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Neurobiology of chronic mild stress: Parallels to major depression

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Abstract

The chronic mild (or unpredictable/variable) stress (CMS) model was developed as an animal model of depression more than 20 years ago. The foundation of this model was that following long-term exposure to a series of mild, but unpredictable stressors, animals would develop a state of impaired reward salience that was akin to the anhedonia observed in major depressive disorder. In the time since its inception, this model has also been used for a variety of studies examining neurobiological variables that are associated with depression, despite the fact that this model has never been critically examined to validate that the neurobiological changes induced by CMS are parallel to those documented in depressive disorder. The aim of the current review is to summarize the current state of knowledge regarding the effects of chronic mild stress on neurobiological variables, such as neurochemistry, neurochemical receptor expression and functionality, neurotrophin expression and cellular plasticity. These findings are then compared to those of clinical research examining common variables in populations with depressive disorders to determine if the changes observed following chronic mild stress are in fact consistent with those observed in major depression. We conclude that the chronic mild stress paradigm: (1) evokes an array of neurobiological changes that mirror those seen in depressive disorders and (2) may be a suitable tool to investigate novel systems that could be disturbed in depression, and thus aid in the development of novel targets for the treatment of depression.

Keywords

Stress; Depression; Neurobiology; Animal model; HPA axis

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1. Introduction

The chronic mild stress model (CMS; also referred to as chronic unpredictable, variable or intermittent stress), is a widely used rodent model of depression, which consists of repeated exposure to an array of varying and unpredictable, mild stressors over a sustained period of time (ranging from 10 days to 8 weeks). The CMS model was originally developed by Paul Willner and colleagues in the late 1980s, and was based on both clinical and preclinical research regarding the etiology of depression (Kessler et al., 1985; Katz, 1982). In humans, long-term exposure to uncontrollable and unpredictable life stressors is often said to be a major precipitant in the development of depressive disorders (Kessler, 1997; Kendler et al., 1999). However, many cases of depression develop in the absence of any notable life stress, and many individuals experience chronic exposure to significant life stressors and yet never develop depression (Kendler et al., 1999; Feder et al., 2009). With that caveat in mind, exposure to life stressors is one of the most reliable precipitating factors in the development of a depressive episode. Based on this knowledge, work performed by Katz and colleagues in the early 1980s demonstrated that exposure of rodents to severe stressors resulted in a reduction in locomotor activity and of their consumption of rewarding, palatable substances (namely sucrose; reviewed in Katz, 1982). This reduction in sucrose consumption was believed to be akin to the impairments in reward processing, which are the foundation for anhedonia, a core symptom of major depression (American Psychiatric Association and American Psychiatric Association Task Force on DSM-IV, 2000). With these findings in mind, Willner and colleagues developed the chronic mild stress model, which consisted of repeated exposure of rodents to a series of unpredictable “microstressors”, making the model more ethical (with the removal of the painful nature of footshock) and ethologically valid than that employed by Katz and colleagues. The endpoint of this model focused exclusively on sucrose intake and preference (as opposed to locomotor activity, which was also used as an endpoint by Katz and colleagues), which was believed to relate operationally to a deficit in hedonic impact in these rodents. The validity of this model was supported by the fact that this reduction in hedonic impact was reversible by chronic treatment with conventional antidepressant agents, which mimicked the time course required for clinical effectiveness of those agents (Willner, 2005; Willner et al., 1987).

As this model began to be adopted by other laboratories around the world, an accumulation of both congruent and discrepant effects was noted with respect to hedonic processing (see entire issue of Psychopharmacology [vol. 134, issue 4] devoted to discrepancies across laboratories). One major argument was that the reductions in sucrose intake were simply a reflection of the reduced body weight and food consumption that are typically concurrent with chronic stress exposure (Matthews et al., 1995). However, subsequent studies controlling for body weight changes, as well as studies demonstrating deficits in sucrose preference (as opposed to intake) argued against this proposition (Gronli et al., 2004; Willner et al., 1996). Moreover, the validity of this model for producing a state of “anhedonia” was supported by additional research demonstrating that deficits were also seen in other measures of reward and hedonic impact such as conditioned place preference, brain stimulation reward and dopaminergic release in response to rewarding stimuli (reviewed in Willner, 2005).

During the two decades since the inception of this model, there has been an explosion of behavioral research, which has extended the behavioral endpoints of this model to other facets of depression beyond hedonic processing and reward salience. For example, exposure of rodents to CMS enhances immobility in the forced swim test and learned helplessness, decreases the frequency of male sexual and aggressive behaviors, reduces self-care and grooming, and increases REM sleep latency (reviewed in (Willner, 1995)). Thus, despite a few anomalous findings from some laboratories, and regardless of some continuing controversy about the reliability of this model from laboratory to laboratory, the chronic mild stress model has been widely accepted as a valid model of "behavioral" depression in rodents.

While the CMS model is accepted as a paradigm that replicates many of the behavioral disturbances seen in depression, there is little consensus on the ability of this model to induce the neurobiological disturbances observed among clinically depressed individuals. This fact is particularly surprising, given that this model is used extensively for neurobiological endpoints, despite the fact that no thorough analysis to date has examined if the effects elicited by exposure to CMS are reminiscent of those seen in depression. Given the utility of this model for the exploration and discovery of putative, novel antidepressant agents, a similar argument could be made for examination of the neurobiological underpinnings of depressive disorder. If the CMS model is found to exhibit validity in producing the neurobiological changes observed in depression, then this model may also prove fruitful in the determination of novel target systems that may be disturbed in depression. This knowledge, coupled with behavioral data revealing the antidepressant potential of novel pharmacotherapeutic agents, may help to further our general understanding of the processes that underlie the development of depressive states, and in turn, target previously unrecognized systems that may be exploited for the development of novel therapeutic agents.

In line with this argument, the aim of the current review is to analyze the research published to date on the neurobiological effects of CMS. This research will then be compared to clinical literature to determine if comparable changes are seen in populations diagnosed with depression. The ultimate aim of this analysis is to summarize and compile the neurobiological alterations evoked by exposure to CMS, and subsequently examine if these changes are parallel to those seen in depression. Further, within this analysis we will also examine the methodologies employed by each laboratory in an attempt to come up with some general points which may assist new investigators intending to employ this model and how best to ensure replication of published effects. Depending on the outcome of this analysis, it may be possible to extend the chronic mild stress paradigm beyond its utility as a behavioral model of depression.

2. Methods

The PubMed literature search engine was used to find and collect all relevant articles analyzed in this review. To find papers that had examined neurobiological systems as an endpoint to chronic mild stress, we performed a multi-termed search. Specifically, for every search we used a base term of "chronic mild stress", "chronic unpredictable stress", "chronic

variable stress" or "chronic intermittent stress". Each of these base terms were then searched in PubMed with the addition of each of the following secondary terms employed to narrow down neurobiological systems of interest: serotonin, 5-HT, tryptophan hydroxylase, monoamine oxidase, 5-HIAA, COMT, noradrenaline, noradrenergic, norepinephrine, dopamine, dopaminergic, tyrosine hydroxylase, acetylcholine, cholinergic, nicotinic, muscarinic, opioid, endorphin, dynorphin, enkephalin, kappa, mu, delta, cannabinoid, endocannabinoid, cb1, anandamide, 2-arachidonoylglycerol, FAAH, GABA, GAD, glutamate, NMDA, AMPA, kainate, metabotropic glutamate, glucocorticoid, mineralocorticoid, neuropeptide, galanin, oxytocin, CRF, CRH, vasopressin, AVP, neuropeptide Y, substance P, CCK, cholecystokinin, neurokinin, tachykinin, neurogenesis, hippocampus proliferation, neurotrophin, BDNF, cAMP, kinase, phosphatase, phospholipase, PKA, PKC, PLA, PLC, creb, receptor, signal transduction. This search was inclusive for all articles that were published by the end of 2010.

These searches resulted in a significant number of articles that did not meet the inclusion criteria (see below), and therefore all of the abstracts that were retrieved by these searches were then screened to ensure that these articles examined a neurobiological endpoint following a chronic mild stress-like protocol. Given the heterogeneity of stress protocols used across laboratories, studies must have included at least three distinct stressors to be considered valid for analysis (as repeated presentation of the same stressor results in habituation and does not produce many of the behavioral effects that are seen following variable stressors). Once articles were considered relevant to the analysis at hand, the following variables were collected from each article: the nature of the stressors applied (type of stress, order of stressors and rotation of stressors); duration of the CMS protocol; duration of stressors applied each day; species and strain of animals used; light cycle under which the animals were housed and the time of day at which the stress-ors were applied; sex of the animals used; housing conditions of the animals during the CMS protocol; age of the animals at the onset of the CMS protocol; time following the cessation of the CMS protocol in which the brains were collected or analyzed for the variable of interest; regions of the brain that were analyzed; technique used for analysis; whether or not a behavioral variable was also assessed in the study and if so, whether there was an effect of CMS on this variable; and the neurobiological effects (significant or not) that were documented in the study following chronic mild stress. These methodological details were used as the highest order and very few papers provided sufficient detail to fill in all of these variables. Accordingly, the largest amount of data that could be recorded from a given paper in these categories was collected for analysis. The inclusion criteria of manuscripts for this analysis were that they detailed the duration of the CMS protocol the species/strain of animal used and presented data regarding a neurobiological endpoint following exposure to chronic mild stress. Exclusion criteria were insufficient detail of experimental methods or examination of the effects of chronic stress only in the presence of another variable (such as concurrent drug treatment or only with concurrent high fat feeding).

The aforementioned variables were then coded for each manuscript into a spreadsheet, which included a category for denoting which neurobiological system (e.g., serotonin, opioid, neurotrophin, etc.) was being examined in that study; if more than one system was explored, the paper was coded under each category. Upon collecting these data, to increase

the clarity of presentation, the findings of our analysis were subdivided into sections based on the endpoint system examined (i.e., serotonin, opioid, neurotrophin, etc.). The effects of CMS on differing measures of each of these systems were then compiled into tables. Once we had categorized the effects of chronic mild stress on a given variable within a given system, we then returned to PubMed to search for clinical studies which had examined this same variable in a human population suffering from depression or in post mortem tissue generated from suicide victims (which is often used as a proxy for depressive disorder). We then determined whether the effects of CMS were congruent with what has been documented in human populations.

For presentation in this manuscript, we have organized articles reviewed by neurobiological system (serotonin, norepinephrine, dopamine, GABA, glutamate, cannabinoid, opioid, CRH/AVP), all other neuropeptides, glucocorticoid/mineralocorticoid receptors, neurotrophins, markers of neurogenesis/proliferation/cell survival and signal transduction pathways (CREB, PKA, etc.) to create a table in which to present the effects of chronic mild stress on that system and then directly juxtapose this to the clinical findings in human populations with depressive disorder.

