drug seeking and is also involved in several aspects of cocaine addiction (Maurice et al., 2002). Dextro-morphine attenuated the morphine-produced conditioned place preference via the σ1R receptor activation (Wu et al., 2007). Some data suggest that σ1R receptors are involved in the acute actions of methamphetamine and that antagonism of these receptors is sufficient to prevent the locomotor stimulatory effects of methamphetamine (Nguyen et al., 2005), but not methamphetamine-induced stereotypical behavior, although a shift from stereotypical biting to stereotypical sniffing was reported (Kitanaka et al., 2009). However, it was postulated that σ1R gene is unlikely to play a major role in substance abuse liability and/or the development of methamphetamine psychosis, since no significant differences were observed in its gene polymorphism between healthy controls and methamphetamine abusers/psychosis (Inada et al., 2004).

2.3. GABAergic system and addiction

Few studies described the gamma-aminobutyric (GABA)-ergic function in alcohol and nicotine dependence (Enoch, 2008; Filip

and Frankowska, 2008; Franklin et al., 2009; Koob, 2004; Leggio et al., 2008). A recent study suggested alterations in the GABAergic system after exposure to different compounds associated with drug-seeking behavior. A single infusion of BDNF into the VTA promoted a shift from a dopamine-independent to a dopamine-dependent opiate reward system; identical to that seen when an opiate-naïve rat becomes dependent and withdrawn. This shift involved a switch in the gamma-aminobutyric acid type A (GABA-A) receptors of VTA GABAergic neurons, from inhibitory to excitatory signaling (Vargas-Perez et al., 2009).

An interaction between few systems in relation to chronic exposure to substances of abuse is likely to occur. For example, the metabotropic glutamate receptor 7 (mGluR7) modulates the rewarding effects of cocaine in rats, which involves ventral pallidal GABAergic mechanism (Li et al., 2009). Differently, modulation of N-methyl-D-aspartate receptor (NMDA-R) function (Rao et al., 1991; Wang et al., 2007; Zheng, 2009) or DA receptors (Ben Ami et al., 2006; Lee et al., 2008) is possible through actions on σ1R.

2.4. Structural adaptations and addiction

The transition from stable to escalated substance use, a hallmark of addiction, is associated with synaptic reorganization in specific regions of the brain (Ferrario et al., 2005). Exposure to amphetamine, cocaine, nicotine or morphine produces persistent changes in the structure of dendrites and dendritic spines on cells in brain regions involved in incentive motivation and reward (such as the NAC), and decision-making and the inhibitory control of behavior (such as the prefrontal cortex). It was suggested that this structural plasticity reflects the persistent behavior associated with drug use (Robinson and Kolb, 1999, 2004).

Accrued experimental evidence shows that addictive substances (non-contingent or contingent drug administration), such as alcohol (Herrera et al., 2003), opiates (Eisch et al., 2000; Eisch and Harburg, 2006), amphetamines (Teuchert-Noodt et al., 2000) and cocaine (Dominguez-Escriba et al., 2006; Noonan et al., 2008; Yamaguchi et al., 2004, 2005) can negatively affect the self-renewal capacity of the hippocampus by diminishing the rate of proliferation of neural progenitors or by impairing the long-term survival of neural precursors, or both. Nonetheless, a number of studies have demonstrated no alteration in the rate of survival of neural progenitor cells in the DG (Dominguez-Escriba et al., 2006; Noonan et al., 2008).

The sub-granular zone (SGZ) of the hippocampal dentate gyrus (DG) and the subventricular zone (SVZ) of the lateral ventricle are the two known neurogenic sites of the adult brain. In the hippocampus, contingents of newly generated cells born in the SGZ of the DG travel short distances to become incorporated as granular neurons in a dynamic process that continues throughout life (Alvarez-Buylla and Lim, 2004; Kempermann et al., 2004). Since the hippocampus is critical to the process of forming and recovering certain types of memory (Squire et al., 2004), the integrity of the neurogenesis process may be required for the acquisition and consolidation of memories (Cao et al., 2004; Crandall et al., 2004; Shors et al., 2001). Some suggested that neurogenesis in the hippocampus has the potential to positively influence working memory (Lee and Kesner, 2003; Winocur et al., 2006), others argue that it might not fulfill a unitary function in memory and may have opposite roles in distinct types of memory (Saxe et al., 2007). Impairment of learning and memory process and transition from initial goal-directed behavior to pathological stimulus-response habits was suggested in maintenance of drug abuse (Hyman et al., 2006; Robbins et al., 2008; von der Goltz and Kiefer, 2009). There remains, however, considerable controversy over the functional significance of these new cells in relation to substances of abuse, since Del Olmo et al. (2006) demonstrated that cocaine self-administration affects LTP (long-term potentiating) but did not notably affect performance in the Morris water maze test. In contrast to these findings, in a different study, they showed an improvement in performance in a difficult Morris water maze task after cocaine self-administration (Del Olmo et al., 2007). Therefore, the function of neurogenesis in the process of addiction remains elusive.

3. The neurosteroids DHEA and DHEAS

3.1. Synthesis and biotransformation

Neuroactive steroids (neurosteroids) are synthesized in the adrenal glands, ovary, testis and in the brain (Panzica and Melcangi, 2008). DHEA and its sulfate ester, DHEAS, represent the most abundant steroid hormones in the human body, although their secretion changes across the lifespan (Azuma et al., 1993; Havelock et al., 2004; Mesiano and Jaffe, 1997; Michael et al., 2000; Regelson and Kalimi, 1994; Tannenbaum et al., 2004). Dehydroepiandrosterone, 5-androsten-3-beta-ol-17-one, is a 19 carbon steroid that is synthesized from cholesterol by two steroid metabolizing enzymes. The first, rate-limiting, and hormonally regulated step in the synthesis of all steroid hormones is the conversion of cholesterol into pregnenolone by the mitochondrial enzyme cholesterol side chain cleavage P450scc. Pregnenolone is converted into DHEA by the enzyme cytochrome P450c17; this single enzyme catalyzes both the 17-α-hydroxylation reaction converting pregnenolone to 17-OH-pregnenolone and the 17,20-lyase reaction converting 17-OH pregnenolone to DHEA (Auchus, 2004; Miller, 2002) (Fig. 1). The sulfation of DHEA into its more stable sulfate ester DHEAS is catalyzed by the enzyme hydroxysteroid sulfotransferase, commonly known as DHEA sulfotransferase. DHEAS can be converted back into DHEA by steroid sulfatase. Steroid hormones affect gene transcription by binding to specific cytoplasmic receptors, and then translocating into the nucleus, or binding to receptors that are resident in the nucleus, where they bind to steroid responsive elements on DNA. Some studies demonstrated that DHEA acts genomically through the androgen receptor in peripheral androgen-dependent tissues (Capitanio et al., 1991; Webb et al., 2006; Widstrom and Dillon, 2004). Neurogenomic effects of DHEA treatment were also identified on a subset of genes directly implicating the regulation of appetite, energy utilization, alertness, apoptosis, and cell survival, in two regions of the CNS that are enriched in AR, hypothalamus and hippocampus (Mo et al., 2009).

3.2. Effect on neurotransmitter' receptors

Neurosteroids penetrating the blood–brain barrier or synthesized *de novo* within the brain (Baulieu, 1998), display rapid, non-genomic modulatory effects on several neurotransmitter systems including glutamatergic, GABAergic and dopaminergic. Gamma aminobutyric acid type A receptor ($GABA_A$-R), glutamate receptors [both NMDA-R and non-NMDA receptors, such as a-amino-3-hydroxy-5-methyl-isoxazole-4-propionic acid (AMPA)] and σ1R are considered major components of the neuromodulatory activity of the neuroactive steroids (Dubrovsky, 2006; Gibbs et al., 2006; Romieu et al., 2006; Schumacher et al., 2003). The neurosteroids act stereoselectively as positive or negative modulators of the various ion-gated channel receptors. DHEA and its sulfate ester DHEAS are negative modulators of the $GABA_A$-R and positive modulators of both NMDA-R and σ1R (Baulieu, 1998; Dubrovsky, 2005). In non-hippocampal brain regions DHEA(S) may inhibit glutamate neurotransmission through σ1Rs, since σ1R agonists were shown to reduce NMDA-induced dopamine release in the striatum (Gonzalez-Alvear and Werling, 1994). In an electrophysiological study with Sprague–Dawley rats, intravenous (i.v.) administration of DHEA potentiated the NMDA neuronal response

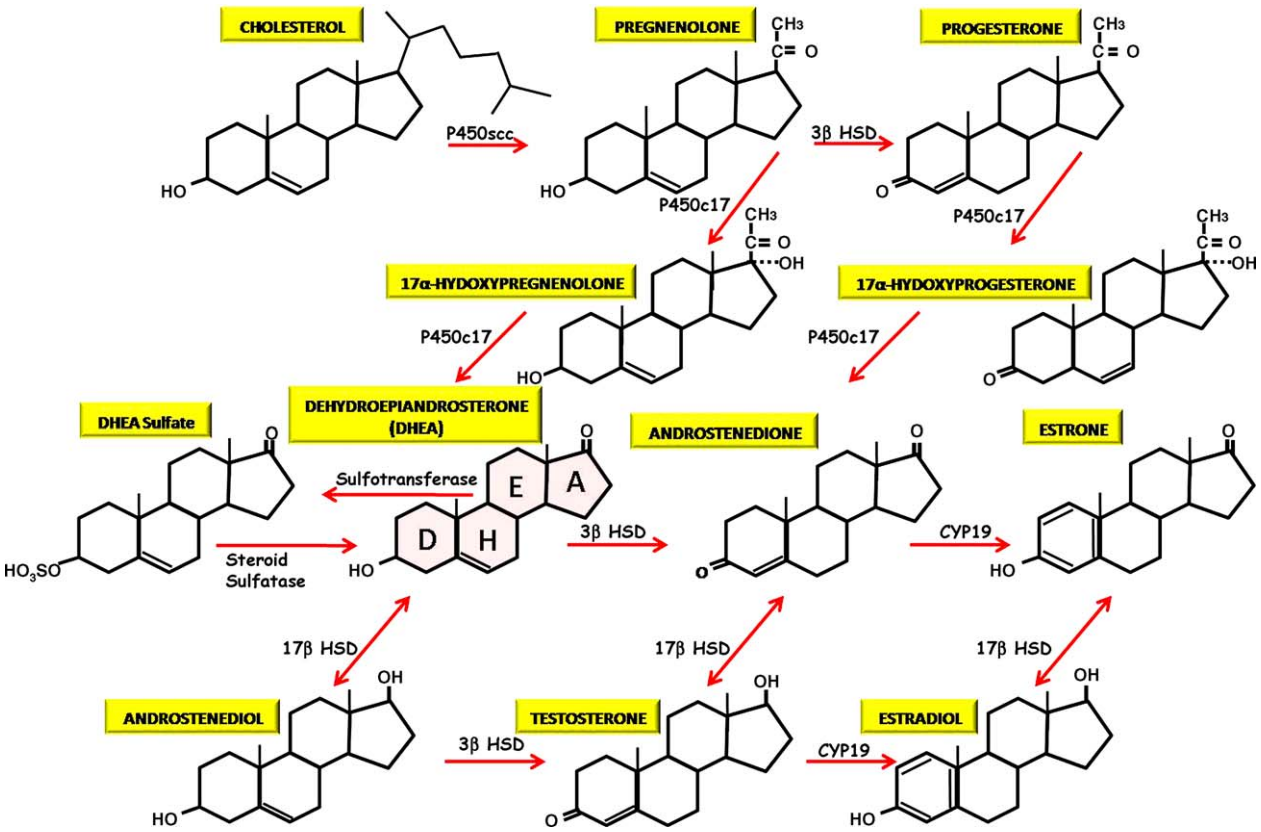

Fig. 1. Biosynthesis of dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), and other steroids.
P450scc = cytochrome P450 side chain cleavage; P450c17 = 17alpha-hydroxylase/17,20-lyase, 3β HSD = 3β-hydrosteroid dehydrogenase, HSS = hydrosteroid sulfatase, CYP19 = P450 aromatase

of CA3 rat hippocampal pyramidal neurons in a dose-dependent manner (Bergeron et al., 1996). This response was dose dependent that peaked at 500 μg/kg. The addition of the σ receptor antagonist haloperidol or σ1 receptor antagonist N-dipropyl-2-(4-methoxy-3-(2-phenylethoxy)phenyl)-ethylamine monohydrochloride (NE-100), inhibited the potentiating effect of DHEA, suggesting that DHEA can modulate the NMDA-R response through σ1 receptors (Bergeron et al., 1996). DHEAS potentiated the NMDA evoked release of norepinephrine from preloaded hippocampal slices, while the addition of σ receptor antagonists haloperidol or 1-[2-(3,4-dichlorophenyl)-ethyl]-4-methylpiperazine (BD1063) blocked the potentiating effect of DHEAS (Monnet et al., 1995). Thus, DHEA(S) can modulate NMDA receptor activity by acting at the σ1 receptor (that is coupled to Gi/o proteins) both *in vivo* and *in vitro* (Bergeron et al., 1996; Maurice et al., 2006; Monnet et al., 1995). DHEAS, but not DHEA, augments cholinergic function in several animal models (George et al., 2006).

