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Chapter 2

ALTERATIONS OF THE BRAIN SEROTONERGIC SYSTEM INDUCED BY DYSFUNCTIONS OF THE ADRENAL GLAND

Carmen Frias-Dominguez[1], PhD,
René Drucker Colín[2], PhD and Stefan Mihailescu[1,*]
[1]Departmento de Fisiología, Facultad de Medicina,
Instituto de Fisiología Celular,
Universidad Nacional Autónoma de México, Mexico DF, Mexico
[2]Instituto de Fisiología Celular,
Universidad Nacional Autónoma de México, Mexico DF, Mexico

ABSTRACT

Major depression is often associated with elevated and flat glucocorticoid hormone levels, probably due to a diminished negative feed-back regulation of corticotropin releasing hormone (CRH). Moreover, the pathologic increase in glucocorticoid hormone secretion (Cushing's disease) is associated with major depression, which improves after the successful treatment of the endocrine disorder. The excess of glucocorticoid hormone secretion alters the activity of the brain's serotonergic (5-HT) system. Thus, clinical studies reported that depressed

* Corresponding author email: stefm@unam.mx.

patients present a decreased binding capacity of 5-HT1A receptors, whereas various experimental studies reported a diminished function of 5-HT1A autoreceptors upon chronic administration of glucocorticoids. However, other experimental studies reported an inverse effect of chronic glucocorticoids, i.e., the increase in sensitivity of 5-HT1A autoreceptors.

Nicotine produces antidepressant effects in both humans and animal models of depression, through the release of endogenous antidepressants such as noradrenaline, dopamine and serotonin. The prevalence of smoking in depressed patients is significantly higher than in the normal population, and various investigators consider smoking to be a form of auto medication in depression. Experiments performed in our laboratory indicated that nicotine, administrated in midbrain slices, increases the firing rate of 70-80% 5-HT dorsal raphe nucleus (DRN) neurons, as well as 5-HT release inside the DRN. Approximately 20-30% DRN 5-HT neurons responded to nicotine administration with inhibition of the firing rate. The stimulatory effect of nicotine results from its direct, postsynaptic effects, as well as from its indirect, presynaptic effects (glutamate and noradrenaline release). The inhibitory effects of nicotine were due to an increased intra-raphe serotonin release.

In order to determine if nicotine or analogs can serve as therapeutic tools for treating the depression induced by elevated glucocorticoid hormone levels, experiments were performed on Wistar rats that were adrenalectomized and implanted subcutaneously with a 70 mg corticosterone capsule each. This experimental model ensures high and stable levels of blood corticosterone levels. After two weeks of exposure to corticosterone, midbrain slices were obtained and the responses of 5-HT DRN neurons to nicotine were studied. In most 5-HT DRN neurons the responses to nicotine were inhibitory, due to an increased function of the 5-HT1A autoreceptors and/or an increased nicotine-induced 5-HT release. These results contradict previous ones obtained from non-adrenalectomized rats, and may be explained by a diminished transport of tryptophan across the blood-brain barrier in adrenalectomized rats.

1. INTRODUCTION

1.1. Glucocorticoid and Mineralocorticoid Hormones and Their Receptors

The secretion of the glucocorticoid hormone cortisol occurs in the fascicular and reticular zones of the adrenal cortex and is stimulated by the adrenocorticotropic hormone (ACTH), a 39 amino acid peptide produced by the anterior pituitary. At its turn, ACTH secretion is controlled by two hypothalamic

hormones: the corticotropin releasing hormone (CRH), a 41 amino acid peptide secreted by the paraventricular nucleus and arginine vasopressin (AVP), a 9 amino acid peptide secreted by the supraoptic nucleus. The limbic system stimulates the secretion of CRH, a process strongly augmented during stress.