3. Neurochemical systems

3.1. Monoamines

3.1.1. Serotonin—For decades, 5-hydroxytryptamine (serotonin; 5-HT) has been described as the major neurochemical system in the brain that is dysregulated in affective disorders. Accordingly, there is an overwhelming amount of research investigating the effects of CMS on the serotonergic system in the brain. The following section will summarize the effects of CMS on serotonergic systems within distinct brain regions, first by describing the effects of CMS on 5-HT (ligand levels and metabolic/catabolic enzymes) and then by describing the effects of CMS on 5-HT receptors (see Table 1 for summary).

The determination of the effects of CMS on 5-HT content in an array of brain regions is performed through either the direct measurement of 5-HT content or as a ratio of the content of 5-HT relative to the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA), which is believed to represent serotonergic turnover. Within the frontal cortical regions, several studies have revealed CMS-induced reductions in either 5-HT content itself (Vancassel et al., 2008; Sheikh et al., 2007; Li et al., 2003, 2009a; Yalcin et al., 2008; Yi et al., 2008; Xu et al., 2008; Rasheed et al., 2008; Vitale et al., 2009; Ahmad et al., 2010; Shi et al., 2010) or reductions in 5-HT turnover (Bekris et al., 2005). However, there have also been contradictory reports of CMS having no effect on 5-HT content or turnover in the frontal cortex (Dalla et al., 2005; Haidkind et al., 2003; Tannenbaum and Anisman, 2003; Johnson and Yamamoto, 2009, 2010; Dang et al., 2009b; Patterson et al., 2010; Laugeray et al., 2010). Indeed, there are almost as many studies demonstrating a null effect of CMS on 5-HT as there are studies demonstrating that CMS results in a reduction in 5-HT levels. It is not clear what methodological differences mediate these differences, as studies reporting both significant and null effects have been performed in rats and mice at comparable ages, in comparable housing conditions and at a range of CMS durations (from 1 to 11 weeks of CMS exposure). It is possible that biochemical methods of detection could contribute to this

discrepancy (i.e. microdialysis versus bulk tissue measurement). Alternatively, the delay following the conclusion of CMS prior to tissue harvesting could be a contributing factor, as the reductions in 5-HT levels were more reliably seen when tissue was harvested closer to the conclusion to CMS.

At the receptor level, it has been consistently reported that CMS exposure upregulates the binding site density of cortical 5-HT_{2A} receptors (Papp et al., 1994a; Ossowska et al., 2001, 2002), while downregulating cortical 5-HT_{1A} receptor mRNA (Pan et al., 2010) and binding (Jang et al., 2004). It remains to be determined if these effects of CMS on 5-HT receptors are related to the changes in ligand content or result from an indirect effect of stress, such as increased secretion of glucocorticoid hormones. However, protracted 5-HT depletion upregulates cortical 5-HT_{2A} receptors (Cahir, 2006), suggesting that the increase in 5-HT_{2A} receptor binding in the cortex following CMS is likely a compensatory response evoked by the reduction in 5-HT neurotransmission. Another study reported that CMS increases 5-HT_{1A} mRNA within the cortex, but had no effect on either 5-HT_{1B} or 5-HT_7 receptor mRNA expression in this region (Li et al., 2009a).

Similar to its effects in the frontal cortex, CMS appears to impair serotonergic neurotransmission within the hippocampus. Specifically, exposure to CMS reduces both 5-HT content (Vancassel et al., 2008; Sheikh et al., 2007; Li et al., 2003, 2009a; Yi et al., 2008; Xu et al., 2008; Rasheed et al., 2008; Ahmad et al., 2010; Shi et al., 2010; Kang et al., 2005; Chen et al., 2009; Zhang et al., 2004) and turnover [in females only; (Dalla et al., 2005)]. There is no effect of CMS on 5-HT transporter binding sites (Lopez et al., 1998) or protein levels (Cunningham et al., 2009), suggesting that these effects are likely due to changes in metabolism/catabolism rather than synaptic clearance. However, there exist several discrepant findings, including reports of no effects of CMS on 5-HT or serotonergic turnover in the hippocampus (Dalla et al., 2005; Tannenbaum and Anisman, 2003; Yalcin et al., 2008; Johnson and Yamamoto, 2009, 2010; Dang et al., 2009a,b; Patterson et al., 2010; Laugeray et al., 2010; Gronli et al., 2007), and even one anomalous report of an increase in hippocampal serotonergic activity following CMS (Bekris et al., 2005). It is possible that there are regionally specific effects of CMS on serotonergic neurotransmission within the hippocampus and differences in tissue dissection endpoints across studies could have either amplified or nullified these effects.

With respect to serotonergic receptors within the hippocampus, all of the work to date has focused on the 5-HT_{1A} receptor due to its ubiquitous regulation by multiple antidepressant regimens (Haddjeri et al., 1998). With radioligand binding to whole hippocampal membrane fractions, CMS has been found to either decrease (Papp et al., 1994a) or have no effect on 5-HT_{1A} receptor binding (Haidkind et al., 2003). However, the study reporting null effects employed tissue that was collected 1 week following the cessation of CMS, suggesting that a reduction in 5-HT_{1A} receptor binding may be reversible. In support of the documented reduction in 5-HT_{1A} receptor binding in whole hippocampal sections, the use of tissue autoradiography has revealed that CMS reduces 5-HT_{1A} receptor binding in all regions of the hippocampus (Jang et al., 2004; Lopez et al., 1998). Similarly, it has been reported that there are reductions in 5-HT_{1A} receptor protein (Wang et al., 2009) and mRNA in whole hippocampal homogenates following CMS (Pan et al., 2010; Wang et al., 2009). In situ

hybridization analysis has similarly revealed that CMS produces a reduction in 5-HT_{1A} mRNA in the dentate gyrus, as well as the CA1 and CA3 regions of the hippocampus (Lopez et al., 1998; Xu et al., 2007). Thus, except for an occasional anomalous study reporting no effect of CMS (van Riel et al., 2003) or a CMS-induced increase (Li et al., 2009a) in hippocampal 5-HT_{1A} receptor mRNA, these data generally demonstrate that CMS exposure results in a reduction in 5-HT_{1A} receptor activity throughout the hippocampus. With respect to other serotonergic receptors, CMS has been reported not to affect 5-HT_{1B} mRNA in whole hippocampus, while two studies have demonstrated increases in 5-HT_7 mRNA in the hippocampus following CMS ((Li et al., 2009a) [whole hippocampi]; (Yau et al., 2001) [CA3 only]).

Within the hypothalamus, CMS does appear to impair 5-HT transmission, but again, some conflicting data exist. For example, studies examining 5-HT activity in whole hypothalamic sections have reported an increase in serotonergic turnover (Bekris et al., 2005), a reduction in 5-HT (Yi et al., 2008; Xu et al., 2008; Li et al., 2009a) or no effect on 5-HT or serotonergic turnover (Haidkind et al., 2003). When specific subregions of the hypothalamus are examined, there appears to be great consistency of results. In general, data suggest that there is no effect of CMS on serotonergic transmission in the paraventricular nucleus of the hypothalamus (Tannenbaum and Anisman, 2003; Sudom et al., 2004; Tannenbaum et al., 2002; Patterson et al., 2010), while in the median eminence, CMS has been reported to increase 5-HT utilization (Tannenbaum and Anisman, 2003). The only published study to date that has examined 5-HT receptor binding in the hypothalamus following CMS reported reduced 5-HT_{1A} receptor binding following CMS (Jang et al., 2004). Analysis of mRNA levels indicated that CMS elevates 5-HT_{1A}, 5-HT_{1B}, and 5-HT_7 mRNA in the whole hypothalamus (Li et al., 2009a). Overall, the effect of CMS on serotonergic activity within the hypothalamus appears to be reflective of an impairment, but this effect is not as prominent as that observed in the hippocampus and frontal cortex. These regional differences may be accounted for in part by the effects of CMS on distinct raphé nuclei that innervate different forebrain regions; however, future research is required to understand fully this phenomenon.

Less research has been performed to examine the influence of CMS on 5-HT transmission within other neural structures. Within the striatum, some studies have reported reductions in 5-HT content (Vancassel et al., 2008; Yalcin et al., 2008; Xu et al., 2008; Ahmad et al., 2010), while others have shown no change in striatal 5-HT following CMS (Li et al., 2003; Johnson and Yamamoto, 2009, 2010; Tata and Yamamoto, 2008; Bekris et al., 2005; Laugeray et al., 2010). Another study yielded no effect of CMS in whole striatum but a reduction in the nucleus accumbens (Yi et al., 2008). This suggests that, similar to its effects in the hippocampus and frontal cortex, 5-HT transmission may be impaired in the striatum following CMS. Within the amygdala, only three studies have examined the effects of CMS on 5-HT. One of these reports found that both 5-HT and 5-HIAA levels were elevated following CMS (Tannenbaum and Anisman, 2003), while the other two found no effect of CMS on 5-HT in the amygdala (Patterson et al., 2010; Laugeray et al., 2010).

Investigators have also examined serotonergic signaling in hindbrain structures. CMS reduces serotonergic activity in the medulla oblongata (Li et al., 2003) and raphé nucleus

(Yalcin et al., 2008; Yang et al., 2008), and 5-HT_{1A} receptors in the dorsal raphé were desensitized following CMS (Froger et al., 2004; Bambico et al., 2009). However, CMS has been found to increase serotonergic activity within the pons (Vitale et al., 2009).

Finally, within the whole brain, both monoamine oxidase A (MAO-A) and MAO-B activity are increased following CMS (Chen et al., 2007; Bhutani et al., 2009; Mao et al., 2009b), which corresponds to a brain wide reduction in 5-HT content following CMS (Bhutani et al., 2009). This suggests the possibility that the aforementioned reductions in serotonergic neurotransmission following CMS may be due to accelerated metabolism by MAO activity.

In general, the studies suggest that the CMS model produces a reduction in 5-HT neurotransmission in most forebrain regions, particularly the frontal cortex and hippocampus. Similarly, an upregulation of cortical 5-HT_{2A} and a downregulation of hippocampal 5-HT_{1A} receptor activity also appear to be relatively consistent effects produced by CMS.

With respect to how these effects of CMS parallel what is seen in clinical populations diagnosed with depression, it is commonly accepted that reduced 5-HT signaling can be a risk factor for developing major depression (Ressler and Nemeroff, 2000). The nature of this reduction in 5-HT signaling is not entirely understood, or well characterized. Of particular interest, a report has demonstrated that medication-free depressed clients exhibit reductions in serotonin synthesis in the cingulate cortex (Rosa-Neto et al., 2004), which could account for reduced 5-HT levels in the frontal cortex. As such, exposure of animals to CMS appears to produce reductions in frontocortical 5-HT signaling similar to what is seen in depression. Elevations in MAO-A levels in the brain of depressed individuals have been reported, in particular within cortical and hippocampal regions (Meyer et al., 2006). This finding coincides quite nicely with the documented increase in MAO activity in the brain following CMS, and could also account for the general forebrain impairment in 5-HT neurotransmission as well as the antidepressant effects of agents that inhibit MAO activity.