3.3. Effect on catecholamine synthesis and secretion

DHEAS has been found to stimulate dopamine release from rat hypothalamic cells in primary cultures (Murray and Gillies, 1997). Some findings suggest that DHEA inhibited catecholamine secretion and cytosolic Ca^{2+} rise coupled with nicotinic acetylcholine receptor (nAChR), in chromaffin cells, without exerting an effect on nicotine binding (Liu and Wang, 2004). Another study compared the stimulatory effects of DHEA and DHEAS on catecholamine synthesis and suggests that neuroactive steroids exert a direct tonic effect on catecholamine synthesis and secretion in PC12 cells (Charalampopoulos et al., 2005). Both DHEA and DHEAS have been found to trigger release of catecholamines, but only DHEAS also increased tyrosine hydroxylase mRNA and protein levels (Charalampopoulos et al., 2005). The same study demonstrated that DHEA and DHEAS elicited their stimulatory effect by actin depolymerization and sub-membrane actin filament disassembly, a fast-response cellular system regulating trafficking of catecholamine vesicles.

In vivo, acute injection of high doses of DHEA (30–200 mg/kg i.p.) was demonstrated to affect brain monoamines. One study reported on reduced DA turnover and increased 5-HT turnover in the rat corpus striatum and nucleus accumbens (Perez-Neri et al., 2008). Another study demonstrated increased concentrations of DA, serotonin (5HT), and 5-hydroxyindoleacetic acid (5-HIAA), and decreased concentrations of norepinephrine (NE) and epinephrine in the paraventricular nucleus (Svec and Porter, 1997). DHEA treatment significantly decreased monoamine oxidase (MAO) activity, lipid peroxidation and lipofuscin accumulation in several brain regions of aging rats (Kumar et al., 2008). In an animal model of depression, DHEA level was found to be in correlation with monoamine content in limbic brain regions of adult but not prepubertal rats (Malkesman et al., 2008). However, only one study comprehensively tested the effect of chronic low dose DHEA (2 mg/kg) on brain monoamine content and turnover. It was found that 14 days treatment increased DA content in the VTA. At the same time 5HT content was increased in the NAC but decreased in the raphe nucleus. A decrease DA turnover was noticed in the prefrontal cortex, hippocampus, hypothalamus, and arcuate nucleolus. As well a decrease 5HT turnover in the raphe nucleus was reported (Maayan et al., 2006a).

3.4. Effect on cell viability and neurogenesis

DHEAS promoted survival of adult human cortical brain tissue *in vitro* (Brewer et al., 2001). In enriched neuronal cultures from three

adult participants, DHEAS was as effective as human recombinant fibroblast growth factor (FGF2) in promoting survival of neurofilament positive, neuron-like cells. DHEAS and FGF2 were synergistic in increasing cell survival (Brewer et al., 2001).

The administration of DHEA alone was neurotoxic to rat hippocampal cultures, but was neuroprotective against the toxic effects of corticosterone when co-administered with corticosterone (Kimonides et al., 1999). These studies suggest that DHEA neuroprotective/neurotoxic action depend on other bioactive physiological factors affected by stress.

In another study, DHEA increased neurogenesis in addition to neuronal survival in cultures of human neural stem cells derived from fetal cortex (Suzuki et al., 2004). Both epidermal growth factor and leukemia inhibitory factor were required to elicit the proliferative effect of DHEA. When other steroids were tested, neither DHEA's precursor, pregnenolone, nor DHEA's metabolites (7a-hydroxy-DHEA, 7b-hydroxy-DHEA, 7-oxo-DHEA, nor-androstenediol) had the same effect on neuronal proliferation as DHEA. The proliferative effects of DHEA could be blocked by the NMDA-R antagonist MK801 and the σ1 receptor antagonists BD1063 and haloperidol, whereas the $GABA_A$-R antagonist bicuculline had no effect (Suzuki et al., 2004). This suggests that DHEA's receptors, NMDA and σ1, are more important mediators than $GABA_A$ receptor in DHEA-related neurogenesis and neuronal survival. If neurogenesis has a role in substance abuse, it will be interesting to see the effect DHEA has on neurogenesis and drug-seeking behavior.

3.5. Effect on cell morphology

Additional intracellular sites where DHEA may act have also been described. DHEA may interact directly with certain cytoskeleton components or novel membrane receptors. DHEA was found to bind to microtubule-associated protein (MAP)-2C with strong affinity (Laurine et al., 2003). MAP-2C, protein is a cytoskeleton member that is detected mainly in dendrites. MAP-2 affects the shape, polarity and plasticity of neurons by controlling microtubule assembly (Johnson and Jope, 1992). Neonatal treatment with pregnenolone and DHEA increased the expression of MAP-2 in the hippocampus and nucleus accumbens in adulthood (Iwata et al., 2005). Some recent studies have demonstrated alterations in MAP2 staining in area 9 and 32 of schizophrenia patients' prefrontal cortex tissue (Broadbelt et al., 2006; Jones et al., 2002). Also, Pavlovian conditioning alters MAP-2 (Woolf et al., 1994). Hence, altered expression of MAP-2 in neuropsychiatric diseases is suggested to affect stability of dendrites and synaptic signal transduction.

4. DHEA/DHEAS and psychiatric conditions

Co-morbidity of drug addiction with stress-related psychiatric conditions were widely documented (Gonzalez-Saiz et al., 2009; Haber et al., 2009; Schulden et al., 2009). The possible connection of DHEA/DHEAS with psychiatric psychopathology was hoisted by two lines of evidence. Studies have suggested a relationship between serum levels of DHEA(S) and depression, anxiety spectrum disorders, post-traumatic stress disorder (PTSD), schizophrenia, and dementia as well as mood, memory, and functional abilities in healthy aging individuals (for review see Schumacher et al., 2003; Strous et al., 2006). As well, several studies have examined the possibility of exogenous DHEA supplementation to have beneficial effects on psychiatric states, although the most of them were small-scale and short-term studies, so definitive conclusions are lacking (Strauss and Stevenson, 1955). These studies will be scrutinized herein.

Findings of elevated DHEA and/or DHEAS levels in psychiatric illness have been noted in some psychiatric conditions associated with high stress levels. These include individuals with PTSD (Sondergaard et al., 2002; Spivak et al., 2000), psychotic depression (Maayan et al., 2000) and ADHD (Strous et al., 2001), as well as anorexia and bulimia (Ebraheim et al., 1992; Monteleone et al., 2001). These elevated DHEA/DHEAS levels were mostly related to the stress associated with these psychiatric conditions (Oberbeck et al., 1998; Sondergaard et al., 2002; Strous et al., 2009). High DHEA levels were identified also in first-hospitalized adolescent subjects with schizophrenia (Strous et al., 2009), but were lower in smoking chronic schizophrenia patients (Iancu et al., 2007). Others reported on elevated cortisol/DHEA and/or cortisol/DHEAS ratios in schizophrenia patients that were positively associated with higher scores for anxiety and anger, depression and hostility, age and age of onset/duration of illness, but were independent of severity of psychopathology and antipsychotic treatment (Ritsner et al., 2004). DHEAS levels appear to be low in patients with autistic disorder and, while speculative, may play a role in the etiopathophysiology of the disorder (Strous et al., 2005). Higher blood levels of DHEA and DHEAS were associated with fewer ADHD symptoms, in particular hyperactivity (Strous et al., 2001). These findings suggest a possible protective effect of these neurosteroids on the expression of some psychiatric symptomatology. Indeed, administering DHEA to patients with schizophrenia who had moderate to severe negative symptoms and who were maintained on antipsychotic medications induced significant improvement, more so in women and corresponding to increased plasma levels of DHEA and DHEAS (Strous, 2005). Another double-blind study reported the efficacy of DHEA augmentation in the management of negative, depressive, and anxiety symptoms of schizophrenia (Strous et al., 2003). Moreover, first studies investigating the therapeutical effects of DHEA revealed promising results in the treatment of major depression (Eser et al., 2006; Ferrando and Freyberg, 2008; Maninger et al., 2009).

5. DHEA and DHEAS and substances of abuse

5.1. Studies in animal models

5.1.1. Neurosteroids and drug-seeking behaviors-general

The modulation of DA, σ1, glutamate and/or $GABA_A$ receptor activities, may be relevant to drug abuse. Previous studies indicate an involvement of neurosteroids in alcohol addiction.

Neurosteroids have an important part in the reward and consumption of alcohol. Withdrawal from alcohol leads to changes in the GABA-AR which increases the sensitivity to the pharmacological effect of neurosteroids (Morrow et al., 2001). High levels of DHEA/DHEAS might serve as a protective mechanism from depression during alcohol withdrawal (Heinz et al., 1999). Some data suggest that the discriminative stimulus effects of lower doses of ethanol are mediated to a greater extent by pregnanolone (PREG) and 3alpha-hydroxy-5-androstan-17-one (androsterone) compared with higher doses (2.0 g/kg) (Grant et al., 2008). DHEAS levels may predict nicotine dependence severity since its levels were inversely correlated with negative affect and craving measures. Allopregnanolone levels were positively correlated with cotinine levels, suggesting that this neuroactive steroid may be upregulated in smokers (Marx et al., 2006).

Moreover, it was found that a prolonged treatment (rather than acute) with neurosteroids such as PREG, PREG-sulfate (PREG-S) and DHEAS prevents the development of tolerance to morphine (Reddy and Kulkarni, 1997a; Ren et al., 2004). Another study has shown that PREG-S elevates the levels of dopamine in the nucleus accumbens and increases the dopaminergic reaction to morphine injection (Barrot et al., 1999).

Studies using animal models demonstrated that the allopregnanolone and ganaxolone steroids attenuate the pro-convulsant and sensitizing properties of cocaine (Kaminski et al., 2003). Other

studies claim that the neuroactive steroids ganaxolone (3alpha-hydroxy-3beta-methyl-5alpha-pregnan-20-one) and Co 2-1068 (3beta-(4acetyl-phenyl)ethynyl-3alpha,21-dihydroxy-5beta+++-20-one-21-hemisuccinate) attenuate cocaine-induced sucrose preference in rats, but not cocaine induced hyperactivity in mice (Vanover et al., 2000).