The glucocorticoid receptor (GR, also known as NR3C1) is a cytosolic protein containing 800 amino acids that is activated by ligand binding. Once formed, the cortisol - GR complex translocates into the cell nucleus where it binds to glucocorticoid response elements (GRE). This last event results in the regulation of gene expression, a process denominated transactivation. The proteins synthetized under the influence of cortisol produce a large variety of effects: decrease in inflammation and increases in gluconeogenesis, acid gastric secretion, renal secretion of ammonia, renal Na^+ reabsorption, K^+ secretion, depression of the immune system and osteoporosis.

Cortisol also binds with high affinity to the mineralcorticoid receptor (MR or NR3C2), a member of the steroid/thyroid receptor superfamily, which also includes the glucocorticoid -, thyroid -, retinoic acid - and vitamin D receptors (Baker et al., 2013). MR binds with a similar affinity mineralocorticoid - (aldosterone and deoxycorticosterone) and glucocorticoid hormones (cortisol and corticosterone). MR is expressed in many tissues, such as the kidney, colon, heart, central nervous system, brown adipose tissue and sweat glands. In the limbic system and hippocampus, both MRs and GRs are expressed. However, the plasma concentration of aldosterone is 100 to 1000 times lower than the one of cortisol and the affinity of cortisol for MRs is about 10 times higher than for GRs. As a consequence, MRs of the hippocampus and other structures are normally occupied by cortisol, and only during special conditions (stress or ultradian cortisol peaks) GRs are also occupied by cortisol (de Kloet et al., 2016). In the kidney and intestine, which are sensitive to aldosterone, the occupancy of MRs by glucocorticoids is prevented by the enzyme 11β-hydroxysteroid dehydrogenase type 2, which converts corticosterone to an inactive form (Funder, 1996). Due to their genomic signaling pathway, MRs and GRs produce high latency (between 15 min and 3 hour) and persistent molecular, cellular and behavioral effects. However, older and newer studies demonstrated that both aldosterone and cortisol present short latency (seconds to minutes) effects, mediated by membrane receptors and insensitive to inhibitors of gene translation (Wehling et al., 1992; Karst et al., 2005; Karst et al., 2010; Groenweg et al., 2012). The intracellular signaling systems used by membrane MRs and GRs involve the activation of second messengers belonging to several pathways (Src kinase of the epidermal growth factor, PLC, protein kinase C, adenylyl cyclase, protein kinase A, PIS-kinase, ERK1/2, Ca^{2+}).

Membrane MRs and GRs activate membrane transporters (sodium-hydrogen exchanger, sodium-potassium-2-chloride co-transporter). The existence of membrane-bound MRs and GRs was demonstrated in neurons from the hypothalamus, hippocampus, in lymphocytes, smooth muscle cells and mammary glands. Several non-genomic effects of steroids are: inhibition of CRH and ACTH release, activation of the Na^{+}-H^{+} exchanger in lymphocytes and arterial smooth muscle, increase in locomotion and risk assessment behavior in a novel environment, facilitation of aggressive behavior in a social challenge, facilitation of memory consolidation and inhibition of working memory, rapid inhibition of the immune response, inhibition of the vasoconstriction (Wehling et al., 1992 and Groeneweg et al., 2012). Since the non-genomic effects of steroid hormones do not always disappear in the presence of GR or MR antagonists, it was postulated that another type of membrane-associated steroid receptor might exist (Groeneweg et al., 2012).

1.2. The Effects of Steroid Hormones on Neuronal Activity

It was shown that GR and MR are present in several areas of the brain, such as the hippocampus, the hypothalamus and amygdala.

In the hypothalamus, corticosterone (the equivalent of cortisol in rats) has an overall inhibitory action by rapidly decreasing the probability of glutamate release and by increasing the probability of GABA release. These effects, which have a short latency (<5 min) and a large duration, depend on a membrane steroid receptor, which is different from MR or GR.

In the hippocampus, corticosterone has excitatory effects: it stimulates the mobility of glutamate AMPA receptors in the postsynaptic membrane and rapidly increases the probability of glutamate release (Karst et al., 2005). These effects are dependent on MRs, short-lasting and reversible with the removal of the hormone (Karst et al., 2005).