At the receptor level, CMS reliably produces an upregulation of frontal cortical 5-HT_{2A} receptor density (Papp et al., 1994a; Ossowska et al., 2001, 2002). Similarly, in major depression (or in *post mortem* tissue from suicides), an upregulation of cortical 5-HT_{2A} receptor activity has been reported consistently (Shelton et al., 2009; Bhagwagar et al., 2006; Oquendo et al., 2006; Escriba et al., 2004; Meyer et al., 2003; Turecki et al., 1999; Arango et al., 1995; Hrdina et al., 1993; McKeith et al., 1987; Mann et al., 1986; Yates et al., 1990). In addition, several studies have revealed that CMS produces a downregulation of 5-HT_{1A} receptor binding within the hippocampus (Jang et al., 2004; Lopez et al., 1998; Xu et al., 2007) and consistently, clinical reports in humans diagnosed with major depression (or following *post mortem* analysis) indicate a reduction in hippocampal 5-HT_{1A} receptor binding (Lopez et al., 1998; Cheetham et al., 1990; Lopez-Figueroa et al., 2004; Drevets et al., 2007). Thus, with respect to the 5-HT system, the CMS model appears to replicate many of the disturbances that are seen in clinical depression.

3.1.2. Norepinephrine—While 5-HT has received the most attention with respect to depression, norepinephrine (NE) is the other monoamine that is widely believed to be

dysfunctional in depression. There is an abundance of research on the effects of CMS on the noradrenergic system, but results are not always consistent (see Table 2 for summary). Within the frontal cortex, several studies have failed to find any effect of CMS on levels of NE, its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG), or the turnover of NE to MHPG (Yi et al., 2008; Haidkind et al., 2003; Tannenbaum and Anisman, 2003; Patterson et al., 2010; Harro et al., 1999; Bondi et al., 2010). However, an equal number of studies have reported a reduction in cortical levels of NE following CMS (Vancassel et al., 2008; Sheikh et al., 2007; Yalcin et al., 2008; Rasheed et al., 2008; Shi et al., 2010; Dang et al., 2009a,b), indicating that in some instances CMS may reduce frontal cortical NE activity. With respect to adrenoceptors, CMS unequivocally increases the binding site density of cortical β-adrenoceptors (Papp et al., 1994a, 2002; Molina et al., 1990; Haidkind et al., 2003; Basso et al., 1993) and β-adrenoceptor-mediated cyclic AMP stimulation (Papp et al., 2002). Only one study has examined α-adrenoceptor binding levels in the cortex following CMS and reported no effect of CMS on this receptor (Haidkind et al., 2003). As cortical β-adrenoceptors are negatively regulated by the presence of NE, a reduction in NE following CMS may promote the upregulation of cortical β-adrenoceptors; however, it is not known if this is the mechanism driving the effects of CMS.

Similar to reported effects in the cortex, studies on CMS effects on hippocampal NE or MHPG levels have had somewhat inconsistent results. Several studies found no effect of CMS on hippocampal NE or MHPG levels (Vancassel et al., 2008; Yi et al., 2008; Tannenbaum and Anisman, 2003; Patterson et al., 2010; Harro et al., 2001), while one study described an increase in hippocampal NE (Prieto et al., 2003), and others reported reduced levels of NE following CMS (Sheikh et al., 2007; Yalcin et al., 2008; Rasheed et al., 2008; Shi et al., 2010; Dang et al., 2009a,b). With respect to hippocampal receptors, CMS does not appear to affect either the inhibitory presynaptic α_2-adrenoceptor (Prieto et al., 2003) or the β-adrenoceptor (Harro et al., 1999). Thus, in general there do not appear to be particularly reliable or dramatic effects of CMS on the noradrenergic system in the hippocampus.

Within the hypothalamus, again, the majority of studies report no effect of CMS on the tissue levels of NE, MHPG or the NE:MHPG ratio in the whole hypothalamus (Yi et al., 2008; Haidkind et al., 2003), or in the paraventricular nucleus (PVN), the median eminence, or the arcuate nucleus regions (Tannenbaum and Anisman, 2003; Patterson et al., 2010; Tannenbaum et al., 2002). In contrast, one study reported an elevation in whole hypothalamic levels of NE (Prieto et al., 2003) and two others have reported elevations in NE utilization within the PVN (Patterson et al., 2010; Sudom et al., 2004). The primary differences among these studies is that for the whole hypothalamic assay, the analysis was performed 24 h following the final stressor, whereas in the study by Haidkind et al. (2003), analysis was done 7 days following the final stressor, suggesting that a recovery of function may have occurred during this period. With respect to the PVN, the increased NE utilization was observed in studies that employed a 14-day CMS exposure (Patterson et al., 2010; Sudom et al., 2004), while the two studies showing no effect employed CMS durations of more than 50 days (Tannenbaum and Anisman, 2003; Tannenbaum et al., 2002). Thus, perhaps there is an effect of CMS on NE activity following shorter exposure periods, and this effect dissipates, possibly through habituation, following longer CMS exposure. Accordingly, these data would suggest that CMS may actually increase hypothalamic NE

activity, but that this effect is transient and normalizes quickly following the cessation of stress. Nevertheless, it is possible that even short-term dysregulation of the NE system may have longer-term consequences on other neural systems; this hypothesis has yet to be investigated.

There is a scattering of studies that have investigated the effects of CMS on NE content in other regions, and again, results are inconsistent. Two studies have reported a reduction in NE levels in the striatum following CMS (Vancassel et al., 2008; Yalcin et al., 2008) while another study reported no effect of CMS on NE within the striatum/nucleus accumbens (Yi et al., 2008). Within the amygdala, one study found increased utilization of NE following CMS (Patterson et al., 2010), while another found no effect of CMS on NE in the amygdala (Tannenbaum and Anisman, 2003). CMS does not appear to influence NE levels within the septum (Harro et al., 2001), locus coeruleus (Patterson et al., 2010) or cerebellum (Harro et al., 1999). Similarly, at the whole brain level, CMS does not appear to affect NE levels (Bhutani et al., 2009). Thus, if there are reductions in NE following CMS, they typically are resticted to discrete brain regions. Only one study to date has examined the effects of CMS on the expression of tyrosine hydroxylase in the locus coeruleus (the primary site of NE synthesis for the forebrain), and found that CMS resulted in a reduction in tyrosine hydroxylase mRNA expression in the locus coeruleus (Duncko et al., 2001). A reduction in tyrosine hydroxylase levels in the locus coeruleus would be consistent with the few reports that have found reductions in NE levels in the frontal cortex and striatum. As a majority of the NE that innervates the hypothalamus, particularly the PVN, originates from the nucleus solitarius, this reduction in tyrosine hydroxylase levels in the locus coeruleus is not contrary to the putative increase in hypothalamic NE levels that has been reported.

In general, the effects of CMS on the noradrenergic system do not appear to be as common or consistent as those seen with the serotonergic system. The one change within this system evoked by CMS that appears to be quite reliable is the upregulation of cortical β-adrenoceptor binding. Further, the evidence on the levels of NE would suggest that if there is an effect of CMS on NE tissue levels it is modest, but may be manifested as a reduction in NE in some forebrain regions. This reduction, in turn, may be due to a reduction in NE synthesis within the locus coeruleus, or possibly increased metabolism, as the aforementioned increase in MAO activity in the brain (Chen et al., 2007) would predictably result in a decrease in NE levels.

Similar to findings following CMS, the studies examining nora-drenergic function in populations of depressed individuals are conflicting. Some reports indicate an impairment in noradrenergic signaling, while others would suggest an enhancement (Ressler and Nemeroff, 2000; Gold and Chrousos, 2002). However, this may be due to differences among subtypes of depression, as an increase in noradrenergic function has been suggested for the melancholic subtype of depression (Wong et al., 2000), albeit, these measures are very indirect and are often collected from serum or cerebrospinal fluid and do not give any insight into neuroanatomical specificity. With respect to adrenoceptors, the majority of studies indicate that β-adrenoceptor density in the cortex is upregulated in depressed suicide victims (Arango et al., 1990, 1992; Mann et al., 1986; Biegon and Israeli, 1988). An increase in cortical β-adrenoceptor binding is consistent with the effects of CMS. It should be noted,

however, that several reports have documented a down-regulation of cortical β-adrenoceptor density in suicide victims (De Paermentier et al., 1989, 1990; Little et al., 1993).

3.1.3. Dopamine—Despite the integral role of dopamine (DA) signaling in reward processing and hedonic tone, there has been substantially less work on the role of DA in depression than on the roles of NE and 5-HT. Similarly, there is comparatively less work on the effects of CMS on DA than on either of NE or 5-HT, and the majority of this work has focused on the cortical and striatal subregions (see Table 3 for summary).

Within the frontal cortex, most studies report that CMS results in a reduction in DA and its primary metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), or a decreased turnover of DA indicative of reduced DA signaling (Sheikh et al., 2007; Rasheed et al., 2008, 2010; Ahmad et al., 2010; Shi et al., 2010; Dang et al., 2009a,b; Harro et al., 2001); [only in females (Dalla et al., 2008)]. Nonetheless, there also exist several reports of no effect of CMS on DA signaling (Tannenbaum and Anisman, 2003; Johnson and Yamamoto, 2009, 2010; Patterson et al., 2010; Haidkind et al., 2003; Di Chiara et al., 1999) and one report of increased DA levels in the frontal cortex following CMS (Yi et al., 2008). Two studies have found that, in response to an acute stressor, DA levels increase significantly more in animals previously exposed to CMS as opposed to those with no prior stress exposure (Di Chiara et al., 1999; Cuadra et al., 2001), suggesting that despite a putative hypodopaminergic tone in the frontal cortex following CMS, the ability of a stressful stimulus to enhance DA transmission may in fact be potentiated by CMS.

The majority of studies examining DA levels in the striatum, or more specifically in the nucleus accumbens, have demonstrated no effect of CMS on basal DA transmission (Dalla et al., 2005, 2008; Tannenbaum and Anisman, 2003; Johnson and Yamamoto, 2009, 2010; Tata and Yamamoto, 2008; Di Chiara et al., 1999; Raudensky and Yamamoto, 2007a). In contrast a few studies have reported a reduction in striatal DA levels (Rasheed et al., 2008; Ahmad et al., 2010) or an increase in DA content and utilization in the nucleus accumbens (Yi et al., 2008; Patterson et al., 2010) following CMS. One study reported genetic strain-dependent effects of CMS such that DA transmission in the striatum was increased in Sprague–Dawley rats, but reduced in Wistar rats (Bekris et al., 2005). Interestingly, similar to results obtained for the frontal cortex, previous CMS exposure appears to potentiate stress-induced DA release in the nucleus accumbens (Di Chiara et al., 1999), while DA release in response to palatable food is reduced following CMS (Di Chiara et al., 1999). These data could indicate an enhancement of neurochemical responses to aversive stimuli and a blunting of responses to rewarding stimuli following CMS, which is conducive to the idea that processing of aversive and hedonic stimuli is disrupted in depression.