Two main animal models are used for studying addiction. The first model is conditioned place preference (CPP), in which substances injections are paired with sensorially distinguished compartments of an apparatus, so that the animal can associate drug induced changes it experiences with environmental cues provided by the apparatus (Aguilar et al., 2009; Mucha et al., 1982). Another animal model is self-administration where animals are trained to press a lever, thereby administering substances of abuse. Animals thus become substance-dependent, developing behavioral and neurological changes that simulate human addiction (for review see Haney, 2009; Panlilio and Goldberg, 2007).

5.1.2. Effect on acquisition of drug-seeking behaviors

One study investigated the influence of high levels of brain DHEA on the acquisition of cocaine self-administration in rats (Maayan et al., 2006a). DHEA pretreatment (continued thereafter concomitantly with cocaine self-administration) attenuated cocaine-seeking behavior and elevated the levels of dopamine and serotonin in several brain regions relevant to cocaine addiction. Chronic cocaine self-administration induced elevation in brain DHEA, its sulfate ester, DHEAS, and PREG. The increased brain DHEA following cocaine self-administration may serve as a compensatory protective mechanism geared to attenuate the craving for cocaine. Such anti-craving activity is further enhanced by DHEA treatment before and during cocaine self-administration (Maayan et al., 2006a).

It should be taken into account that there are several processes involved in drug-seeking behavior such as reward, stress short and long memory. DHEA may be involved in one or more of these phases by affecting different neural mechanisms such as the hypothalamic–pituitary–adrenal (HPA) axis, the activity of Glu-R (both NMDA and non-NMDA as AMPA/kainate), nicotinic receptor, σ1R in addition to the enhancement of DA release.

Cocaine simultaneously affects mood and the neuroendocrine hormones such as adrenocorticotropic hormone (ACTH) and corticosterone (CORT) (Levy et al., 1991; Mendelson et al., 2002; Moldow and Fischman, 1987; Saphier et al., 1993). Goeders (1997) claims that CORT is necessary during acquisition, and that self-administration does not occur unless this stress-related hormone is increased above the threshold critical for reward. Drugs blocking central corticotropin releasing hormone (CRH) receptors or decreasing ACTH and CORT can attenuate self-administration (Goeders, 1997, 2002a,c). In addition, other clinical and preclinical studies link stress to drug dependence as stress is accompanied by the release of neuroactive hormones which activate brain circuitries similar to psychostimulants such as cocaine (Majewska, 2002). Studies using several strains of rats showed that stress and elevated glucocorticoid increased acquisition and maintenance of psychostimulants use (Goeders, 1997; Piazza and Le Moal, 1998; Piazza et al., 1991). It was also reported that extrahypothalamic brain CRH systems may be involved in behavioral and physiological manifestations of drug-seeking behavior induced by environmental stressors (Sarnyai et al., 2001). DHEA treatment, with similar doses caused a decrease in both CORT and ACTH levels (Maayan et al., 2005, 2006a). Such a decrease, may explain, at least in part, the attenuation in cocaine-seeking behavior. However, new findings indicate that the CORT level is directly related to DHEA's attenuation of drug-seeking behavior (data not shown) and that other mechanisms may exist.

An additional mechanism to explain DHEA effect on drug-seeking behavior is the interrelationship of σ1R, DHEA and reward. Although originally it was thought that the sigma receptor was a subtype of the opioid receptor, it is now clear that both σ1R and σ2R are unique brain proteins. σ1R regulates glutamate NMDA-R function and the release of neurotransmitters such as DA, and thus may be involved in neuropsychiatric disorders and reward (Hayashi and Su, 2003, 2004; Su and Hayashi, 2003). σ1R is critically involved in the rewarding effect of cocaine as measured in the CPP procedure in mice (Romieu et al., 2003), and σ1R-agonists pretreatment facilitated cocaine self-administration (Hiranita et al., 2010). Sutton et al. (2003) found that rats repeatedly exposed to cocaine develop glutamate deficits in the NAC. DHEAS which promotes presynaptic glutamate release in the prelimbic cortex via activation of σ1R (Dong et al., 2007) may alleviate drug-seeking behavior. Alternatively, DHEA, which is a positive modulator of the NMDA-R (Dubrovsky, 2005; Mellon and Griffin, 2002a,b; Rupprecht and Holsboer, 1999) may attenuate this cocaine-induced effect by enhancing glutamate activity. A decrease in the brain extracellular glutamate was obtained during the extinction process and was suggested to contribute to the susceptibility to relapse (Baker et al., 2003). Glutamatergic activity was connected to decision-making and working memory processes (Finn, 2002). This rise, which was accompanied by the eradication of the cocaine "memory" during the extinction process (Geier and Luna, 2009; Koob, 2009; Peters et al., 2009; Wang, 2008) may explain the lack of memory gain during the acquisition phase if glutamate activity is increased by DHEA.

In addition, AMPA-R antagonists attenuate behavioral sensitization and self-administration in mice (Jackson et al., 1998; Reeves et al., 2004); PREG sulfate acts as an AMPA-R negative modulator (Dubrovsky, 2005). Therefore one may assume that DHEAS (partially converted from DHEA) acts similarly. This is supported by Kimonides et al. (1998), finding that DHEAS attenuates AMPA and kainate neurotoxicity in hippocampal neurons. It is possible that as an antagonist of the AMPA-R, DHEAS may also attenuate cocaine self-administration and contribute to the glutamate to the glutamate homeostasis suggested by Kalivas (2009). The rewarding effect of cocaine which promotes its reinforcement is mediated by the blockade of the presynaptic DA transporter, thus increasing DA activity in the mesolimbic or meso-cortical DA reward system. DHEA caused an increase in DA content and in the content of DA and 5-HT metabolites in the VTA and NAC following. It is possible that such an increase in DA may attenuate the need for cocaine intake and cocaine seeking-behavior (Maayan et al., 2006a).

In Maayan's study (2006a), rats initiated cocaine self-administration already with high basal levels of both peripheral and brain DHEA, due to the pre-treatment phase, thus it can be assumed that timing is a crucial factor in the anti-craving effect of DHEA which is achieved only by pretreatment followed by continuous concomitant treatment with DHEA. Our observation of cocaine craving is supported by Reddy and Kulkarni (1997a,b) who showed that DHEA treatment prevented the development of tolerance to benzodiazepines (BZ) in mice. In addition, DHEAS treatment prevents the development of morphine tolerance and attenuates abstinent behavior in mice (Reddy and Kulkarni, 1997a,b; Ren et al., 2004). Assuming that overlapped mechanisms are involved in brain response to different substances of abuse, these studies may support each other, since DHEA is converted partially to DHEAS both peripherally and in brain by sulfatransferase (Maayan et al., 2005, 2006a). The authors emphasize that control and DHEA-treated rats displayed similar levels of lever-pressing for water reinforcement during the maintenance phase of water self-administration, verifying that DHEA treatment specifically disrupted lever-pressing for cocaine reinforcement and not by impairment of physical performance.

As demonstrated in Fig. 2, rats showed no interest in pressing the active lever even when the dose of infused cocaine was nullified; supporting the assumption that DHEA has probably an anti-craving effect and not a potentiating one. One cannot exclude the possibility that DHEA on its own may be a substitute to cocaine though in CPP model no such effect has been found (Romieu et al., 2003). Consequently, this attenuation in cocaine-seeking behavior by DHEA may be explained either by causing an anti-craving effect (the rats show no interest in cocaine) or by potentiating the effect of cocaine (need for lower doses of cocaine in order to get the same reinforcement). However a descending phase of the dose response proved that DHEA treatment did not over-potentiated activation of lever presses when decreasing or withholding of cocaine infusion (Maayan et al., 2006a).

5.1.3. Effect on maintenance of drug-seeking behaviors

Recently it has been successfully shown that chronic exposure to exogenous DHEA (2 mg/kg) attenuated cocaine self-administration and decreased the cocaine-seeking behavior of the rats to <20% of their maintenance levels (Doron et al., 2006a).

No surge in active lever response accompanied initiation of DHEA treatment, which would have been expected if DHEA blocked the reward effect of cocaine. This result is interesting, since most difficulties of addicts to stay on an anti-drug program occur during the first weeks, when expectation for reward is highest (Self and Choi, 2004). Indeed, when higher doses of DHEA (10–20 mg/kg) were co-administered with cocaine for a short period of time (4 days), a markedly increased cocaine-induced CPP was reported (Romieu et al., 2003). Extinction of responding maintained by appetitive rewards has been suggested to induce multiple stress events including activation of the hypothalamus–pituitary–adrenal axis, glucocorticoid secretion, and central β-endorphin release (Shaham et al., 2003; Vescovi et al., 1992). Hence, it was previously suggested that alleviation of distress associated with cocaine withdrawal may facilitate achieving abstinence (Self and Choi, 2004; Wilkins et al., 2005). Furthermore, during withdrawal, cocaine addicts have high plasma cortisol levels, which peak 6 days after initiation of the withdrawal and then gradually decrease (Buydens-Branchey et al., 2002). As the levels of plasma cortisol decrease, the levels of DHEAS gradually increase. Only patients in which a spontaneous increase in DHEAS levels was observed were identified as being successful at abstaining from cocaine usage over time (Wilkins et al., 2005). Although a connection between DHEA/DHEAS, low distressed mood levels, and changes in CNS salience during withdrawal was suggested (Wilkins et al., 2005), it seems that appropriate DHEA dose is critical for relapse prevention (Shoptaw et al., 2004). The effect of exogenously applied DHEA (2 mg/kg) on cocaine-seeking behavior may be due to its conversion to DHEAS in the serum and brain (Maayan et al., 2005, 2006a), in addition to increases in other bioactive neurosteroids (Dubrovsky, 2005). These neurosteroids may interact with various neurosystems involved in mood and drug-seeking behaviors, such as glutamatergic, GABAergic, and dopaminergic systems. Since DHEA can function as an antidepressant in both animals and humans (Maayan et al., 2005, 2006a; Wolkowitz et al., 1997), it may lower the depression/distress involved with cocaine withdrawal (Self and Choi, 2004), similar to the β-endorphin-induced lowering of frustration during extinction (Roth-Deri et al., 2003, 2004). An additional possible mechanism for the DHEA-induced attenuation the maintenance of cocaine-seeking behavior suggests the involvement of σR. Based on data indicating that DHEA acts as an agonist of these receptors (Maurice et al., 1999), it is possible that long administration of cocaine downregulates σ1R and DHEA acts in a compensatory neuroadaptation mechanism that leads to attenuation of cocaine-seeking behavior (Ben Ami et al., 2006).