The first administration of corticosterone in the basolateral amygdala produced an increased probability of glutamate release, which lasted several hours and was dependent on MRs. However, subsequent administrations of corticosterone in the same area produced a decrease in the probability of glutamate release, an effect that involved endocanabinoids release and GRs (Karst et al., 2010).

In the central nervous system, numerous other non-genomic effects of corticosteroids were described: changes in neurotransmitter release, changes in

the activity of ionic channels, activation of NMDA receptors, neuroplasticity and kinase phosphorylation (Groeneweg et al., 2012 for review).

1.3. The Effects of Glucocorticoid Hormone Excess on the Central Nervous System

The excess of glucocorticoid hormone has deleterious effects on both the structure and the functions of the central nervous system. The main structural alteration induced by glucocorticoid hormones in the brain is atrophy, which especially affects the prefrontal cortex and the hippocampus. There are four theories that explain brain atrophy: 1) the decrease of neuronal glucose uptake, which leads to neuronal death; 2) the increase in glutamate release in several brain areas, especially in the hippocampus, which leads to dendrite atrophy; 3) the decrease in the synthesis of neurotrophic factors, such as nerve growth factor-b; 4) the suppression of neurogenesis in the dentate gyrus, which induces the reduction in volume of hippocampus (Jacobs et al., 2000, Patil et al., 2007).

The Cushing Syndrome (CS) is the most frequent cause of hypercortisolism. It is produced by corticotroph pituitary tumors (pituitary-dependent CS), which release ACTH. More seldom CS is produced by extra-pituitary tumors, which secrete CRH (Ectopic Cushing Syndrome) (Pivonello et al., 2015). The glucocorticoid hormone hypersecretion is produced by unilateral adrenocortical tumors or by bilateral adrenal hyperplasia (Pivonello et al., 2008) in only 20% of CS cases. The CS generates numerous metabolic disorders, such as visceral obesity, insulin resistance, type II diabetes mellitus, dyslipidemia, systemic arterial hypertension, atherosclerosis, thromboembolism, osteoporosis, increased susceptibility to infections and neuropsychiatric disorders (Starkman, 2013).

The earliest installed neuropsychiatric alteration in CS patients was irritability (86%), followed by depressed mood (77%) (Starkman, 2013). Depression associated with CS presented itself in various forms, from short (1 to 3 days) periods of sadness to a constant loss of hope. 17% of CS patients presented suicidal thoughts and 5% of them intended to commit suicide (Starkman, 2013). An important percentage (66%) of CS patients presented generalized anxiety, whereas other CS patients presented autonomic alterations, such as shaking, palpitations or sweating (Starkman, 2013). In 70% of CS patients fatigue was constant a complaint, whereas the decrease of libido was one of the earliest manifestations. Increases or decreases of appetite were present in about half of the patients (Starkman, 2013). Cognitive disturbances,

which also accompany CS, consist in memory alterations (83% of the CS patients), impaired concentration (66%), inattention, distractibility and forgetfulness (Starkman, 2013).

On the other hand, patients suffering from major depression presented flat and elevated levels of plasma cortisol, as well as an early escape from suppression of cortisol secretion by dexamethasone (Caroll et al. 1976). This suggests that, in major depression, there is a deregulation of the hypothalamic-pituitary-adrenal axis dependent on an abnormal drive from the limbic system, which induces an increase in glucocorticoid hormone release.

1.4. Serotonin Stimulates the Release of Glucocorticoid Hormones by Multiple Mechanisms

It was demonstrated that the agonists of 5-HT1A receptors 8-OH-DPAT ((8-hydroxy-2-(di-N-propylamino)tetralin)) and isapirone induce the increase in plasma corticosterone levels (Lorens and Van der Kar, 1987; Koenig et al., 1987) by stimulating CRH (Fuller, 1992) and ACTH release (Gilbert et al., 1988).