With respect to DA receptors, several studies have examined DA receptor binding in the whole limbic forebrain, which essentially encompasses cortical and striatal regions. In the limbic forebrain (consisting of forebrain areas rostral to the amygdala), CMS increases D1 (Ossowska et al., 2001, 2002), but decreases D2 receptor binding (Papp et al., 1994b), whereas in the frontal cortex, CMS has been found to downregulate D1 receptor activity, but not affect D2 receptor activity (Rasheed et al., 2010). Focusing in on the striatum, other studies have revealed that CMS increases D1 receptor binding (Rasheed et al., 2010; Papp et

al., 1994b) but does not affect D2 receptor binding in this region (Haidkind et al., 2003; Rasheed et al., 2010; Papp et al., 1994b). However, one study reported a reduction in D2 receptor mRNA within the nucleus accumbens following CMS (Dziedzicka-Wasylewska et al., 1997), while another report found no effects of CMS on the D1 or D2 mRNA levels in the nucleus accumbens (Bergstrom et al., 2008). In the frontal cortex, a reduction in D1 receptor binding has been found following CMS, while there was no effect on D2 receptor binding (Rasheed et al., 2010).

Most reports indicate that CMS does not affect DA levels in whole hypothalamus (Yi et al., 2008; Haidkind et al., 2003) or within the PVN or median eminence (Patterson et al., 2010; Tannenbaum et al., 2002). One study, however, found reductions in DA levels following exposure to CMS (Bekris et al., 2005; Dalla et al., 2005). Several studies report reductions in hippocampal DA levels following CMS (Sheikh et al., 2007; Rasheed et al., 2008, 2010; Dang et al., 2009a,b; Ahmad et al., 2010; Shi et al., 2010), although two studies found no effect of CMS on DA transmission in the hippocampus (Harro et al., 2001; Dalla et al., 2008). Additionally, other reports indicate that CMS exposure does not affect DA levels or turnover within the septum (Harro et al., 2001), amygdala (Rasheed et al., 2010) or the orbitofrontal cortex (Rasheed et al., 2010). However, one study found that CMS did not affect either D1 or D2 receptor binding in the amygdala or orbitofrontal cortex, but increased D1 (but not D2) receptor binding in the hippocampus (Rasheed et al., 2010).

Within the midbrain, where the cell bodies of the dopaminergic neurons that innervate the forebrain reside, CMS increases tyrosine hydrolxylase (the enzyme critical for DA synthesis) in the ventral tegmental area (Ortiz et al., 1996), while concurrently reducing D2 receptor mRNA in both the ventral tegmental area and the substantia nigra (Dziedzicka-Wasylewska et al., 1997).

There is no clear understanding of the effects of CMS on DA transmission in the brain. Several studies do suggest that corticostriatal regions may exhibit a reduction in basal and positive stimulus-induced DA transmission following CMS, which is consistent with a report indicating that CMS resulted in a brain wide reduction of DA levels (Bhutani et al., 2009). This is also consistent with the aforementioned increase in MAO activity (Chen et al., 2007), as DA is a substrate for MAO, and so a brain wide increase in MAO activity could relate to the brain wide reduction in DA content.

In studies of populations of depressed individuals, there has not been convincing evidence of alterations in dopaminergic receptor activity. No differences between controls and depressed patients in striatal/extra-striatal D2 receptor binding have been reported (Hirvonen et al., 2008; Montgomery et al., 2007; Allard and Norlen, 2001; Klimke et al., 1999; Parsey et al., 2001). Increases in D2 receptor binding in the putamen have been documented (Meyer et al., 2006), as well as reductions in striatal D1 receptor binding (Dougherty et al., 2006; Cannon et al., 2009). These findings are the exact opposite of the findings documented in the CMS model. Further work is required to characterize the dopaminergic system in the CMS model and in depression to elucidate whether the changes in these systems converge and if so, to what extent.

3.2. Excitatory/inhibitory amino acid transmitters

3.2.1. GABA—Gamma amino butyric acid (GABA) is the primary inhibitory neurotransmitter in the brain. GABAergic signaling is believed to be dysregulated more in anxiety disorders than depressive disorders; however these two disorders are often inexorably intertwined (Kessler et al., 2008). To date, there is very little research on the effects of CMS on the GABAergic system in the brain (see Table 4 for summary).

To our knowledge, only two studies have actually examined GABA content following CMS, and both report that previous exposure to CMS reduces hippocampal GABA levels (Gronli et al., 2007; Garcia-Garcia et al., 2009). One more recent study examined basal GABA levels in the hippocampus following CMS and found a reduction in GABA content in the ventral hippocampus, but not in the dorsal hippocampus (Elizalde et al., 2010a). Similarly, GABA levels are reduced in the frontal cortex following CMS (Garcia-Garcia et al., 2009). In line with this, CMS also reduces the expression of the vesicular GABA transporter in both hippocampus and frontal cortex (Garcia-Garcia et al., 2009). Several other studies have examined the effects of CMS on mRNA levels of the enzyme responsible for GABA synthesis, glutamic acid decarboxylase (GAD) 65 and 67; however, these studies have not yielded consistent findings. The first study demonstrated that GAD65 mRNA was increased in several hypothalamic regions (the anterior hypothalamic area, dorsomedial nucleus, medial preoptic area, suprachiasmatic nucleus, and peri-PVN) as well as the perifornical nucleus and the anterior region of the bed nucleus of the stria terminalis (BNST). GAD67 mRNA was also increased in the medial preoptic area, BNST, and hippocampus following CMS (Bowers et al., 1998). However, subsequent studies by the same research group employing the same CMS paradigm failed to find any effect of CMS on GAD65 or GAD67 mRNA in any region of the BNST, hypothalamus, amygdala, septum, hippocampus or frontal cortex (Herman and Larson, 2001; Herman et al., 2003). Herman and Larson (2001) reported a reduction in GAD65 mRNA in the posteriomedial BNST and medial preoptic area, which was only observed following CMS exposure in aged but not young or middle-aged rats. One additional study found that CMS reduced the expression of GAD65 protein in both the hippocampus and frontal cortex (Garcia-Garcia et al., 2009). Similarly, CMS was found to reduce GAD65 levels in the ventral, but not dorsal, hippocampus (Elizalde et al., 2010a). Thus, while evidence on the effects of CMS on the mRNA levels of the synthetic enzymes involved in GABA production are somewhat inconsistent, in general CMS appears to cause a reduction in GABA levels, at least within the hippocampus and frontal cortex.

Two studies have examined the effects of CMS on GABA receptor subunit expression. The first study reported that CMS decreased mRNA expression of β1 and β2 subunits of the GABA-A receptor within the PVN, but increased mRNA expression of the GABA-A receptor β2 subunit within the CA1, CA3 and dentate gyrus regions of the hippocampus (Cullinan and Wolfe, 2000). A second study found that CMS decreased expression of the GABA-A receptor δ subunit, but increased expression of the GABA-A receptor α5 subunit, within the PVN (Verkuyl et al., 2004). Further work is required to determine if these changes in GABA receptor subunit mRNA levels are paralleled by functional changes in GABA receptors at the protein level.

Clinical research on the role of the GABAergic system in depression has been sparse. One study examining GAD67 mRNA in depressed patients found no differences in the prefrontal cortex (Molnar et al., 2003). With respect to GABA receptor activity, one study found reductions in the number of α1, α3, α4 and δ subunits of the GABA-A receptor in the frontal cortex of depressed suicide victims (Merali et al., 2004). As no studies to date have examined expression patterns of GABA-A receptor subunits in the frontal cortex following CMS, it is not possible to determine whether the effects of CMS on the GABAergic receptor system parallel those seen in depression.

3.2.2. Glutamate—Glutamate is the primary excitatory neurotransmitter in the brain. Interest in the role of glutamate in depression has increased following the recent clinical findings of the antidepressant potential of NMDA receptor antagonists and AMPA receptor enhancers (see Skolnick et al., 2009; Machado-Vieira et al., 2009). However, there is still little to no research investigating the effects of CMS on glutamatergic signaling in the brain (see Table 5 for summary).

Few studies have examined the effects of CMS on synaptic and vesicular levels of glutamate. Within the hippocampus, CMS increases the expression of both the glial glutamate transporter-2 (responsible for glutamate clearance from the synapse) and the vesicular glutamate transporter-1 (responsible for transporting glutamate into vesicles), and doubles vesicular levels of glutamate (Raudensky and Yamamoto, 2007b). A second report replicated some of these findings in that CMS significantly elevated levels of glial glutamate transporter levels in the hippocampus; however, this study did not show an increase in the levels of vesicular gluta-mate transporter levels (Garcia-Garcia et al., 2009). Consistent with the finding of increased levels of vesicular glutamate in the hippocampus, tissue analysis revealed that CMS increased glutamate concentrations in the hippocampus when examined 24 h following the conclusion of CMS (Garcia-Garcia et al., 2009; Lou et al., 2010), but not when examined 4 weeks following CMS (Elizalde et al., 2010a). In contrast to these findings on increased gluta-mate levels, however, reduced levels of the mRNA for the vesicular glutamate transporter-1 in the CA1, but not CA3 or DG region of the hippocampus were reported (Elizalde et al., 2010b). Interestingly, this decrease is sustained for a prolonged period following the conclusion of CMS; at 4 weeks, when glutamate levels within the hippocampus are no longer elevated, there is still a sustained reduction in vesicular glutamate transporter-1 levels in the ventral hippocampus (Elizalde et al., 2010a,b). Within the frontal cortex, CMS does not affect the expression of the glial glutamate transporters and vesicular glutamate transporters (Garcia-Garcia et al., 2009; Banasr et al., 2010), but has been found to reduce mRNA levels of the vesicular glutamate transporter (Elizalde et al., 2010b). However, reductions in glial metabolism of glutamate have been found, suggesting that CMS increases glutamate signaling in the prefrontal cortex (Banasr et al., 2010). Consistent with this hypothesis, tissue analysis has demonstrated that frontal cortical levels of glutamate are elevated following CMS when examined 24 h after the final stressor (Garcia-Garcia et al., 2009; Lou et al., 2010), but are no longer different at 4 weeks following the cessation of CMS (Elizalde et al., 2010a). Thus, within the frontal cortex and hippocampus, it appears that CMS produces an increase in glutamatergic transmission, which is relatively transient and returns to normal levels following a sustained recovery

period, whereas there appears to be a sustained reduction in the vesicular glutamate transporter. However, these effects appear to be regionally specific as an in vivo microdialysis study found no effect of CMS on basal extracellular levels of glutamate in the striatum (Tata and Yamamoto, 2008).