5.1.4. Effect on reinstatement to drug-seeking behaviors

Hardly any literature is found on neuroactive steroids and drug reinstatement. Nie and Janak (2003) trained rats were to lever-press for 0.1 ml of 10% ethanol or 5% sucrose solutions. Responding was then extinguished, and subjects were tested for reinstatement of lever-press responding. Allopregnanolone promoted responding for ethanol, but not sucrose, following a period of abstinence, suggesting that GABA-A receptor modulation may contribute to processes involved in reinstatement of ethanol-seeking behavior. Another study reported that progesterone, and to a greater extent allopregnanolone, decreased cocaine-primed reinstatement in females, while had no effect on cocaine-primed reinstatement in males (Anker et al., 2009). The effect of DHEA on cocaine-induced reinstatement of drug seeking in rats exposed to withdrawal conditions was also examined. Rats receiving DHEA (2 mg/kg) daily showed a minimal response to acute priming with cocaine. This may suggest that DHEA can protect against relapse to cocaine usage following re-exposure to the drug (Doron et al., 2006a). DHEA, which is a positive modulator of the NMDA-R (Dubrovsky, 2005; Mellon and Griffin, 2002a,b; Rupprecht and Holsboer, 1999) may attenuate this cocaine-induced effect by enhancing glutamate activity. A decrease in the brain extracellular glutamate was obtained during the extinction process and was suggested to contribute to the susceptibility to relapse (Baker et al., 2003). Glutamatergic activity was connected to decision-making and working memory processes (Finn, 2002) and DHEAS (partly converted from DHEA) facilitates LTP (Chen et al., 2006). Substance dependence is accompanied by usurpation of natural memory mechanisms resulting in long-lasting memories of the drug experience (Geier and Luna, 2009; Kauer and Malenka, 2007; Koob, 2009; Peters et al., 2009; Wang, 2008). Elevating endogenous glutamate or glutamate receptors reduces the propensity for relapse (Baker et al., 2003; Sutton et al., 2003). Therefore, the consequence of increasing glutamate activity may be eradication of memories associated with substance reward-related learning and gaining of new memories linked to drug extinction. If glutamate activity is increased by DHEA in the addicted brain, it may help drug extinction and attenuate relapse and may be in accordance with the glutamate homeostasis suggested by Kalivas et al. (2009).

In addition, Sutton et al. (2003) found that increasing GluR1 subunit of AMPA receptors in the NAC may promote extinction of cocaine seeking. AMPA-R antagonists attenuate behavioral sensitization and self-administration in mice (Jackson et al., 1998; Reeves et al., 2004). The neurosteroid sulfate, PREG-S, act as an AMPA-R negative modulator (Dubrovsky, 2005). Therefore one may assume that DHEA sulfate acts similarly. This may be supported by Kimonides et al. (1998), finding that DHEAS attenuates AMPA and kainate neurotoxicity in hippocampal neurons. However it is not likely that DHEAS act directly on the AMPA-R (Leskiewicz et al., 1998; Randall et al., 1995).

Nonetheless, it will be interesting to further examine the effect of DHEA treatment in other models of reinstatement such as cue and stress.

5.2. Clinical studies

In a research monograph written by Wilkins et al. at the end of the previous millennium (1996) the authors suggested that DHEAS plasma levels may discriminate between treatment outcomes in groups of cocaine addicts. They found that those who had high basal levels of DHEAS remained abstinent following treatment for cocaine dependence. Later, Buydens-Branchey et al. (2002), compared levels of cortisol and DHEA in cocaine addicts during abstinence. They demonstrated that levels of cortisol were highest on day 6 of abstinence and then subsequently decreased. DHEAS levels were low on day 6 and highest on day 18 of abstinence. Analy-

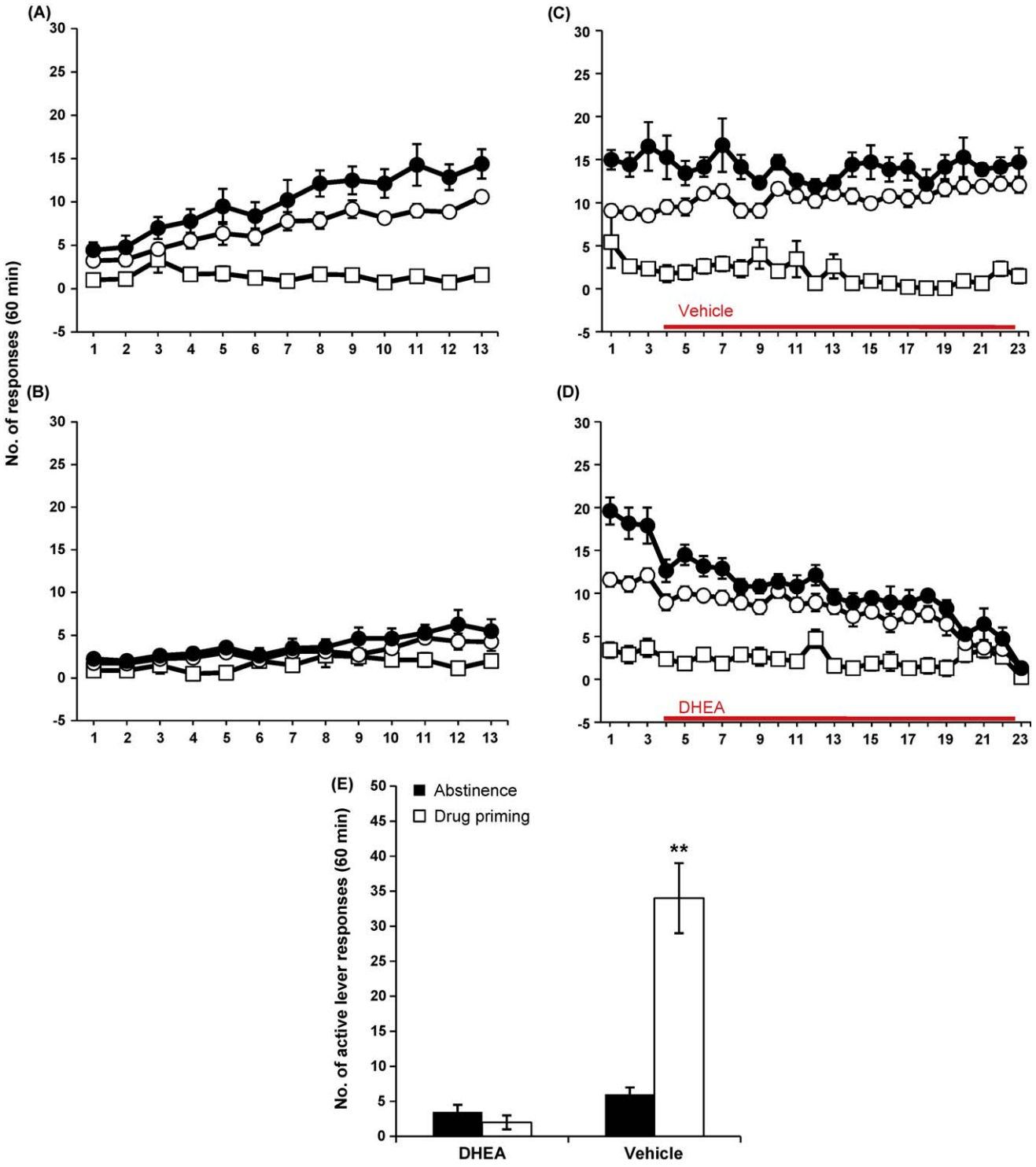

Fig. 2. Effect of DHEA on cocaine seeking behavior and relapse.
Rats were operated and implanted with i.v. catheters. After 10 days of rehabilitation they were trained to self-administer cocaine (1 mg/kg) in a FR-1 paradigm.
Panels A and B: *Effect of DHEA on cocaine acquisition*. Saline (A) or DHEA (2 mg/kg, B) was administrated consecutively 5 day before training and during training, 90 min before entering the rat into the self-administration chamber. Presses on the active-, non-active levers and number of drug infusions were recorded. A marked effect of DHEA pretreatment on drug-seeking behavior was noticed (modified from Maayan et al., 2006a).
Panels C and D: *Effect of DHEA on cocaine maintenance*. After rats reached stable maintenance (the figure indicate the three last days of maintenance before treatment) vehicle (C) or DHEA (2 mg/kg, D) was administrated consecutively during maintenance (bar), 90 min before entering the rat into the self-administration chamber when the drug was available. Presses on the active-, non-active levers and number of drug infusions were recorded. A gradual decrease in cocaine self-administration is depicted (modified from Doron et al., 2006a).
Panel E: *Effect of DHEA on cocaine-priming induced reinstatement*. Rats were treated with DHEA (2 mg/kg,) or saline consecutively during maintenance 90 min before entering the into the self-administration chamber, when the drug was available. After reaching the abstinence criterion (pressing <10% of maintenance), rats were reinstated with 10 mg cocaine i.v. and entered the chamber without accesses to cocaine. Craving was evaluated by measuring their presses on the active lever. As shown, craving was abolished ($^{**}P < 0.01$) by DHEA treatment (modified from Doron et al., 2006a).

ses revealed a significant effect of frequency of use of the drug. More sustained cocaine use was associated with higher cortisol levels and less pronounced cortisol decline after discontinuation of cocaine use, but drug intake variables had no influence on DHEAS levels. Cortisol levels declined more noticeably whereas DHEAS/cortisol ratios rose more dramatically during cocaine abstinence in aggressive than in non-aggressive addicts.

Other studies (Wilkins et al., 2005) identified each of the patient outcome groups by levels of circulating DHEAS and distressed mood at treatment entry. Results have shown that cocaine addicts with high circulatory DHEAS levels relapsed less to cocaine abuse after 3 weeks of non-pharmacological treatment, during a follow-up of 6 months. The authors suggest that in abstinence patients, distressed mood during withdrawal may have been mitigated through antidepressant-like actions of enhanced endogenous DHEAS activity (Brzoza et al., 2008; Genud et al., 2009; Wolkowitz and Reus, 2003), thus contributing to improved abstinence and treatment retention. Patients with high levels of distressed mood at treatment entry and low DHEAS levels may express higher susceptibility to cease the rehabilitation or may more easily relapse. Hence, correlations between endogenous DHEA levels and treatment outcome suggest the possibility that patients may benefit from adjunctive pharmacotherapy with DHEA.

Nonetheless, the clinical evidence for DHEA effect on addicts is limited and inconclusive. One placebo-controlled pilot designed study suggests that DHEA treatment produces worse treatment outcome (i.e. measures of drug use) in cocaine addicts (Shoptaw et al., 2004). A randomized, double-blind controlled study (Maayan et al., 2008) tested the use of DHEA as an adjunctive compound to a routine medication protocol in heroin addicts undergoing a rehabilitation program. This study suggests that opioid addicts do not respond uniformly to DHEA treatment with respect to withdrawal symptoms, depression, and anxiety associated with treatment outcome. However, no data on actual outcome measures (drug use) in this population are available. Therefore, further trials are needed before conclusions can be drawn.

6. Concluding remarks

Both DHEA and its sulfated ester, DHEAS, are excitatory neurosteroids (Majewska, 2002; Robel and Baulieu, 1995) having neurostimulant features. In addition, DHEA is an endogenous antidepressant having anti-glucocorticoid properties (Schneider, 2003; Wolkowitz et al., 1997) and a protective effect against the development of both depression and anxiety in mice (Maayan et al., 2006b). Accumulation of recent findings using animal models shows that high endogenous levels of DHEA and/or DHEAS may contribute to substances-of-abuse intake and reinstatement.

The illicit use of substances is a persistent problem worldwide. As yet, there is no effective pharmacotherapy for substance addiction (Carroll et al., 1999). Even though the precise mechanism by which DHEA facilitates abrogation of substance-seeking behavior is not yet elucidated, based on preclinical data, the possibility of DHEA for facilitating rehabilitation of substance addicts may be possible. However, further study is needed to examine whether DHEA improves outcome in a subgroup of addicts and, if so, what factors are associated with that response, in order to enable the design of a safe and well-tolerated DHEA treatment program for drug addicts.

References

Aguilar, M.A., Rodriguez-Arias, M., Minarro, J., 2009. Neurobiological mechanisms of the reinstatement of drug-conditioned place preference. Brain Res. Rev. 59, 253–277.