Corticosteroids also increase the expression of messenger ARN for hippocampal glucocorticoid and mineralocorticoid receptors (Seckl et al., 1990).

1.5. Glucocorticoid Hormones Increase Serotonin Synthesis

Immunocitochemistry studies (Härfstrand et al., 1986) revealed the presence of cytoplasmic GR receptor in 5-HT neurons belonging to the B1 to B9 groups, in noradrenergic cells belonging to the A1 to A7 groups and in dopaminergic neurons of A12 to A14 groups. In the same study, MRs could not be detected in 5-HT DRN neurons.

It was demonstrated that chronic exposure to high corticosterone concentrations increases the expression of the enzyme tryptophan hydroxylase (TPH) in 5-HT raphe neurons (Azmitia and McEwen, 1974). Later it was shown that 5-HT raphe neurons present two forms of TPH denominated TPH1 and TPH2. Normally, the levels of TPH2 are higher than the ones of TPH1. In rats, the expression of TPH2 presents a circadian rhythm, with the maximum during the peak secretion of corticosterone (Malek et al., 2005). Bilateral adrenalectomy suppresses the circadian rhythm of corticosterone secretion, an

effect that can by reverted by oral administration of corticosterone (Malek et al. 2007). These data strongly suggest that corticosterone increases the expression of TPH2 and stimulate 5-HT synthesis.

1.6. Nicotine Effects on 5-HT DRN Neurons and Mood

5-HT dorsal raphe nucleus (DRN) neurons, which provide most of brain serotonergic innervation, express both $\alpha 4\beta 2$ and $\alpha 7$ somatic nicotinic acetylcholine receptors (nAChRs). In rat midbrain slices, nicotine (1 μM) increases the firing rate of ~80% of 5-HT DRN neurons and serotonin release. In the remaining 20% of 5-HT DRN neurons, nicotine induces a decrease of the firing rate, an effect dependent on local serotonin release, which stimulates of 5-HT1A autoreceptors (Mihailescu et al., 1998; 2001; 2002). The stimulatory effects of nicotine on 5-HT DRN neurons are both direct-dependent on stimulation of somatodendritic nAChRs (Galindo-Charles et al., 2008), and indirect-dependent on presynaptic glutamate release (Garduño et al., 2002). It is thought that these effects may explain, at least in part, the antidepressant effects of nicotine observed in both animal models of depression and in patients with major depression. Epidemiological studies indicated that cigarette smoking is more frequent in depressed patients than in the normal population (Glasman et al., 1990), and that nicotine applied as patches improves mood in non-smoking depressed patients (Salín-Pascual y Drucker-Colín 1998). Nicotine's antidepressant effects were also present in animal models of depression and were explained by increases in serotonin (Vazquez-Palacios 2004), noradrenaline (Mitchell,1993; Benwell and Balfour, 1997) and dopamine release in areas of the brain, such as the hippocampus (Czubak et al., 2010) and the accumbens nucleus (Fowler et al., 2008).

2. GLUCOCORTICOID HORMONES EFFECTS ON 5-HT1A RECEPTORS

The 5-HT1A receptor is the most frequently encountered subtype in the 5-HT1 receptor family and was identified in the cerebral cortex, hippocampus, septum, raphe nuclei, basal ganglia and thalamus (Mestikawy et al., 1991). It is involved in the regulation of ACTH secretion, appetite, sexual behavior, thermoregulation, anxiety and depression. It has a postsynaptic location and, in

the DRN, functions like an inhibitory autoreceptor. The 5-HT1A receptor is coupled to a $G_{i/o}$ protein and its stimulation produces the inhibition of adenylyl cyclase and the opening of an inward rectifier potassium (GIRK) channel. In 5-HT DRN neurons 5-HT1A receptor is somatic and does not inhibit adenylyl cyclase but opens a GIRK channel, producing hyperpolarization and decrease in the neuronal firing rate. Sargent et al. (2000) detected a decreased binding capacity of 5-HT1A receptors in patients with major depression. It was suggested that a normal function of 5-HT1A receptors has an antidepressant effect.