At the receptor level, CMS reduces the binding site density of glycine/NMDA (N-methyl-D-aspartate) receptor binding sites in the cerebral cortex (Nowak et al., 1998) and the protein expression of both the NR2A and NR2B subunits of the NMDA receptor in the frontal cortex (Lou et al., 2010). Metabotropic glutamate receptor 5 protein levels are also elevated in the CA1 and reduced in the CA3 regions of the hippocampus following CMS (Wieronska et al., 2001), while NR2A and NR2B subunits of the NMDA receptor are both reduced following CMS within the hippocampus (Lou et al., 2010). Within the PVN, CMS decreases the mRNA expression of the NR2B receptor subunit, but does not affect the mRNA expression of the NR1, nor the NR2A subunits (Ziegler et al., 2005). At the level of the ventral tegmental area, CMS increases the protein expression of the NMDA receptor 1 subunit and the AMPA receptor GluR1 subunit (Fitzgerald et al., 1996). A separate study found no effect of CMS on GluR1 protein expression in the VTA following CMS, but did report an increase in GluR1 expression in the nucleus accumbens and a decrease in the prefrontal cortex and the dentate gyrus (Toth et al., 2008).

Based on these data, it would appear that within the hippocampus and frontal cortex, CMS has a clear facilitatory effect on glutamate signaling through an increase in glutamate release and a reduction in synaptic clearance of glutamate. Outside of these regions, given the paucity of research, there are few conclusions that can be made with respect to the effects of CMS on the glutamatergic system. At the clinical level, similar to the reported impairments in glutamate clearance and predicted increase in pre-frontal cortical glutamate following CMS (Garcia-Garcia et al., 2009; Banasr and Duman, 2008), *post mortem* analysis of depressed individuals has documented increases in prefrontal cortical levels of glutamate (Hashimoto et al., 2007).

3.3. Acetylcholine

There has been very little research examining the cholinergic system in the CMS model (see Table 6). Increases in cholinesterase expression in the hippocampus following CMS have been reported (Dang et al., 2009b), whereas reductions in cholinesterase activity have been reported in the cortex, hypothalamus, and striatum (but not hippocampus) following CMS (Das et al., 2005). Also, one report has documented reductions in muscarinic cholinergic receptors in the hippocampus and cortex, but not hypothalamus, following CMS (Zhang et al., 2007). Changes in cholinergic function following CMS may relate to changes in cognitive function from stress and depression, but further work is required in this domain to understand further the effects of CMS on the cholinergic system. This is particularly relevant since there is a body of evidence which has indicated that dysfunction of the cholinergic system may be present in major depression, such as impaired acetylcholinesterase activity or increased activity at central nicotinic receptors (Mineur and Picciotto, 2010; Bertrand, 2005).

3.4. Glucocorticoid/mineralocorticoid receptors

A large body of evidence demonstrates that a high proportion of depressed individuals exhibit glucocorticoid hypersecretion (Parker et al., 2003; Holsboer, 2000). Consistent with the hypothesis that glucocorticoids are involved in the pathogenesis of depression, pharmacological agents that inhibit glucocorticoid secretion or block glucocorticoid receptors (GR) have shown therapeutic efficacy in the treatment of depression (Reus and Wolkowitz, 2001). Because the focus of the current review is not on the endocrine effects of CMS, we did not examine the effects of CMS on circulating levels of glucocorticoid hormones. However, we did compile data regarding the effects of CMS on GR, as well as the mineralocorticoid receptor (MR), the other receptor to which glucocorticoids bind (see Table 7 for summary).

Consistent with the idea that CMS results in glucocorticoid hypersecretion, several studies have reported downregulation of GR mRNA expression (Froger et al., 2004; Zheng et al., 2006; Xu et al., 2006); and GR cytosolic binding (Froger et al., 2004; Kim et al., 1999) within the whole hippocampus. Regional analysis has further demonstrated that CMS reduces GR mRNA expression within the dentate gyrus (Herman et al., 1995; Yau et al., 2001) and the CA1 region (Herman et al., 1995) of the hippocampus. In addition to reducing hippocampal GR expression, CMS was found to reduce GR mRNA and cytosolic GR binding in the frontal cortex (Froger et al., 2004; Herman et al., 1995), as well as increase GR mRNA expression in the dorsal raphé (Froger et al., 2004). One study failed to find an effect of CMS on GR mRNA in the frontal cortex or hypothalamus (Pan et al., 2010), and two studies failed to find any effect of CMS on GR mRNA in any subregion of the hippocampus (Lopez et al., 1998; van Riel et al., 2003). As there is no notable difference in either the species or strain used between these studies, the CMS duration or time post-CMS in which these measurements were taken, it is not clear why findings differed among these different studies.

Similar to GR activity, activity at the mineralocorticoid receptor (MR) is typically reduced following CMS. For example, MR mRNA within the whole hippocampus was reduced by CMS (Yin et al., 2007). Similarly, cytosolic MR binding within whole hippocampus is reduced by CMS (Kim et al., 1999). However, regional analysis has produced somewhat mixed results: reports suggest reduced MR mRNA in the CA1, CA3 and dentate gyrus (Yau et al., 2001; Herman et al., 1995), reduced MR mRNA within the CA2, CA3 and CA4 (Lopez et al., 1998) and elevated MR mRNA within the dentate gyrus (van Riel et al., 2003) following CMS. Consistent with the general trend seen with MR mRNA in the intact hippocampus, cytosolic binding of MR within the whole hippocampus is reduced by CMS (in males but not females; Kim et al., 1999). CMS does not affect MR binding in the prefrontal cortex, hypothalamus or anterior pituitary (Kim et al., 1999).

Collectively, these studies indicate that both GR and MR levels are reduced following CMS, specifically within the hippocampus. GR, but not MR, expression also appears to be reduced within the frontal cortex. Very few studies have examined expression levels of GR and MR in humans although GR mRNA is reduced in the frontal cortex and the dentate gyrus of the hippocampus in depressed patients (Webster et al., 2002). This is relatively consistent with what was found using the CMS model. However, another report detected no differences

between suicide victims and a control group in GR mRNA expression within the hippocampus (Lopez et al., 1998). With respect to MR, little research has been performed with respect to major depression. One study reports a significant increase in MR expression in the PVN of subjects with major depression (Wang et al., 2008). Other studies of MR mRNA levels have found no changes in the prefrontal cortex (Xing et al., 2004), but a reduction in the hippocampus (Lopez et al., 1998), both of which are consistent with the findings reported following CMS. Collectively, it would appear that the alterations in GR and MR expression evoked by CMS largely parallel the changes seen in depression, but further work is required at both the clinical and preclinical level on these variables to confirm these changes.

3.5. Neuropeptides and neurolipids

3.5.1. CRH/AVP—Two neuropeptides, corticotrophin-releasing hormone (CRH) and arginine vasopressin (AVP) have received significant attention with respect to the neurobiology and treatment of depression. This is largely due to the fact that these neuropeptides are very sensitive to stress induction and involved in HPA regulation, and antagonists of receptors within these systems produce antidepressant behavioral effects in preclinical paradigms (Holsboer and Ising, 2010). Accordingly, several studies have examined the regulation of these systems in the CMS model (see Table 8 for summary).

The major region of interest is the hypothalamus, given the significant role of this structure in the stress response. Within the PVN, following exposure to stress, CRH is synthesized and released into the portal vasculature where it stimulates the release of ACTH from the anterior pituitary. Once in the bloodstream, ACTH promotes secretion of glucocorticoids from the adrenal cortex. CMS has been shown to result in an increase in CRH mRNA and protein within the PVN (Bergstrom et al., 2008; Ziegler et al., 1999); however, several null findings have also been reported (Kim et al., 2006; Stout et al., 2000; Michel et al., 2005). Additionally, it has also been reported that there is a higher density of CRH positive neurons in the PVN following CMS (Wang et al., 2010b). Similarly, CRH mRNA and protein levels are also elevated in the whole hypothalamus (Guo et al., 2009a), and CRH protein levels are elevated specifically within the anterior hypothalamus and median eminence following CMS (Chappell et al., 1986; Anisman et al., 2007). Thus, there does appear to be a general finding of increased CRH in the hypothalamus, although this is not entirely consistent, depending on the nuclei examined or the technique employed.

Interestingly, AVP does not appear to respond to CMS in a similar fashion, as nearly every single report to date has found no effect of CMS on AVP mRNA levels in the PVN (Bergstrom et al., 2008; Prewitt and Herman, 1997; Choi et al., 2008a,b; Ostrander et al., 2006; Pan et al., 2007) or AVP protein levels in the median eminence (Anisman et al., 2007). One anomalous report, however, has documented an increase in AVP mRNA following CMS within individual parvocellular neurons within the PVN (Herman et al., 1995); the reason for this finding is not well understood as many of the null findings reported above were from the same group employing the exact same CMS protocol, but could be due to the fact that this measure of quantitation is more sensitive and thus able to detect a very minor effect. Despite

elevated levels of CRH in the hypothalamus following CMS, CMS has been reported not to affect CRHR1 mRNA or protein levels within the hypothalamus (Pan et al., 2010).

The other major brain regions involved in the effects of these neuropeptides are the amygdala and BNST. However, within these regions, studies have been limited to measures of CRH, not AVP. Within the BNST, CRH increases following CMS (Duncko et al., 2001; Kim et al., 2006; Stout et al., 2000), although not in every report (Chappell et al., 1986). The few studies examining the amygdala have reported that CMS does not affect either CRH levels (Stout et al., 2000; Sandi et al., 2008) or CRH receptor binding (Stout et al., 2000). However, one report found an increase in the density of CRH immunpositive neurons in the central nucleus of the amygdala (Wang et al., 2010b).

CRH is also a signaling molecule in the hippocampus and cortex, and CMS elevates CRH levels within both of these structures (Pan et al., 2010, 2007), although one report found no effect of CMS on CRH protein levels in either of these structures (Chappell et al., 1986). With respect to CRH receptors in this region, the data are relatively inconsistent. It has been reported that CMS either decreases (Iredale et al., 1996) or does not affect CRHR1 receptor activity in the frontal cortex (Pan et al., 2010; Stout et al., 2000). A reduction in CRHR1 mRNA and protein, but not CRHR2 mRNA, has been reported in the orbitofronal cortex following CMS in two different strains of mice (Anisman et al., 2007). In the hippocampus, CRHR1 mRNA has been reported either to increase (Iredale et al., 1996) or not be affected (Pan et al., 2010) by CMS.