Alvarez-Buylla, A., Lim, D.A., 2004. For the long run: maintaining germinal niches in the adult brain. Neuron 41, 683–686.

Anker, J.J., Holtz, N.A., Zlebnik, N., Carroll, M.E., 2009. Effects of allopregnanolone on the reinstatement of cocaine-seeking behavior in male and female rats. Psychopharmacology (Berl.) 203, 63–72.

Auchus, R.J., 2004. Overview of dehydroepiandrosterone biosynthesis. Semin. Reprod. Med. 22, 281–288.

Azuma, T., Matsubara, T., Shima, Y., Haeno, S., Fujimoto, T., Tone, K., Shibata, N., Sakoda, S., 1993. Neurosteroids in cerebrospinal fluid in neurologic disorders. J. Neurol. Sci. 120, 87–92.

Baker, D.A., McFarland, K., Lake, R.W., Shen, H., Tang, X.C., Toda, S., Kalivas, P.W., 2003. Neuroadaptations in cystine-glutamate exchange underlie cocaine relapse. Nat. Neurosci. 6, 743–749.

Barrot, M., Vallee, M., Gingras, M.A., Le Moal, M., Mayo, W., Piazza, P.V., 1999. The neurosteroid pregnenolone sulphate increases dopamine release and the dopaminergic response to morphine in the rat nucleus accumbens. Eur. J. Neurosci. 11, 3757–3760.

Baulieu, E.E., 1998. Neurosteroids: a novel function of the brain. Psychoneuroendocrinology 23, 963–987.

Ben Ami, O., Kinor, N., Perelman, A., Yadid, G., 2006. Dopamine-1 receptor agonist, but not cocaine, modulates sigma(1) gene expression in SVG cells. J. Mol. Neurosci. 29, 169–176.

Bergeron, R., de Montigny, C., Debonnel, G., 1996. Potentiation of neuronal NMDA response induced by dehydroepiandrosterone and its suppression by progesterone: effects mediated via sigma receptors. J. Neurosci. 16, 1193–1202.

Brewer, G.J., Espinosa, J., McIlhaney, M.P., Pencek, T.P., Kesslak, J.P., Cotman, C., Viel, J., McManus, D.C., 2001. Culture and regeneration of human neurons after brain surgery. J. Neurosci. Methods 107, 15–23.

Broadbelt, K., Ramprasaud, A., Jones, L.B., 2006. Evidence of altered neurogranin immunoreactivity in areas 9 and 32 of schizophrenic prefrontal cortex. Schizophr. Res. 87, 6–14.

Brzoza, Z., Kasperska-Zajac, A., Badura-Brzoza, K., Matysiakiewicz, J., Hese, R.T., Rogala, B., 2008. Decline in dehydroepiandrosterone sulfate observed in chronic urticaria is associated with psychological distress. Psychosom. Med. 70, 723–728.

Buydens-Branchey, L., Branchey, M., Hudson, J., Dorota, M.M., 2002. Perturbations of plasma cortisol and DHEA-S following discontinuation of cocaine use in cocaine addicts. Psychoneuroendocrinology 27, 83–97.

Cao, L., Jiao, X., Zuzga, D.S., Liu, Y., Fong, D.M., Young, D., During, M.J., 2004. VEGF links hippocampal activity with neurogenesis, learning and memory. Nat. Genet. 36, 827–835.

Capitanio, N., Capitanio, G., De Nitto, E., Villani, G., Papa, S., 1991. H+/e− stoichiometry of mitochondrial cytochrome complexes reconstituted in liposomes. Rate-dependent changes of the stoichiometry in the cytochrome c oxidase vesicles. FEBS Lett. 288, 179–182.

Carroll, F.I., Howell, L.L., Kuhar, M.J., 1999. Pharmacotherapies for treatment of cocaine abuse: preclinical aspects. J. Med. Chem. 42, 2721–2736.

Chao, J., Nestler, E.J., 2004. Molecular neurobiology of drug addiction. Annu. Rev. Med. 55, 113–132.

Charalampopoulos, I., Dermitzaki, E., Vardouli, L., Tsatsanis, C., Stournaras, C., Margioris, A.N., Gravanis, A., 2005. Dehydroepiandrosterone sulfate and allopregnanolone directly stimulate catecholamine production via induction of tyrosine hydroxylase and secretion by affecting actin polymerization. Endocrinology 146, 3309–3318.

Chen, L., Dai, X.N., Sokabe, M., 2006. Chronic administration of dehydroepiandrosterone sulfate (DHEAS) primes for facilitated induction of long-term potentiation via sigma 1 (sigma1) receptor: optical imaging study in rat hippocampal slices. Neuropharmacology 50, 380–392.

Conrad, K.L., Tseng, K.Y., Uejima, J.L., Reimers, J.M., Heng, L.J., Shaham, Y., Marinelli, M., Wolf, M.E., 2008. Formation of accumbens GluR2-lacking AMPA receptors mediates incubation of cocaine craving. Nature 454, 118–121.

Crandall, J., Sakai, Y., Zhang, J., Koul, O., Mineur, Y., Crusio, W.E., McCaffery, P., 2004. 13-cis-retinoic acid suppresses hippocampal cell division and hippocampal-dependent learning in mice. Proc. Natl. Acad. Sci. U.S.A. 101, 5111–5116.

Del Olmo, N., Higuera-Matas, A., Miguens, M., Garcia-Lecumberri, C., Ambrosio, E., 2007. Cocaine self-administration improves performance in a highly demanding water maze task. Psychopharmacology (Berl.) 195, 19–25.

Del Olmo, N., Higuera-Matas, A., Miguens, M., Garcia-Lecumberri, C., Borcel, E., Solis, J.M., Ambrosio, E., 2006. Hippocampal synaptic plasticity and water maze learning in cocaine self-administered rats. Ann. N. Y. Acad. Sci. 1074, 427–437.

Di Chiara, G., 1999. Drug addiction as dopamine-dependent associative learning disorder. Eur. J. Pharmacol. 375, 13–30.

Dominguez-Escriba, L., Hernandez-Rabaza, V., Soriano-Navarro, M., Barcia, J.A., Romero, F.J., Garcia-Verdugo, J.M., Canales, J.J., 2006. Chronic cocaine exposure impairs progenitor proliferation but spares survival and maturation of neural precursors in adult rat dentate gyrus. Eur. J. Neurosci. 24, 586–594.

Dong, L.Y., Cheng, Z.X., Fu, Y.M., Wang, Z.M., Zhu, Y.H., Sun, J.L., Dong, Y., Zheng, P., 2007. Neurosteroid dehydroepiandrosterone sulfate enhances spontaneous glutamate release in rat prelimbic cortex through activation of dopamine D1 and sigma-1 receptor. Neuropharmacology 52, 966–974.

Doron, R., Fridman, L., Gispan-Herman, I., Maayan, R., Weizman, A., Yadid, G., 2006a. DHEA, a neurosteroid, decreases cocaine self-administration and reinstatement of cocaine-seeking behavior in rats. Neuropsychopharmacology.

Dubrovsky, B., 2006. Neurosteroids, neuroactive steroids, and symptoms of affective disorders. Pharmacol. Biochem. Behav. 84, 644–655.

Dubrovsky, B.O., 2005. Steroids, neuroactive steroids and neurosteroids in psychopathology. Prog. Neuropsychopharmacol. Biol. Psychiatry 29, 169–192.