In the brain slices obtained from adrenalectomized rats, acute and prolonged exposure to corticosterone (30-100 nM) decreased the inhibitory response of 5-HT dorsal raphe nucleus (DRN) neurons to the 5-HT1A receptor agonist 8-hydroxy-2-(di-N-propylamino) tetralin (8-OH-DPAT) (Laaris et al., 1995). This effect was reproduced by the GC receptors agonist of RU 28362 and antagonized by the blocker of GC receptors RU-38486.

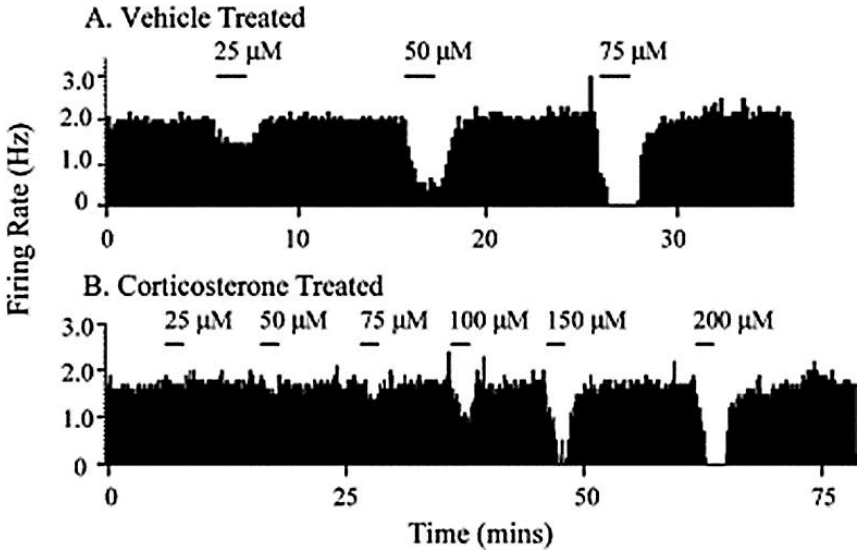

Figure 1. Chronic corticosterone administration attenuates 5-HT1A receptor-mediated autoinhibition in the DRN *in vitro*. Examples of electrophysiological recordings obtained from DRN slices from animals which had either ethanol vehicle (A) or corticosterone (B) added to the drinking water for 25-31 days prior to sacrifice. Inhibitory responses were obtained using 2 min exposure to increasing concentrations of 5-HT. Note the reduced sensitivity of the neurone obtained from the corticosterone-treated animal. From Fairchild et al., 2003, with permission.