In general, these findings appear to parallel what is observed in major depression. The number of neurons expressing CRH immunoreactivity is increased in patients with mood disorders (Bao et al., 2005; Raadsheer et al., 1994) and CRH mRNA levels are dramatically elevated in the PVN of depressed individuals (Wang et al., 2008; Raadsheer et al., 1994). Similarly, CRHR1 and AVP type 1A receptor mRNA levels are also elevated in the PVN of depressed individuals (Wang et al., 2008). Significant evidence exists supporting the hypothesis that CRH circuits and signaling are hyperactive in major depression. For example, both CSF levels of CRH (Wong et al., 2000; Nemeroff et al., 1984; Banki et al., 1987) and CRH protein levels in the locus coeruleus (Ordway et al., 2003) are elevated in depressive illness. Moreover, CRH levels are also elevated in the frontal cortex (Merali et al., 2004), with CRHR1 (but not CRHR2) levels reduced in suicide victims (Nemeroff et al., 1988; Merali et al., 2004). A comparison of these variables suggests that CMS generally parallels the disturbances in the CRH signaling system observed in depression. Further work on the effects of CMS on AVP signaling is required to see if similar, parallel changes are seen.

3.5.2. Opioids—Opioids have garnered increasing attention with respect to depression given their role in reward processing and hedonic behaviors. However, few studies to date have examined the effects of CMS on opioid peptides or their receptors in the brain (see Table 9 for summary). Using in vivo microdialysis, one group of investigators examined levels of met-enkephalin in the rostral regions of the nucleus accumbens (Bertrand et al., 1997). Basal enkephalin levels were not different in controls compared to animals exposed to CMS. However, enkephalin levels increased in control, but not CMS-exposed, animals

following an episode of social interaction, suggesting a possible deficit in stimulus-evoked opioid release in the nucleus accumbens following CMS (Bertrand et al., 1997). In contrast, one study found increased levels of metenkephalin in the nucleus accumbens following CMS, but no change in met-enkephalin levels in the ventral tegmental area (Dziedzicka-Wasylewska and Papp, 1996; Papp et al., 1996). The former study employed CMS for a duration of 3 weeks, while the latter employed one of 8 weeks, suggesting that there could be time-dependent changes in accumbal enkephalin levels following CMS. In support of this hypothesis, another study, employing a CMS duration of 4 weeks, found no effects of CMS on either enkephalin or dynorphin mRNA in the nucleus accumbens (Bergstrom et al., 2008).

3.5.3. Other neuropeptides—There is an array of neuropeptide molecules that have received some attention in depression and a relatively small number of studies have done wide scale analysis of the effects of CMS on the expression of different neuropeptides and/or their receptors (see Table 10 for summary). Following is a brief summary of these effects.

CMS increases the expression of the melanin concentration hormone (MCH) receptor 1 in the hippocampus, but not in the whole brain or the frontal cortex (Roy et al., 2007). Two studies have examined the effects of CMS on neuropeptide Y expression. One study found that CMS decreased the expression of neuropeptide Y protein within the paraventricular and periventricular nuclei of the hypothalamus, the paraventricular thalamus and the arcuate nucleus (Kim et al., 2003). A second study found elevations in mRNA within the arcuate nucleus, reductions of neuropeptide Y mRNA within the dentate gyrus and no effect within the locus coeruleus (Sergeyev et al., 2005). With respect to cholecystokinin (CCK), CMS increased the protein expression of CCK within the paraventricular and periventricular nuclei of the hypothalamis as well as the paraventricular thalamus (Kim et al., 2003), but did not affect CCK receptor binding within the cerebral cortex or the cerebellum (Harro et al., 1999).

The neuropeptide galanin has received an increased amount of attention recently with respect to depression given the localization of this peptide in midbrain monoaminergic cell bodies and the finding that pharmacological manipulation of galanin signaling produces antidepressant effects (Barr et al., 2006; Lu et al., 2005, 2007). CMS reduces the mRNA expression of galanin within the dorsomedial hypothalamus and lateral hypothalamus, but not within the arcuate nucleus, the central nucleus of the amygdala, the raphe, or the locus coeruleus (Sergeyev et al., 2005).

The mRNA expression of substance P, on the other hand, is increased in the medial amygdala, as well as the ventromedial, dorsomedial, and lateral hypothalamus following CMS (Sergeyev et al., 2005). Finally, one study examining the effects of CMS on the expression of nociceptin/orphanin FQ (NOFQ) found no effects of CMS on the NOFQ peptide in the cortex, hippocampus, thalamus, septum, hypothalamus, midbrain, and cerebellum (Devine et al., 2003).

3.5.4. Endocannabinoid—The endocannabinoid system is a neuroactive lipid signaling system. This system has received growing attention in the patho-physiology of depression given that the endocannabinoid system is essential to stress-induced physiological processes (Hill and McEwen, 2010). Activation of the endocannabinoid system exerts an antidepressant action (Hill et al., 2009) and clinical trials with the cannabinoid CB_1 receptor antagonist found that anxiety and depression developed in a significant proportion of individuals (Hill and Gorzalka, 2009). Following exposure to CMS (see Table 11 for summary), reductions of CB_1 receptor binding and protein expression have been found in the hippocampus (Hill et al., 2005, 2008; Reich et al., 2009); however, no change in CB_1 receptor mRNA in the hippocampus has been reported (Bortolato et al., 2007). It is worth noting that an increase in CB_1 receptor protein was reported in females following CMS, which is directly opposite to the reduction seen in males (Reich et al., 2009). CMS was also shown to produce an increase in CB_1 receptor mRNA (Bortolato et al., 2007) and CB_1 receptor binding (Hill et al., 2008) in the pre-frontal cortex, whereas in the ventral striatum (largely, the nucleus accumbens), CMS reduced CB_1 receptor binding (Hill et al., 2008) and impaired CB_1-mediated regulation of glutamatergic transmission (Wang et al., 2010a). Additionally, CMS was found to decrease CB_1 receptor binding in the hypothalamus, but not the amygdala or midbrain (Hill et al., 2008), although CB_1 mRNA was reported to be reduced in the midbrain following CMS (Bortolato et al., 2007).

With respect to endocannabinoid ligands, varying results have been reported. One study found that CMS resulted in a reduction of the endocannabinoid ligand 2-arachidonoylyglycerol (2-AG), but not the other endocannabinoid, anandamide (AEA), in the hippocampus (Hill et al., 2005). However, subsequent reports found reductions in anandamide in the prefrontal cortex, hippocampus, amygdala, hypothalamus, striatum and midbrain, and elevations in 2-AG in the hypothalamus and midbrain following CMS (Hill et al., 2008), whereas other studies found no effects of CMS on anandamide or 2-AG in any brain region, except for an increase in 2-AG in the thalamus (Bortolato et al., 2007; Wang et al., 2010a). Protein levels of the enzyme fatty acid amide hydrolase, which hydrolyzes anandamide, were shown to be elevated in the hippocampus following CMS (Reich et al., 2009), consistent with reductions in AEA content (Hill et al., 2008).

Few studies to date have examined disturbances in the central endocannabinoid system in clinical depression. However, the CB_1 receptor is upregulated in the prefrontal cortex of depressed individuals (Hungund et al., 2004), which is concordant with the increased CB_1 receptor expression observed following CMS (Bortolato et al., 2007; Hill et al., 2008). Future research will have to examine other brain regions to observe whether reductions in hippocampal CB_1 receptors following CMS are seen in individuals with depression.

3.6. Signal transduction, neurotrophins and cellular resilience

3.6.1. Neurotrophin—Neurotrophins, particularly brain derived neurotrophic factor (BDNF), have received widespread attention for their role in the etiology and treatment of depression. Evidence that this system is dysregulated in depression comes from the findings that: (a) circulating levels of BDNF are reduced among patients with mood disorders, and (b) antidepressant agents augment BDNF expression and signaling in the brain (see

Hashimoto et al., 2004; Castren and Rantamaki, 2008; Duman and Monteggia, 2006). Accordingly, a wide range of studies has examined the effects of CMS on BDNF (see Table 12).

Reports on the effects of CMS on the mRNA levels of BDNF are not consistent with each other. Within whole hippocampus, CMS consistently reduces BDNF mRNA expression (Nibuya et al., 1999; Song et al., 2006; Mao et al., 2009a, 2010a,b; Hu et al., 2010a,b). However, the reliability of this effect is lost when subregions of the hippocampus are analyzed. Specifically, BDNF mRNA was found to be reduced by CMS in the CA1, but not CA3 or DG subregions (Elizalde et al., 2010b), increased in the CA3 and DG regions of the hippocampus (Bergstrom et al., 2008; Lee et al., 2006; Larsen et al., 2010), or unaffected in the CA1, CA3 and DG (Allaman et al., 2008). These differences may be due to the time points chosen post-CMS to examine BDNF expression, as mRNA levels are quite dynamic. Accordingly, examination of BDNF protein levels has produced much more consistent results. Specifically, studies which have examined levels of BDNF protein in the whole hippocampus have typically documented a pronounced reduction following CMS (Dang et al., 2009a; Zheng et al., 2006; Xu et al., 2006; Li et al., 2007, 2008; Lewitus et al., 2009; Elizalde et al., 2010b; Mao et al., 2010a,b; Hu et al., 2010a,b; Fortunato et al., 2010). Similarly, regional analysis has revealed that the effects of CMS are more prominent in the dorsal as opposed to the ventral regions of the hippocampus (Toth et al., 2008) and at the subregion level, CMS reduces BDNF protein levels in all of the CA1, CA3 (Xu et al., 2007; Zhang et al., 2010) and dentate gyrus regions (Zhang et al., 2010; Gronli et al., 2006; Xu et al., 2007). Only two studies have failed to find an effect of CMS on the protein expression of BDNF within the hippocampus (Lucca et al., 2008; Garcia et al., 2009) while two have documented an increase (Fortunato et al., 2010; Luo et al., 2010). Thus, the general consensus is that CMS produces robust reductions in hippocampal BDNF protein levels, and variable effects on hippocampal BDNF mRNA levels (although more often than not, reductions in BDNF mRNA levels are seen following CMS). Similarly, CMS increases mRNA expression of the TrkB receptor through which BDNF signals, which is believed to be a compensatory response to persistently low levels of BDNF within the hippocampus (Nibuya et al., 1999).

With respect to other structures, CMS reduces both BDNF mRNA and protein levels (Xu et al., 2006; Mao et al., 2009a, 2010a,b) within the frontal cortex, although this effect was not observed in two other reports (Zhang et al., 2010; Luo et al., 2010). Within the striatum, there are only two studies to date which have examined BDNF protein following CMS and both have documented a decrease following CMS (Toth et al., 2008; Gersner et al., 2010). However, CMS does not appear to affect the BDNF protein levels in the nucleus accumbens or ventral tegmental area (Toth et al., 2008; Gersner et al., 2010), nor BDNF mRNA expression in the amygdala (Allaman et al., 2008).

Many human studies have examined circulating levels of BDNF in depression, but few have examined central levels of BDNF. One study found that in medication-free depressed individuals who committed suicide, BDNF levels were reduced in both the hippocampus and frontal cortex (Karege et al., 2005), which parallels the findings seen in the CMS model. A more recent study also found reductions in hippocampal BDNF levels in the brains of

depressed individuals, but no corresponding changes in TrkB levels (Dunham et al., 2009). As such, CMS appears to parallel the effects of depression on reduced levels of BDNF in hippocampus and frontal cortex, but more research in humans is required to replicate the reductions in central BDNF levels seen in CMS animal models.