Ebraheim, N.A., Waldrop, J., Yeasting, R.A., Jackson, W.T., 1992. Danger zone of the acetabulum. J. Orthop. Trauma 6, 146–151.
Eisch, A.J., Barrot, M., Schad, C.A., Self, D.W., Nestler, E.J., 2000. Opiates inhibit neurogenesis in the adult rat hippocampus. Proc. Natl. Acad. Sci. U.S.A. 97, 7579–7584.
Eisch, A.J., Harburg, G.C., 2006. Opiates, psychostimulants, and adult hippocampal neurogenesis: Insights for addiction and stem cell biology. Hippocampus 16, 271–286.
Enoch, M.A., 2008. The role of GABA(A) receptors in the development of alcoholism. Pharmacol. Biochem. Behav. 90, 95–104.
Eser, D., Schule, C., Baghai, T.C., Romeo, E., Uzunov, D.P., Rupprecht, R., 2006. Neuroactive steroids and affective disorders. Pharmacol. Biochem. Behav. 84, 656–666.
Falkenstein, E., Tillmann, H.C., Christ, M., Feuring, M., Wehling, M., 2000. Multiple actions of steroid hormones—a focus on rapid, nongenomic effects. Pharmacol. Rev. 52, 513–556.
Ferrando, S.J., Freyberg, Z., 2008. Treatment of depression in HIV positive individuals: a critical review. Int. Rev. Psychiatry 20, 61–71.
Ferrario, C.R., Gorny, G., Crombag, H.S., Li, Y., Kolb, B., Robinson, T.E., 2005. Neural and behavioral plasticity associated with the transition from controlled to escalated cocaine use. Biol. Psychiatry 58, 751–759.
Filip, M., Frankowska, M., 2008. GABA(B) receptors in drug addiction. Pharmacol. Rep. 60, 755–770.
Finn, P.R., 2002. Motivation, working memory, and decision making: a cognitive-motivational theory of personality vulnerability to alcoholism. Behav. Cogn. Neurosci. Rev. 1, 183–205.
Franklin, T.R., Harper, D., Kampman, K., Kildea-McCrea, S., Jens, W., Lynch, K.G., O'Brien, C.P., Childress, A.R., 2009. The GABA B agonist baclofen reduces cigarette consumption in a preliminary double-blind placebo-controlled smoking reduction study. Drug Alcohol Depend. 103, 30–36.
Geier, C., Luna, B., 2009. The maturation of incentive processing and cognitive control. Pharmacol. Biochem. Behav. 93, 212–221.
Genud, R., Merenlender, A., Gispan-Herman, I., Maayan, R., Weizman, A., Yadid, G., 2009. DHEA lessens depressive-like behavior via GABA-ergic modulation of the mesolimbic system. Neuropsychopharmacology 34, 577–584.
George, O., Vallee, M., Le Moal, M., Mayo, W., 2006. Neurosteroids and cholinergic systems: implications for sleep and cognitive processes and potential role of age-related changes. Psychopharmacology (Berl.) 186, 402–413.
Gibbs, T.T., Russek, S.J., Farb, D.H., 2006. Sulfated steroids as endogenous neuromodulators. Pharmacol. Biochem. Behav. 84, 555–567.
Goeders, N.E., 1997. A neuroendocrine role in cocaine reinforcement. Psychoneuroendocrinology 22, 237–259.
Goeders, N.E., 2002a. The HPA axis and cocaine reinforcement. Psychoneuroendocrinology 27, 13–33.
Goeders, N.E., 2002c. Stress and cocaine addiction. J. Pharmacol. Exp. Ther. 301, 785–789.
Gonzalez-Alvear, G.M., Werling, L.L., 1994. Regulation of [3H]dopamine release from rat striatal slices by sigma receptor ligands. J. Pharmacol. Exp. Ther. 271, 212–219.
Gonzalez-Saiz, F., Rojas, O.L., Castillo, I.I., 2009. Measuring the impact of psychoactive substance on health-related quality of life: an update. Curr. Drug Abuse Rev. 2, 5–10.
Grant, K.A., Helms, C.M., Rogers, L.S., Purdy, R.H., 2008. Neuroactive steroid stereospecificity of ethanol-like discriminative stimulus effects in monkeys. J. Pharmacol. Exp. Ther. 326, 354–361.
Haber, P.S., Demirkol, A., Lange, K., Murnion, B., 2009. Management of injecting drug users admitted to hospital. Lancet 374, 1284–1293.
Haney, M., 2009. Self-administration of cocaine, cannabis and heroin in the human laboratory: benefits and pitfalls. Addict. Biol. 14, 9–21.
Havelock, J.C., Auchus, R.J., Rainey, W.E., 2004. The rise in adrenal androgen biosynthesis: adrenarche. Semin Reprod. Med. 22, 337–347.
Hayashi, T., Su, T.P., 2003. Intracellular dynamics of σ-1 receptors (σ1 binding sites) in NG108-15 cells. J. Pharmacol. Exp. Ther. 306, 726–733.
Hayashi, T., Su, T.P., 2004. Sigma-1 receptor ligands: potential in the treatment of neuropsychiatric disorders. CNS Drugs 18, 269–284.
Heinz, A., Weingartner, H., George, D., Hommer, D., Wolkowitz, O.M., Linnoila, M., 1999. Severity of depression in abstinent alcoholics is associated with monoamine metabolites and dehydroepiandrosterone-sulfate concentrations. Psychiatry Res. 89, 97–106.
Herrera, D.G., Yague, A.G., Johnsen-Soriano, S., Bosch-Morell, F., Collado-Morente, L., Muriach, M., Romero, F.J., Garcia-Verdugo, J.M., 2003. Selective impairment of hippocampal neurogenesis by chronic alcoholism: protective effects of an antioxidant. Proc. Natl. Acad. Sci. U.S.A. 100, 7919–7924.
Hiranita, T., Soto, P.L., Tanda, G., Katz, J.L., 2010. Reinforcing effects of sigma-receptor agonists in rats trained to self-administer cocaine. J. Pharmacol. Exp. Ther. 332, 515–524.
Hyman, S.E., Malenka, R.C., Nestler, E.J., 2006. Neural mechanisms of addiction: the role of reward-related learning and memory. Annu. Rev. Neurosci. 29, 565–598.
Iancu, I., Tchernihovsky, E., Maayan, R., Poreh, A., Dannon, P., Kotler, M., Weizman, A., Strous, R.D., 2007. Circulatory neurosteroid levels in smoking and non-smoking chronic schizophrenia patients. Eur. Neuropsychopharmacol. 17, 541–545.
Inada, T., Iijima, Y., Uchida, N., Maeda, T., Iwashita, S., Ozaki, N., Harano, M., Komiyama, T., Yamada, M., Sekine, Y., Iyo, M., Sora, I., Ujikec, H., 2004. No association found between the type 1 sigma receptor gene polymorphisms and methamphetamine abuse in the Japanese population: a collaborative study by the Japanese Genetics Initiative for Drug Abuse. Ann. N.Y. Acad. Sci. 1025, 27–33.
Iwata, M., Muneoka, K.T., Shirayama, Y., Yamamoto, A., Kawahara, R., 2005. A study of a dendritic marker, microtubule-associated protein 2 (MAP-2), in rats neonatally treated neurosteroids, pregnenolone and dehydroepiandrosterone (DHEA). Neurosci. Lett. 386, 145–149.
Jackson, A., Mead, A.N., Rocha, B.A., Stephens, D.N., 1998. AMPA receptors and motivation for drug: effect of the selective antagonist NBQX on behavioural sensitization and on self-administration in mice. Behav. Pharmacol. 9, 457–467.
Johnson, G.V., Jope, R.S., 1992. The role of microtubule-associated protein 2 (MAP-2) in neuronal growth, plasticity, and degeneration. J. Neurosci. Res. 33, 505–512.
Jones, L.B., Johnson, N., Byne, W., 2002. Alterations in MAP2 immunocytochemistry in areas 9 and 32 of schizophrenic prefrontal cortex. Psychiatry Res. 114, 137–148.
Jung-Testas, I., Hu, Z.Y., Baulieu, E.E., Robel, P., 1989. Steroid synthesis in rat brain cell cultures. J. Steroid Biochem. 34, 511–519.
Kalivas, P.W., 2004. Glutamate systems in cocaine addiction. Curr. Opin. Pharmacol. 4, 23–29.
Kalivas, P.W., 2009. The glutamate homeostasis hypothesis of addiction. Nat. Rev. Neurosci. 10 (8), 561–572.
Kaminski, R.M., Gasior, M., Carter, R.B., Witkin, J.M., 2003. Protective efficacy of neuroactive steroids against cocaine kindled-seizures in mice. Eur. J. Pharmacol. 474, 217–222.
Kauer, J.A., Malenka, R.C., 2007. Synaptic plasticity and addiction. Nat. Rev. Neurosci. 8, 844–858.
Kempermann, G., Wiskott, L., Gage, F.H., 2004. Functional significance of adult neurogenesis. Curr. Opin. Neurobiol. 14, 186–191.
Kimonides, V.G., Khatibi, N.H., Svendsen, C.N., Sofroniew, M.V., Herbert, J., 1998. Dehydroepiandrosterone (DHEA) and DHEA-sulfate (DHEAS) protect hippocampal neurons against excitatory amino acid-induced neurotoxicity. Proc. Natl. Acad. Sci. U.S.A. 95, 1852–1857.
Kimonides, V.G., Spillantini, M.G., Sofroniew, M.V., Fawcett, J.W., Herbert, J., 1999. Dehydroepiandrosterone antagonizes the neurotoxic effects of corticosterone and translocation of stress-activated protein kinase 3 in hippocampal primary cultures. Neuroscience 89, 429–436.
Kitanaka, J., Kitanaka, N., Tatsuta, T., Hall, F.S., Uhl, G.R., Tanaka, K., Nishiyama, N., Morita, Y., Takemura, M., 2009. Sigma1 receptor antagonists determine the behavioral pattern of the methamphetamine-induced stereotypy in mice. Psychopharmacology (Berl.) 203, 781–792.
Knackstedt, L.A., Kalivas, P.W., 2009. Glutamate and reinstatement. Curr. Opin. Pharmacol. 9, 59–64.
Koob, G.F., 2004. A role for GABA mechanisms in the motivational effects of alcohol. Biochem. Pharmacol. 68, 1515–1525.
Koob, G.F., 2009. Dynamics of neuronal circuits in addiction: reward, antireward, and emotional memory. Pharmacopsychiatry 42 (Suppl. 1), S32–S41.
Kumar, P., Taha, A., Sharma, D., Kale, R.K., Baquer, N.Z., 2008. Effect of dehydroepiandrosterone (DHEA) on monoamine oxidase activity, lipid peroxidation and lipofuscin accumulation in aging rat brain regions. Biogerontology 9, 235–246.
Laurine, E., Lafitte, D., Gregoire, C., Seree, E., Loret, E., Douillard, S., Michel, B., Briand, C., Verdier, J.M., 2003. Specific binding of dehydroepiandrosterone to the N terminus of the microtubule-associated protein MAP2. J. Biol. Chem. 278, 29979–29986.
Lee, I., Kesner, R.P., 2003. Time-dependent relationship between the dorsal hippocampus and the prefrontal cortex in spatial memory. J. Neurosci. 23, 1517–1523.
Lee, I.T., Chen, S., Schetz, J.A., 2008. An unambiguous assay for the cloned human sigma1 receptor reveals high affinity interactions with dopamine D4 receptor selective compounds and a distinct structure-affinity relationship for butyrophenones. Eur. J. Pharmacol. 578, 123–136.
Leggio, L., Kenna, G.A., Swift, R.M., 2008. New developments for the pharmacological treatment of alcohol withdrawal syndrome. A focus on non-benzodiazepine GABAergic medications. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 1106–1117.
Leshner, A.I., 1997. Drug abuse and addiction treatment research. The next generation. Arch. Gen. Psychiatry 54, 691–694.
Leskiewicz, M., Budziszewska, B., Jaworska-Feil, L., Kajta, M., Lason, W., 1998. Effect of neurosteroids on glutamate binding sites and glutamate uptake in rat hippocampus. Pol. J. Pharmacol. Pharm. 50, 355–360.
Levy, A.D., Li, Q.A., Kerr, J.E., Rittenhouse, P.A., Milonas, G., Cabrera, T.M., Battaglia, G., Alvarez Sanz, M.C., Van de Kar, L.D., 1991. Cocaine-induced elevation of plasma adrenocorticotropin hormone and corticosterone is mediated by serotonergic neurons. J. Pharmacol. Exp. Ther. 259, 495–500.
Li, X., Li, J., Peng, X.Q., Spiller, K., Gardner, E.L., Xi, Z.X., 2009. Metabotropic glutamate receptor 7 modulates the rewarding effects of cocaine in rats: involvement of a ventral pallidal GABAergic mechanism. Neuropsychopharmacology 34, 1783–1796.
Liu, P.S., Wang, P.Y., 2004. DHEA attenuates catecholamine secretion from bovine adrenal chromaffin cells. J. Biomed. Sci. 11, 200–205.
Maayan, R., Lotan, S., Doron, R., Shabat-Simon, M., Gispan-Herman, I., Weizman, A., Yadid, G., 2006a. Dehydroepiandrosterone (DHEA) attenuates cocaine-seeking behavior in the self-administration model in rats. Eur. Neuropsychopharmacol. 16, 329–339.
Maayan, R., Morad, O., Dorfman, P., Overstreet, D.H., Weizman, A., Yadid, G., 2005. The involvement of dehydroepiandrosterone (DHEA) and its sulfate ester (DHEAS) in blocking the therapeutic effect of electroconvulsive shocks in an animal model of depression. Eur. Neuropsychopharmacol. 15, 253–262.
Maayan, R., Touati-Werner, D., Ram, E., Strous, R., Keren, O., Weizman, A., 2006b. The protective effect of frontal cortex dehydroepiandrosterone in anxiety and depressive models in mice. Pharmacol. Biochem. Behav. 85, 415–421.