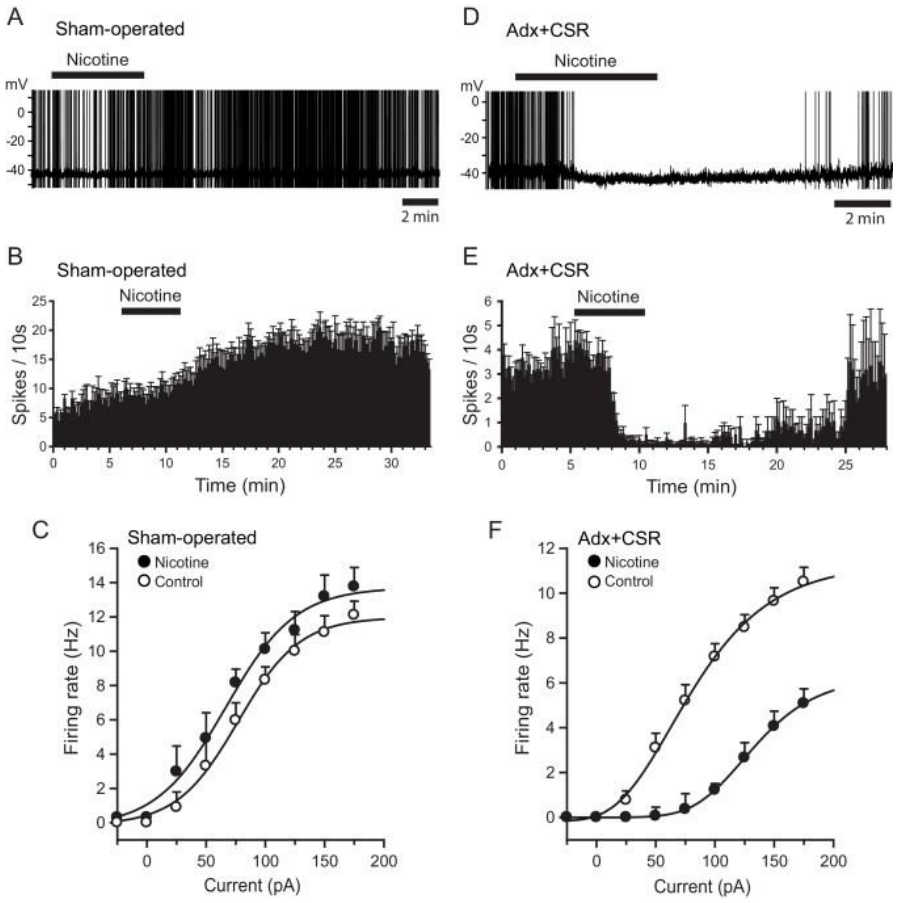

Figure 2. Comparative effects of nicotine on identified 5-HT DRN neurons obtained from sham-operated and Adx + CSR (adrenalectomized and corticosterone – treated) rats. (A) Stimulatory effect of bath application of nicotine (1 μM) on the firing rate of a 5-HT DRN neuron from the sham-operated group. (B) Frequency histogram showing the increase in firing rate induced by nicotine (1 μM) in neurons obtained from sham-operated rats; data represent means ± SEM (n = 15). (C) Upward shift of the intensity–frequency curves of 5-HT DRN neurons from sham-operated rats (n = 7) after nicotine administration (closed circles). (D) Inhibitory effect of nicotine (1 μM) on the firing rate of a 5-HT DRN neuron from the Adx + CSR group. (E) Frequency histogram showing the transitory inhibition of the firing rate induced by nicotine (1 μM) in Adx + CSR neurons; data represent means ± SEM (n = 9). (F) Downward shift of the intensity–frequency curves obtained from Adx + CSR 5-HT DRN neurons (n = 7) after nicotine administration (closed circles). ADX+Corticosterone stands for adrenalectomized and corticosterone treated rats. From Frías-Dominguez et al., 2012, with permission.

In the study of Fairchild et al. (2003), the effect of acute and chronic corticosterone on the function of 5-HT1A autoreceptors of 5-HT DRN neurons was tested *in vitro*. In brain slices obtained from normal and adrenalectomized rats, acute administration of corticosterone did not change the basal firing rate of DRN 5-HT neurons or the function of 5-HT1A autoreceptors, despite the large duration of corticosterone administration (1-6 hours). Chronic administration of corticosterone was achieved by oral administration of the compound during 21-30 days in a dose of ≈5 mg/day. After this interval, brain slices were obtained and the effect of submaximal doses of serotonin on the 5-HT1A receptor dependent hyperpolarization was tested. It was observed that 5-HT1A receptor's function was attenuated by approx. 50% (Figure 1), and this effect was attributed to activation of GRs of 5-HT DRN neurons.

The function of 5-HT1A autoreceptors in rats chronically exposed to high levels of corticosterone was also examined in the study of Leitch et al. (2003). Normal rats were implanted subcutaneously with a capsule containing 75 mg of corticosterone, and the concentration of serotonin was measured in the hippocampus by microdialysis. After 21 days of corticosterone exposure, the agonist of 5-HT1A receptor, 8-OH-DPAT, was administered and the changes in hippocampal serotonin release were assessed. Compared to controls, in corticosterone-treated rats the decrease in serotonin release induced by 8-OH-DPAT was significantly reduced, which suggests a decreased 5-HT1A receptor function.