3.6.2. Signal transduction pathways—In an attempt to move beyond receptor/ligand-based theories of pathology, signal transduction pathways have become a new focus in depression research. There are a surprising number of studies examining the effects of CMS on different molecules involved in signal transduction (see Table 13 for summary).

The most studied transduction molecule is cyclic-AMP response element binding protein (CREB), largely because of its ability to regulate BDNF transcription and its regulation by antidepressant treatments. Like many other signal transduction molecules, CREB is activated by phosphorylation and so studies have examined both total CREB levels and levels of phosphorylated CREB (pCREB). It has been reported that CMS has no effect on CREB mRNA(Pan et al., 2010) or protein (Xu et al., 2007; Gronli et al., 2006; Li et al., 2009b) within the hippocampus, although two studies have reported a reduction in hippocampal levels of CREB mRNA following CMS (Li et al., 2009a; Song et al., 2006). CMS reliably reduces pCREB levels in the hippocampus with no published reports contradicting this finding (Xu et al., 2006; Li et al., 2009b; Pan et al., 2010; Gronli et al., 2006; Kong et al., 2009; Hu et al., 2010a). As pCREB is the active form of this molecule, these data would indicate that the effects of CREB on gene transcription are likely dampened following CMS.

Within the frontal cortex, CMS has been found to either have no effect on CREB mRNA or reduce CREB mRNA (Li et al., 2009a). At the protein level, CMS has been reliably found to reduce phosphorylated CREB in the frontal cortex (Pan et al., 2010; Xu et al., 2006). The hypothalamus is the only other region that has been examined. One report found no effects of CMS on CREB mRNA or levels of pCREB, while another reported reductions in hypothalamic CREB mRNA following CMS (Li et al., 2009b).

Another important signaling system that has received signifi-cant attention is the adenylate cyclase (AC)-cAMP-protein kinase A (PKA) pathway. AC activity is induced by stimulatory G proteins (G_s) and inhibited by inhibitory G proteins (G_i and G_o). Furthermore, in addition to activating PKA, cAMP also binds to CREB to induce CREB translocation to the nucleus where it can effect gene transcription. Thus, this pathway modulates both intracellular signaling cascades and dictates the nuclear effects of CREB. Within the hippocampus, CMS reduces AC activity (Li et al., 2009a) and AC subunit 2 mRNA expression (Li et al., 2009a), cAMP levels (Li et al., 2009a) and PKA activity (Kong et al., 2009). These reductions in the AC-cAMP pathway could relate to the aforementioned changes in CREB signaling, and they also likely mediate the reductions in PKA activity. Similar effects are seen in the cortex where CMS reduces AC activity and cAMP levels (but not AC subunit 2 mRNA; Li et al., 2009a) suggesting, again, that dysregulation of this pathway may mediate the downstream effects on CREB, and possibly BDNF changes following CMS. However, these effects do not hold in other structures. For example, CMS does not affect AC activity in the hypothalamus, and actually elevates both cAMP levels and the expression of AC subunit 2 mRNA (Li et al., 2009a). Similarly, PKA expression (Ortiz et al., 1996) and activity (Araujo

et al., 2003) is increased in the nucleus accumbens following CMS. To date, CMS has not been found to affect PKA expression in the caudate-putamen (Ortiz et al., 1996). Thus, collectively these data suggest that CMS decreases activity of the AC-cAMP-PKA pathway in the hippocampus and frontal cortex, but increases activity in this pathway in the hypothalamus and nucleus accumbens.

A scattering of studies has examined other signal transduction molecules in the hippocampus following CMS. One study reported that CMS decreased phosphorylation of the extracellular regulated kinase (ERK) 1/2 and CamKIV pathways (Kong et al., 2009) but another study found no effects of CMS on the protein levels of either the phosphorylated or non-phosphorylated variant of ERK1/2 (Li et al., 2009a). CMS also decreases levels of phosphorylated JNK, but not JNK or p38 protein levels (Li et al., 2009a). Additionally, one study reported that CMS had no effect on total levels of protein kinase C (PKC) in the hippocampus (Kong et al., 2009); however, CMS increased hippocampal levels of the ζ and γ isozyme protein levels of PKC selectively (Palumbo et al., 2007). Two conflicting reports have examined the effect of CMS on hippocampal levels of neuronal nitric oxide synthase (nNOS); one report found an early and sustained increase in nNOS levels following CMS (Zhou et al., 2007) while another found a reduction in hippocampal nNOS activity following CMS (Palumbo et al., 2007). One recent report also examined changes in signal transduction pathways within the VTA, and demonstrated that CMS increases levels phosphorylated ERK1/2 within the VTA (Iniguez et al., 2010).

Finally, two studies have examined the effects of CMS on G proteins. One study reported that CMS decreased protein levels of the $G_{i\alpha}$ subunit in the nucleus accumbens, but not the caudateputamen (Ortiz et al., 1996). The second report examined mRNA expression of regulator of G protein signaling type 4 protein (RGS4) following CMS and found decreased RGS4 mRNA expression in the PVN of the hypothalamus and the pituitary, but increased levels in the locus coeruleus (Ni et al., 1999).

The effects of CMS on cAMP, CREB and PKA mirror those seen in depression in the few studies that have been conducted. One study reported reductions in the mRNA levels of CREB, the DNA binding activity of CREB, and the basal and stimulated levels of PKA in the hippocampus of depressed, suicide victims (Dwivedi et al., 2003). Additional studies by this group examining teenage suicide victims found similar reductions in these pathways in the frontal cortex, but not the hippocampus, suggesting that there may be an ontogenetic trajectory of the dysregulation of this signaling system in depression (Pandey et al., 2005, 2007). Additional studies have reported reductions in PKA levels and activity (Shelton et al., 2009; Dwivedi et al., 2004) within the frontal cortex. Similarly, protein levels of AC (Cowburn et al., 1994; Reiach et al., 1999) as well as stimulated levels of AC activity (Cowburn et al., 1994; Lowther et al., 1996; Dowlatshahi et al., 1999; Valdizan et al., 2003) were reduced in the frontal and temporal cortex of depressed subjects. PKC activity, conversely, has been either reduced (Pandey et al., 1997, 2003) or unchanged (Hrdina et al., 1998) in the frontal cortex and hippocampus of suicide victims, similar to the contrasting reports seen following CMS. Collectively, these human data would suggest that the AC-cAMP-PKA signaling cascade is reduced in depression, particularly in the frontal cortex, which corresponds very well with the reductions in this signaling pathway following CMS.

3.6.3. Neurogenesis/cell proliferation and survival—One of the primary roles of BDNF and other signal transduction pathways is to increase cellular resilience and survival. With the discovery that antidepressants increase cell proliferation, survival and neurogenesis in the adult hippocampus, interest spread to the putative role of neurogenesis in depression. Accordingly, there is an abundance of research that has examined the effects of CMS on hippocampal cell proliferation, survival and neurogenesis (see Table 14).

Of all of the alterations elicited by CMS, effects on cell proliferation (i.e., the proliferation of quiescent progenitor cells), hippocampal neurogenesis (i.e., the generation of new neurons within the hippocampus) and survival (i.e., the maturation and survival of a newborn cell, usually at least 21–28 days following proliferation and commitment to neuronal fate) are the most reliable. With administration of the nucleoside analogue bromodeoxyuridine (BrdU), or expression of the endogenous cell cycle protein Ki67, to label proliferating cells, CMS was shown to reduce cell proliferation in the subgranular zone of the dentate gyrus of the hippocampus (Chen et al., 2009; Xu et al., 2007; Elizalde et al., 2010b; Toth et al., 2008; Sandi et al., 2008; Li et al., 2007, 2008, 2006; Kong et al., 2009; Zhou et al., 2007; Alonso et al., 2004; Liu et al., 2008; Silva et al., 2008; Bessa et al., 2009; Jayatissa et al., 2009; Guo et al., 2009b; Goshen et al., 2008), and effects on proliferation appear to be more robust in the ventral compared to the dorsal hippocampus (Jayatissa et al., 2009, 2006, 2010). This suppression of cell proliferation exhibits some degree of selectivity, since comparable effects on cell proliferation are not seen in the subventricular zone (Silva et al., 2008). Several studies have found no effects of CMS on cell proliferation in the dentate gyrus (Shi et al., 2010; Lee et al., 2006; Sousa et al., 1998; Nowak et al., 2010; Lagunas et al., 2010; Wu and Wang, 2010; Wang et al., 2008; Kim et al., 2006) although it should be noted that in two of these studies CMS successfully suppressed neurogenesis, despite no effect on proliferation (Wang et al., 2008; Kim et al., 2006; Lee et al., 2006). Oddly, one report even found an increase in cell proliferation following CMS, however this was only true in the Lewis strain of rat which is also documented to have alterations in HPA axis function (Wu and Wang, 2010). Because there is a large range of durations and doses of BrdU administered to label dividing cells in studies using BrdU as a marker for cell proliferation, methodological issues may account for some of these discrepancies.

Similar to the reductions in cell proliferation, CMS reliably impairs hippocampal neurogenesis. Through examination of cells positive for BrdU (following a period of days to weeks following administration to rule out an immediate effect of proliferation), counterstained for the expression of neuron-specific proteins doublecortin or neuronal nuclei, CMS was shown to impair neurogenesis and neuronal differentiation in the hippocampus (Toth et al., 2008; Lewitus et al., 2009; Zhou et al., 2007; Silva et al., 2008; Bessa et al., 2009; Goshen et al., 2008; Li et al., 2006; Holderbach et al., 2006; Mineur et al., 2007; Oomen et al., 2007; Hua et al., 2008). Similar to the effects on proliferation, these reductions in neuro-genesis are prominent in the ventral region of the hippocampus (Elizalde et al., 2010b), and are not seen in the subventricular zone, suggesting some degree of regional selectivity (Silva et al., 2008). These effects are also not sex specific as reductions in neurogenesis following CMS are also observed in females (Mineur et al., 2007). Consistent with the reductions in neurogenesis, CMS reduces cell survival in the

hippocampus (Wang et al., 2008; Lee et al., 2006; Mineur et al., 2007; Oomen et al., 2007), an effect that is also seen in females (Mineur et al., 2007).

Thus, for the most part, CMS appears unequivocally to impair neurogenesis in the hippocampus. Recent evidence indicates that CMS also impairs cell proliferation of glial cells and gliogenesis within the frontal cortex (Banasr et al., 2010, 2007; Banasr and Duman, 2008) and hippocampus (Liu et al., 2009). Given the growing interest in glial cells in depression and their role in glutamate clearance at the synapse, this will likely be a growing area of research.