Maayan, R., Touati-Werner, D., Shamir, D., Yadid, G., Friedman, A., Eisner, D., Weizman, A., Herman, I., 2008. The effect of DHEA complementary treatment on heroin addicts participating in a rehabilitation program: a preliminary study. Eur. Neuropsychopharmacol. 18, 406–413.
Maayan, R., Yagorowski, Y., Grupper, D., Weiss, M., Shtaif, B., Kaoud, M.A., Weizman, A., 2000. Basal plasma dehydroepiandrosterone sulfate level: a possible predictor for response to electroconvulsive therapy in depressed psychotic inpatients. Biol. Psychiatry 48, 693–701.
Majewska, M.D., 2002. HPA axis and stimulant dependence: an enigmatic relationship. Psychoneuroendocrinology 27, 5–12.
Malkesman, O., Braw, Y., Ram, E., Maayan, R., Weizman, A., Kinor, N., Yadid, G., Weller, A., 2008. Dehydroepiandrosterone and monoamines in the limbic system of a genetic animal model of childhood depression. Eur. Neuropsychopharmacol. 18, 255–261.
Maninger, N., Wolkowitz, O.M., Reus, V.I., Epel, E.S., Mellon, S.H., 2009. Neurobiological and neuropsychiatric effects of dehydroepiandrosterone (DHEA) and DHEA sulfate (DHEAS). Front. Neuroendocrinol. 30, 65–91.
Martin-Soelch, C., Chevalley, A.F., Kunig, G., Missimer, J., Magyar, S., Mino, A., Schultz, W., Leenders, K.L., 2001. Changes in reward-induced brain activation in opiate addicts. Eur. J. Neurosci. 14, 1360–1368.
Marx, C.E., Trost, W.T., Shampine, L., Behm, F.M., Giordano, L.A., Massing, M.W., Rose, J.E., 2006. Neuroactive steroids, negative affect, and nicotine dependence severity in male smokers. Psychopharmacology (Berl.) 186, 462–472.
Maurice, T., 2004. Neurosteroids and sigma1 receptors, biochemical and behavioral relevance. Pharmacopsychiatry 37 (Suppl. 3), S171–S182.
Maurice, T., Gregoire, C., Espallergues, J., 2006. Neuro(active)steroids actions at the neuromodulatory sigma1 (sigma1) receptor: biochemical and physiological evidences, consequences in neuroprotection. Pharmacol. Biochem. Behav. 84, 581–597.
Maurice, T., Martin-Fardon, R., Romieu, P., Matsumoto, R.R., 2002. Sigma(1) (sigma(1)) receptor antagonists represent a new strategy against cocaine addiction and toxicity. Neurosci. Biobehav. Rev. 26, 499–527.
Maurice, T., Phan, V.L., Urani, A., Kamei, H., Noda, Y., Nabeshima, T., 1999. Neuroactive neurosteroids as endogenous effectors for the sigma1 (sigma1) receptor: pharmacological evidence and therapeutic opportunities. Jpn. J. Pharmacol. 81, 125–155.
Maurice, T., Romieu, P., 2004. Involvement of the sigma1 receptor in the appetitive effects of cocaine. Pharmacopsychiatry 37 (Suppl. 3), S198–S207.
Mellon, S.H., Griffin, L.D., 2002a. Neurosteroids: biochemistry and clinical significance. Trends Endocrinol. Metab. 13, 35–43.
Mellon, S.H., Griffin, L.D., 2002b. Synthesis, regulation, and function of neurosteroids. Endocr. Res. 28, 463.
Mendelson, J.H., Mello, N.K., Sholar, M.B., Siegel, A.J., Mutschler, N., Halpern, J., 2002. Temporal concordance of cocaine effects on mood states and neuroendocrine hormones. Psychoneuroendocrinology 27, 71–82.
Mesiano, S., Jaffe, R.B., 1997. Developmental and functional biology of the primate fetal adrenal cortex. Endocr. Rev. 18, 378–403.
Michael, A., Jenaway, A., Paykel, E.S., Herbert, J., 2000. Altered salivary dehydroepiandrosterone levels in major depression in adults. Biol. Psychiatry 48, 989–995.
Miller, W.L., 2002. Androgen biosynthesis from cholesterol to DHEA. Mol. Cell. Endocrinol. 198, 7–14.
Mo, Q., Lu, S., Garippa, C., Brownstein, M.J., Simon, N.G., 2009. Genome-wide analysis of DHEA- and DHT-induced gene expression in mouse hypothalamus and hippocampus. J. Steroid Biochem. Mol. Biol. 114, 135–143.
Moldow, R.L., Fischman, A.J., 1987. Cocaine induced secretion of ACTH, beta-endorphin, and corticosterone. Peptides 8, 819–822.
Monnet, F.P., Mahe, V., Robel, P., Baulieu, E.E., 1995. Neurosteroids, via sigma receptors, modulate the [3H]norepinephrine release evoked by N-methyl-D-aspartate in the rat hippocampus. Proc. Natl. Acad. Sci. U.S.A. 92, 3774–3778.
Monteleone, P., Luisi, M., Colurcio, B., Casarosa, E., Ioime, R., Genazzani, A.R., Maj, M., 2001. Plasma levels of neuroactive steroids are increased in untreated women with anorexia nervosa or bulimia nervosa. Psychosom. Med. 63, 62–68.
Morrow, A.L., VanDoren, M.J., Penland, S.N., Matthews, D.B., 2001. The role of GABAergic neuroactive steroids in ethanol action, tolerance and dependence. Brain Res. Brain Res. Rev. 37, 98–109.
Mucha, R.F., van der, K.D., O'Shaughnessy, M., Bucenieks, P., 1982. Drug reinforcement studied by the use of place conditioning in rat. Brain Res. 243, 91–105.
Murray, H.E., Gillies, G.E., 1997. Differential effects of neuroactive steroids on somatostatin and dopamine secretion from primary hypothalamic cell cultures. J. Neuroendocrinol. 9, 287–295.
Nestler, E.J., Malenka, R.C., 2004. The addicted brain. Sci. Am. 290, 78–85.
Nguyen, E.C., McCracken, K.A., Liu, Y., Pouw, B., Matsumoto, R.R., 2005. Involvement of sigma (sigma) receptors in the acute actions of methamphetamine: receptor binding and behavioral studies. Neuropharmacology 49, 638–645.
Nie, H., Janak, P.H., 2003. Comparison of reinstatement of ethanol- and sucrose-seeking by conditioned stimuli and priming injections of allopregnanolone after extinction in rats. Psychopharmacology (Berl.) 168, 222–228.
Noonan, M.A., Choi, K.H., Self, D.W., Eisch, A.J., 2008. Withdrawal from cocaine self-administration normalizes deficits in proliferation and enhances maturity of adult-generated hippocampal neurons. J. Neurosci. 28, 2516–2526.
O'Brien, C.P., 1998. Stroke in young women who use cocaine or amphetamines. Epidemiology 9, 587–588.
Oberbeck, R., Benschop, R.J., Jacobs, R., Hosch, W., Jetschmann, J.U., Schurmeyer, T.H., Schmidt, R.E., Schedlowski, M., 1998. Endocrine mechanisms of stress-induced DHEA-secretion. J. Endocrinol. Invest. 21, 148–153.
Panlilio, L.V., Goldberg, S.R., 2007. Self-administration of drugs in animals and humans as a model and an investigative tool. Addiction 102, 1863–1870.
Panzica, G.C., Melcangi, R.C., 2008. The endocrine nervous system: source and target for neuroactive steroids. Brain Res. Rev. 57, 271–276.
Perez-Neri, I., Mendez-Sanchez, I., Montes, S., Rios, C., 2008. Acute dehydroepiandrosterone treatment exerts different effects on dopamine and serotonin turnover ratios in the rat corpus striatum and nucleus accumbens. Prog. Neuropsychopharmacol. Biol. Psychiatry 32, 1584–1589.
Peters, J., Kalivas, P.W., Quirk, G.J., 2009. Extinction circuits for fear and addiction overlap in prefrontal cortex. Learn. Mem. 16, 279–288.
Piazza, P.V., Le Moal, M., 1998. The role of stress in drug self-administration. Trends Pharmacol. Sci. 19, 67–74.
Piazza, P.V., Maccari, S., Deminiere, J.M., Le Moal, M., Mormede, P., Simon, H., 1991. Corticosterone levels determine individual vulnerability to amphetamine self-administration. Proc. Natl. Acad. Sci. U.S.A. 88, 2088–2092.
Randall, R.D., Lee, S.Y., Meyer, J.H., Wittenberg, G.F., Gruol, D.L., 1995. Acute alcohol blocks neurosteroid modulation of synaptic transmission and long-term potentiation in the rat hippocampal slice. Brain Res. 701, 238–248.
Rao, T.S., Mick, S.J., Cler, J.A., Emmett, M.R., Dilworth, V.M., Contreras, P.C., Gray, N.M., Wood, P.L., Iyengar, S., 1991. Effects of sigma ligands on mouse cerebellar cyclic guanosine monophosphate (cGMP) levels in vivo: further evidence for a functional modulation of N-methyl-D-aspartate (NMDA) receptor complex-mediated events by sigma ligands. Brain Res. 561, 43–50.
Reddy, D.S., Kulkarni, S.K., 1997a. Chronic neurosteroid treatment prevents the development of morphine tolerance and attenuates abstinence behavior in mice. Eur. J. Pharmacol. 337, 19–25.
Reddy, D.S., Kulkarni, S.K., 1997b. Reversal of benzodiazepine inverse agonist FG 7142-induced anxiety syndrome by neurosteroids in mice. Methods Find. Exp. Clin. Pharmacol. 19, 665–681.
Reeves, R., Thiruchelvam, M., Cory-Slechta, D.A., 2004. Expression of behavioral sensitization to the cocaine-like fungicide triadimefon is blocked by pretreatment with AMPA, NMDA and DA D1 receptor antagonists. Brain Res. 1008, 155–167.
Regelson, W., Kalimi, M., 1994. Dehydroepiandrosterone (DHEA)–the multifunctional steroid. II. Effects on the CNS, cell proliferation, metabolic and vascular, clinical and other effects. Mechanism of action? Ann. N. Y. Acad. Sci. 719, 564–575.
Ren, X., Noda, Y., Mamiya, T., Nagai, T., Nabeshima, T., 2004. A neuroactive steroid, dehydroepiandrosterone sulfate, prevents the development of morphine dependence and tolerance via c-fos expression linked to the extracellular signal-regulated protein kinase. Behav. Brain Res. 152, 243–250.
Ritsner, M., Maayan, R., Gibel, A., Strous, R.D., Modai, I., Weizman, A., 2004. Elevation of the cortisol/dehydroepiandrosterone ratio in schizophrenia patients. Eur. Neuropsychopharmacol. 14, 267–273.
Robbins, T.W., Ersche, K.D., Everitt, B.J., 2008. Drug addiction and the memory systems of the brain. Ann. N. Y. Acad. Sci. 1141, 1–21.
Robel, P., Baulieu, E.E., 1995. Dehydroepiandrosterone (DHEA) is a neuroactive neurosteroid. Ann. N. Y. Acad. Sci. 774, 82–110.
Robinson, T.E., Kolb, B., 1999. Alterations in the morphology of dendrites and dendritic spines in the nucleus accumbens and prefrontal cortex following repeated treatment with amphetamine or cocaine. Eur. J. Neurosci. 11, 1598–1604.
Robinson, T.E., Kolb, B., 2004. Structural plasticity associated with exposure to drugs of abuse. Neuropharmacology 47 (Suppl. 1), 33–46.
Romieu, P., Lucas, M., Maurice, T., 2006. σ1 Receptor ligands and related neuroactive steroids interfere with the cocaine-induced state of memory. Neuropsychopharmacology 31, 1431–1443.
Romieu, P., Martin-Fardon, R., Bowen, W.D., Maurice, T., 2003. Sigma 1 receptor-related neuroactive steroids modulate cocaine-induced reward. J. Neurosci. 23, 3572–3576.
Roth-Deri, I., Schindler, C.J., Yadid, G., 2004. A critical role for beta-endorphin in cocaine-seeking behavior. Neuroreport 15, 519–521.
Roth-Deri, I., Zangen, A., Aleli, M., Goelman, R.G., Pelled, G., Nakash, R., Gispan-Herman, I., Green, T., Shaham, Y., Yadid, G., 2003. Effect of experimenter-delivered and self-administered cocaine on extracellular beta-endorphin levels in the nucleus accumbens. J. Neurochem. 84, 930–938.
Rupprecht, R., Holsboer, F., 1999. Neuroactive steroids: mechanisms of action and neuropsychopharmacological perspectives. Trends Neurosci. 22, 410–416.
Saphier, D., Welch, J.E., Farrar, G.E., Goeders, N.E., 1993. Effects of intracerebroventricular and intrahypothalamic cocaine administration on adrenocortical secretion. Neuroendocrinology 57, 54–62.
Sarnyai, Z., Shaham, Y., Heinrichs, S.C., 2001. The role of corticotropin-releasing factor in drug addiction. Pharmacol. Rev. 53, 209–243.
Saxe, M.D., Malleret, G., Vronskaya, S., Mendez, I., Garcia, A.D., Sofroniew, M.V., Kandel, E.R., Hen, R., 2007. Paradoxical influence of hippocampal neurogenesis on working memory. Proc. Natl. Acad. Sci. U.S.A. 104, 4642–4646.
Schneider, H.P., 2003. Androgens and antiandrogens. Ann. N. Y. Acad. Sci. 997, 292–306.
Schulden, J.D., Thomas, Y.F., Compton, W.M., 2009. Substance abuse in the United States: findings from recent epidemiologic studies. Curr. Psychiatry Rep. 11, 353–359.
Schumacher, M., Weill-Engerer, S., Liere, P., Robert, F., Franklin, R.J., Garcia-Segura, L.M., Lambert, J.J., Mayo, W., Melcangi, R.C., Parducz, A., Suter, U., Carelli, C., Baulieu, E.E., Akwa, Y., 2003. Steroid hormones and neurosteroids in normal and pathological aging of the nervous system. Prog. Neurobiol. 71, 3–29.
Self, D.W., 2004. Regulation of drug-taking and -seeking behaviors by neuroadaptations in the mesolimbic dopamine system. Neuropharmacology 47 (Suppl. 1), 242–255.