The studies of Laaris et al. (1995), Fairchild et al. (2003) and Leitch et al. (2003) strongly suggest that chronic exposure to high corticosterone concentrations reduces the function of 5-HT1A autoreceptors. There are, however, two other works in which an opposite effect of corticosterone upon 5-HT1A autoreceptors, i.e., sensitization, was obtained. In one of these studies (Judge et al., 2004) performed on adrenalectomized rats subcutaneously implanted with corticosterone for two weeks, submaximal doses of serotonin had a higher inhibitory effect on the firing rate of 5-HT DRN neurons than in control neurons. A similar effect was observed in the study of Frías-Dominguez et al. (2013), performed in adrenalectomized rats implanted subcutaneously for two weeks, with two 70 mg corticosterone capsules. In midbrain slices obtained from adrenalectomized and corticosterone-treated rats, nicotine produced an inhibitory effect on the firing rate of 5-HT DRN neurons, which was antagonized by WAY100635, a specific antagonist of 5-HT1A receptors. In sham-operated animals, the effect of nicotine on the firing rate of 5-HT DRN neurons was stimulatory. Therefore, the study of Frías-Dominguez as the one of Judge et al., the chronic exposure to high glucocorticoid levels increases the

function of 5-HT1A receptors. Analyzing the available data in the literature, we noticed the desensitization of 5-HT1A autoreceptors in the presence of high levels of corticosterone was always observed in studies in which the animals were not adrenalectomised (Fairchild et al., 2003; Leitch et al., 2003), whereas in the studies in which adrenalectomy was performed (Judge et al., 2004; Frías-Dominguez et al. 2013), there was an increase in 5-HT1A receptor function. Adrenalectomy does not only suppress the corticosteroids hormone production, but also the production of adrenaline. Recent studies indicated that stimulation of peripheral ß2 and ß3- adrenoreceptors (Tsuiki et al., 2000; Claustre et al., 2008) increases the synthesis of serotonin in the DRN and other areas of the brain, very likely by increasing the transfer of l-tryptophan from the peripheral to the cerebral circulation through the large neutral amino acid transporter of the blood-brain barrier (Edwards et al., 1989). We hypothesize here that in adrenalectomised rats there is a lower synthesis and release of serotonin due to lower tryptophan availability, which leads to lower levels of extracellular serotonin, and therefore to a higher excitability of 5-HT1A autoreceptors. An additional explanation for the increased function of 5-HT_{1A} autoreceptors observed in our experiments is that corticosterone strongly increases the affinity of 5-HT_{1A} receptors for their agonists (Bellido et al., 2004). Likewise, corticosterone increases the activity of both type 1 (Abumaria et al., 2008) and type 2 (Malek et al., 2007) tryptophan hydroxylase in 5-HT DRN neurons, thus leading to an increase in the synthesis of serotonin. Moreover, it was also shown that corticosterone decreases serotonin re-uptake in the hippocampus by inhibiting the organic cation transporter 3 (OCT3) (Baganz et al., 2010), which is expressed in the DRN (Amphoux et al., 2006). A corticosterone-dependent increase in 5-HT1A receptor expression may be excluded since high levels of corticosterone decrease (Saenz del Burgo et al., 2013) or do not change (Fairchild et al., 2003 and Neumaier et al., 2000) 5-HT1A mRNA autoreceptor expression. Likewise, an increase in α4β2 affinity or number may be excluded since glucocorticoids decrease the currents induced by stimulation of nAChRs (Shi et al., 2002) and do not alter α4β2 nAChRs expression (Robinson et al., 1996). It was shown that chronic corticosterone diminishes the expression of mRNA encoding for type 2 subunit of inward rectifying potassium channels (Fairchild et al., 2003), which decreases the effect of 5-HT1A-receptor stimulation.

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