Self, D.W., Choi, K.H., 2004. Extinction-induced neuroplasticity attenuates stress-induced cocaine seeking: a state-dependent learning hypothesis. Stress 7, 145–155.
Shabat-Simon, M., Levy, D., Amir, A., Rehavi, M., Zangen, A., 2008. Dissociation between rewarding and psychomotor effects of opiates: differential roles for glutamate receptors within anterior and posterior portions of the ventral tegmental area. J. Neurosci. 28, 8406–8416.
Shaham, Y., Shalev, U., Lu, L., De Wit, H., Stewart, J., 2003. The reinstatement model of drug relapse: history, methodology and major findings. Psychopharmacology (Berl.) 168, 3–20.
Shoptaw, S., Majewska, M.D., Wilkins, J., Twitchell, G., Yang, X., Ling, W., 2004. Participants receiving dehydroepiandrosterone during treatment for cocaine dependence show high rates of cocaine use in a placebo-controlled pilot study. Exp. Clin. Psychopharmacol. 12, 126–135.
Shors, T.J., Miesegaes, G., Beylin, A., Zhao, M., Rydel, T., Gould, E., 2001. Neurogenesis in the adult is involved in the formation of trace memories. Nature 410, 372–376.
Sondergaard, H.P., Hansson, L.O., Theorell, T., 2002. Elevated blood levels of dehydroepiandrosterone sulphate vary with symptom load in posttraumatic stress disorder: findings from a longitudinal study of refugees in Sweden. Psychother. Psychosom. 71, 298–303.
Spivak, B., Maayan, R., Kotler, M., Mester, R., Gil-Ad, I., Shtaif, B., Weizman, A., 2000. Elevated circulatory level of GABA(A)—antagonistic neurosteroids in patients with combat-related post-traumatic stress disorder. Psychol. Med. 30, 1227–1231.
Squire, L.R., Stark, C.E., Clark, R.E., 2004. The medial temporal lobe. Annu. Rev. Neurosci. 27, 279–306.
Strauss, E.B., Stevenson, W.A., 1955. Use of dehydroisoandrosterone in psychiatric practice. J. Neurol. Neurosurg. Psychiatry 18, 137–144.
Strous, R.D., 2005. Dehydroepiandrosterone (DHEA) augmentation in the management of schizophrenia symptomatology. Essent. Psychopharmacol. 6, 141–147.
Strous, R.D., Golubchik, P., Maayan, R., Mozes, T., Tuati-Werner, D., Weizman, A., Spivak, B., 2005. Lowered DHEA-S plasma levels in adult individuals with autistic disorder. Eur. Neuropsychopharmacol. 15, 305–309.
Strous, R.D., Maayan, R., Kaminsky, M., Blumensohn, R., Weizman, A., Spivak, B., 2009. DHEA and DHEA-S levels in hospitalized adolescents with first-episode schizophrenia and conduct disorder: a comparison study. Eur. Neuropsychopharmacol. 19, 499–503.
Strous, R.D., Maayan, R., Lapidus, R., Stryjer, R., Lustig, M., Kotler, M., Weizman, A., 2003. Dehydroepiandrosterone augmentation in the management of negative, depressive, and anxiety symptoms in schizophrenia. Arch. Gen. Psychiatry 60, 133–141.
Strous, R.D., Maayan, R., Weizman, A., 2006. The relevance of neurosteroids to clinical psychiatry: from the laboratory to the bedside. Eur. Neuropsychopharmacol. 16, 155–169.
Strous, R.D., Spivak, B., Yoran-Hegesh, R., Maayan, R., Averbuch, E., Kotler, M., Mester, R., Weizman, A., 2001. Analysis of neurosteroid levels in attention deficit hyperactivity disorder. Int. J. Neuropsychopharmacol. 4, 259–264.
Su, T.P., Hayashi, T., 2003. Understanding the molecular mechanism of sigma-1 receptors: towards a hypothesis that sigma-1 receptors are intracellular amplifiers for signal transduction. Curr. Med. Chem. 10, 2073–2080.
Sutton, M.A., Schmidt, E.F., Choi, K.H., Schad, C.A., Whisler, K., Simmons, D., Karanian, D.A., Monteggia, L.M., Neve, R.L., Self, D.W., 2003. Extinction-induced upregulation in AMPA receptors reduces cocaine-seeking behaviour. Nature 421, 70–75.
Suzuki, M., Wright, L.S., Marwah, P., Lardy, H.A., Svendsen, C.N., 2004. Mitotic and neurogenic effects of dehydroepiandrosterone (DHEA) on human neural stem cell cultures derived from the fetal cortex. Proc. Natl. Acad. Sci. U.S.A. 101, 3202–3207.
Svec, F., Porter, J., 1997. The effect of dehydroepiandrosterone (DHEA) on Zucker rat food selection and hypothalamic neurotransmitters. Psychoneuroendocrinology 22 (Suppl. 1), S57–S62.
Tannenbaum, C., Barrett-Connor, E., Laughlin, G.A., Platt, R.W., 2004. A longitudinal study of dehydroepiandrosterone sulphate (DHEAS) change in older men and women: the Rancho Bernardo Study. Eur. J. Endocrinol. 151, 717–725.
Teuchert-Noodt, G., Dawirs, R.R., Hildebrandt, K., 2000. Adult treatment with methamphetamine transiently decreases dentate granule cell proliferation in the gerbil hippocampus. J. Neural Transm. 107, 133–143.
Van den Oever, M.C., Goriounova, N.A., Li, K.W., Van der Schors, R.C., Binnekade, R., Schoffelmeer, A.N., Mansvelder, H.D., Smit, A.B., Spijker, S., De Vries, T.J., 2008. Prefrontal cortex AMPA receptor plasticity is crucial for cue-induced relapse to heroin-seeking. Nat. Neurosci. 11, 1053–1058.
Vanover, K.E., Suruki, M., Huber, M., Wilent, W.B., Carter, R.B., 2000. Neuroactive steroids attenuate cocaine-induced sucrose intake in rats, but not cocaine-induced hyperactivity in mice. Psychopharmacology (Berl.) 149, 269–276.
Vargas-Perez, H., Kee, R.T., Walton, C.H., Hansen, D.M., Razavi, R., Clarke, L., Bufalino, M.R., Allison, D.W., Steffensen, S.C., van der Kooy, D., 2009. Ventral tegmental area BDNF induces an opiate-dependent-like reward state in naive rats. Science 324, 1732–1734.
Vescovi, P.P., Coiro, V., Volpi, R., Passeri, M., 1992. Diurnal variations in plasma ACTH, cortisol and β-endorphin levels in cocaine addicts. Horm. Res. 37, 221–224.
von der Goltz, C., Kiefer, F., 2009. Learning and memory in the aetiopathogenesis of addiction: future implications for therapy? Eur. Arch. Psychiatry Clin. Neurosci. 259 (Suppl. 2), S183–S187.
Wang, D., Noda, Y., Tsunekawa, H., Zhou, Y., Miyazaki, M., Senzaki, K., Nitta, A., Nabeshima, T., 2007. Role of N-methyl-D-aspartate receptors in antidepressant-like effects of sigma 1 receptor agonist 1-(3,4-dimethoxyphenethyl)-4-(3-phenylpropyl)piperazine dihydrochloride (SA-4503) in olfactory bulbectomized rats. J. Pharmacol. Exp. Ther. 322, 1305–1314.
Wang, Y.T., 2008. Probing the role of AMPAR endocytosis and long-term depression in behavioural sensitization: relevance to treatment of brain disorders, including drug addiction. Br. J. Pharmacol. 153 (Suppl. 1), S389–S395.
Webb, S.J., Geoghegan, T.E., Prough, R.A., Michael Miller, K.K., 2006. The biological actions of dehydroepiandrosterone involves multiple receptors. Drug Metab. Rev. 38, 89–116.
Widstrom, R.L., Dillon, J.S., 2004. Is there a receptor for dehydroepiandrosterone or dehydroepiandrosterone sulfate? Semin Reprod. Med. 22, 289–298.
Wilkins, J.N., Majewska, M.D., Van Gorp, W., Li, S.H., Hinken, C., Plotkin, D., Setoda, D., 2005. DHEAS and POMS measures identify cocaine dependence treatment outcome. Psychoneuroendocrinology 30, 18–28.
Wilkins, J.N., Van Gorp, W., Hinken, C., Wclech, B., Wheatley, S., 1996. Relaps to cocaine use may be predicted in early abstinence by measures of dehydroepiandrosterone sulphate levels. In: Harris, L.S. (Ed.), Problems of Drug Dependence: Proceeding of the 58th Annual Scientific Meeting of the College on Problems of Drug Dependence. NIDA Research Monograph, p. 183.
Winocur, G., Wojtowicz, J.M., Sekeres, M., Snyder, J.S., Wang, S., 2006. Inhibition of neurogenesis interferes with hippocampus-dependent memory function. Hippocampus 16, 296–304.
Wolkowitz, O.M., Reus, V.I., 2003. Neurotransmitters, neurosteroids and neurotrophins: new models of the pathophysiology and treatment of depression. World J. Biol. Psychiatry 4, 98–102.
Wolkowitz, O.M., Reus, V.I., Roberts, E., Manfredi, F., Chan, T., Raum, W.J., Ormiston, S., Johnson, R., Canick, J., Brizendine, L., Weingartner, H., 1997. Dehydroepiandrosterone (DHEA) treatment of depression. Biol. Psychiatry 41, 311–318.
Woolf, N.J., Young, S.L., Johnson, G.V., Fanselow, M.S., 1994. Pavlovian conditioning alters cortical microtubule-associated protein-2. Neuroreport 5, 1045–1048.
Wu, H.E., Schwasinger, E.T., Terashvili, M., Tseng, L.F., 2007. dextro-Morphine attenuates the morphine-produced conditioned place preference via the sigma(1) receptor activation in the rat. Eur. J. Pharmacol. 562, 221–226.
Yamaguchi, M., Suzuki, T., Seki, T., Namba, T., Juan, R., Arai, H., Hori, T., Asada, T., 2004. Repetitive cocaine administration decreases neurogenesis in adult rat hippocampus. Ann. N. Y. Acad. Sci. 1025, 351–362.
Yamaguchi, M., Suzuki, T., Seki, T., Namba, T., Liu, J., Arai, H., Hori, T., Shiga, T., 2005. Decreased cell proliferation in the dentate gyrus of rats after repeated administration of cocaine. Synapse 58, 63–71.
Zheng, P., 2009. Neuroactive steroid regulation of neurotransmitter release in the CNS: action, mechanism and possible significance. Prog. Neurobiol. 89 (2), 134–152.