While the effects of CMS on neurogenesis are robust, it is difficult if not impossible to relate them to clinically depressed individuals given the paucity of studies on neurogenesis in human populations. Two studies to date have quantified proliferating cells in the dentate gyrus of the hippocampus. Neither of these studies found a suppression of cell proliferation in the dentate gyrus of depressed individuals (Boldrini et al., 2009; Reif et al., 2006). However, it should be noted that in the study by Reif et al. (2006), nearly all of the subjects had been on antidepressant treatment at the time of death, and in the study by Boldrini et al. (2009), people who had been taking antidepressants exhibited increases in cell proliferation relative to untreated depressed individuals and controls. Further, Boldrini et al. (2009) found that unmedicated, depressed individuals exhibited roughly 50% less proliferating cells in the hippocampus than control subjects, but low subject numbers and high variability prevented this effect from achieving statistical significance. Thus, until further studies regarding neurogenesis in depressed humans are reported, comparisons will be limited. In related research, several studies have reliably documented reductions in hippocampal volume in depressed subjects (Sheline, 1996; Sheline et al., 1999, 2003; MacQueen et al., 2003; Campbell et al., 2004), but whether this reduction is due to suppressed neurogenesis, a loss of glial cells, or a reduction in the dendritic tree has yet to be established.

4. Discussion

A review of studies using the CMS model of depression demonstrates that this paradigm exerts reasonably reliable effects on neurobiological variables that exhibit coincident alterations in clinical populations with major depressive disorder or in suicide victims. This analysis supports the contention that the CMS model exhibits a strong degree of utility in measuring neurobio-logical endpoints that relate to the pathophysiology of depression. More importantly, this analysis also supports the contention that specific neurobiological variables may be used, either alone or in conjunction with behavioral endpoints, to determine the efficacy of antidepressant agents. That is, the reversal of established neurobiological endpoints, which are altered by CMS and dysregulated in depression, by novel antidepressant agents may provide an innovative measure of antidepressant efficacy. As the present review of current literature has indicated, there are a few neurobiological endpoints that satisfy the dual criteria of being reliably altered in the CMS model (that is, the effect is seen by more than one laboratory on more than one occasion) and exhibiting alterations that parallel those observed in clinical depression (however, it should be noted that this is not necessarily a reflection of the model, but more a paucity of both preclinical and clinical data on a common system in a common structure). Our analysis suggests that the following

variables meet these criteria: downregulation of hippocampal 5-HT_{1A} receptors, upregulation of cortical β-adrenoreceptors, downregulation of hippocampal GR, upregulation of prefrontal cortical cannabinoid CB_1 receptors, reductions in frontocortical and hippocampal BDNF protein and reductions in cortical AC-PKA signaling. As such, future studies should be able to employ these markers reliably as endpoints of analysis in the CMS model to investigate the antidepressant potential of novel pharmacotherapeutic agents.

It is possible that the lack of reliability or consistency between and/or within studies with regard to the remaining neurobiological endpoints is simply due to the fact that the CMS paradigm may not accurately model these endpoints. However, it is quite possible that this is due to the lack of consistency between and within laboratories on the CMS methodology. Despite the fact that the initial characterization of the CMS model utilized an 8-week exposure period, the term CMS has been used for studies as short as 7 days in duration. One can see how the broad use of a term such as CMS can result in contradictory findings since the model used with this moniker varies so dramatically from institute to institute. An advantage of doing a large-scale analysis, as we have performed here, is that it facilitates the identification of specific variables that may be important for researchers to consider when employing the CMS model. For example, an important variable that comes to light from this analysis is the precise post-CMS time interval when measurements should ideally be taken. Most studies employing the CMS model performed their tissue extraction on the day following the last day of CMS, a point at which residual effects of CMS would be apparent, but immediate effects of stress exposure would be absent given the lag time since the last stress exposure. However, we observed that when studies employed a longer rest period following CMS exposure (such as 1 week following CMS termination; see Vancassel et al., 2008 versus Haidkind et al., 2003) most of these effects were not present. While these findings are encouraging, in the sense that they suggest a recovery of function following the cessation of stress exposure, they also highlight the importance of consistency in experimental methodology and the importance of standardizing time points of analysis. As such, we would recommend that studies examining the neurobio-logical effects of CMS should perform their tissue extraction within 1 day following the conclusion of the CMS paradigm to maximize the likelihood of detecting a significant effect. In addition, termination of animals at longer time intervals, such as 1 or 2 weeks post-CMS or longer, would provide important information on how long-lasting the effects of CMS are on specific outcome measures. Whether effects are transient or long-lasting is important in extrapolating the adverse effects of chronic stressors from the animal model to the human situation.

Several other methodological variables became apparent in the current analysis, which future investigators should consider when employing the CMS model. For example, housing conditions may be an extremely important variable in determining whether or not an effect of CMS occurs. In studies that employed individually housed animals, there was no effect of CMS on hippocampal CB_1 receptors (Bortolato et al., 2007), while those studies which employed group-housed animals reliably found a reduction in CB_1 receptor activity in the hippocampus (Hill et al., 2005, 2008; Reich et al., 2009). By contrast, CB_1 receptor activity in the prefrontal cortex was upregulated regardless of housing condition (Bortolato et al., 2007; Hill et al., 2008). These data highlight the fact that some effects of CMS may occur independent of housing conditions, while others may be exquisitely sensitive to them. This

may be due to the fact that long-term social isolation is stressful enough for the “control” animals that the baseline itself is altered, making it difficult to detect a further effect of stress. However, reconciliation of this issue is somewhat hindered by the fact that if investigators are planning to perform coordinated behavioral and neurobiological analyses of endpoints, individual housing may be required (e.g., in tests of sucrose consumption), and so housing animals in groups may not be a viable option. In fact, this consideration in turn brings another variable into light for consideration, which is the validation of the CMS paradigm itself within a current study. With respect to behavioral endpoints (see Willner, 2005), there appears to be substantial variability in the ability of a laboratory to achieve an “anhedonic” or depressive-like behavioral phenotype following CMS. As such, the possibility also exists that inconsistencies in the literature regarding neurobiological variables following CMS may reflect whether the “anhedonic” phenotype itself was reached. That is to say, perhaps studies that did not find changes in neurobiological variables following CMS also would not have seen the development of anhedonia in that cohort of animals. The problem with this approach is that it would require all investigators to probe anhedonia in the exact same animals with which they are doing the analysis of neurobiological variables. As mentioned above, to test for sucrose consumption (or any other measure of anhedonia typically), animals require training with the substance and individual housing to be able to accurately measure their individual response. Accordingly, both the engagement in the behavioral task itself or the housing condition of the animal, may influence the neurobio-logical variable of consideration. As such, one caveat researchers must consider if they generate null findings is whether the animals they are analyzing are exhibiting anhedonic traits following CMS, and thus would even be suitable for studies regarding the neuro-biology of depression. One possibility is to validate the paradigm itself within a given laboratory on one cohort of animals, prior to employing this paradigm for neurobiolgical studies. Or researchers could choose to perform behavioral and neurobiological assessments within the same animal. Both of these approaches possess their own limitations, but regardless, these factors should be considered by all researchers before they interpret any data generated from the CMS model. We would advise that any laboratory that is intending to employ the CMS should first validate that, within their environment, the CMS model is sufficient to produce behavioral changes akin to anhedonia or depression. If it is not known whether CMS is capable of producing behavioral changes within a given laboratory, the generation of a null finding will be uninterpretable with respect to whether this is a bona fide null finding or simply did not occur because the paradigm was not producing a “depressive”-like state.

Another variable that comes to light from the current analysis is the duration of CMS to employ. The original CMS paradigm (Willner et al., 1987) was designed as an 8-week paradigm that would allow 3 weeks of initial stress exposure prior to the onset of antidepressant treatment, and would then continue for the following 5 weeks. The rationale behind this comes from a clinical standpoint: simply, depression must be established before the onset of antidepressant treatment. However, the current analysis of the literature demonstrates that many of the effects of CMS, especially the robust and reliable effects, are present as early as 10 days following the onset of CMS exposure, and are nearly all present following 3 weeks of CMS. Furthermore, while not addressed in this review, many studies

have found that concurrent antidepressant administration during this 3-week period alone was sufficient to reverse the effects of CMS. These data would suggest that instead of the traditional 8-week CMS paradigm, a 3-week duration of CMS is likely sufficient for investigating the effects of this model on most neurobiological systems; however, by not having an initial exposure period to stress prior to the administration of antidepressants, this may decrease the validity of the model (as antidepressant treatment would follow the development of depression in a clinical setting and the two would not begin in tandem). Given the time and financial costs associated with employing the 8-week CMS model, the fact that the 3-week model, and perhaps even the 10-day model, appears to be as reliable as the 8-week model makes its employment more feasible for many investigators, but the original 8-week model should be considered if the studies are trying to more accurately model the onset of depression and subsequent administration of an antidepressant.

One point that this review definitively highlights as a drawback in the current CMS research is the paucity of studies employing females. In humans, the incidence and prevalence of depression is dramatically higher in women (Kessler, 2003), yet the majority of preclinical studies employ male as opposed to female rodents. Of particular importance, however, is the fact that the few studies that have employed both females and males have found that many of the alterations that are observed in males do not occur in females (see Dalla et al., 2005). Moreover, females may show unique neurobiological changes that are not observed in males (see Dalla et al., 2005). Undoubtedly, circulating gonadal steroids (particularly estrogens and androgens) contribute to the underlying discrepancy in sex differences with respect to depression rates. Future research must address the sex differences that occur in response to CMS and how these relate to the discrepancy in rates of major depression that occur between men and women, and the role that gonadal hormones play in these differences.

Finally, one additional point worth mentioning is the recent innovative approach some researchers have taken to the utilization of the CMS model. Using concurrent behavioral and neurobiological analyses, several reports have used behavioral analysis of sucrose consumption to identify those rodents which develop an “anhedonic” state following CMS versus those that do not, and subsequently use this subdivision to identify neurobiological changes that may represent epiphenomena of stress versus changes that may be specific to the development of an anehdonic state following stress exposure (Bergstrom et al., 2008, 2007; Jayatissa et al., 2009). In humans, despite significant exposure to chronic stress in our society, only a select population of individuals develop depression. This suggests that there may be specific neurobiological changes which occur following stress that may relate to resilience versus vulnerability to mood disorders (Feder et al., 2009). The employment of the CMS model to separate those animals that develop anhedonia following stress from those that do not may be a novel approach to understand the neurobiology and stress resilence/vulnerability to depression, and may prove to be a very valuable asset of the CMS model.

In conclusion, we have performed a detailed and comprehensive analysis of the studies that have utilized the CMS model of depression to characterize the effects that this paradigm exerts on an array of neurobiological systems. Our hope is that this summary will be valuable to preclinical researchers involved in examining neurobiological substrates of depression or pursuing drug discovery research by providing a comprehensive list of what

studies have been performed, which neurobiological systems have been investigated, and what endpoints of analysis have been shown to be reliable and relevant to depression. On a behavioral level, the CMS model has proven to be a very valuable asset to preclinical research on depression by helping to confirm the effectiveness of conventional antidepressants and identify novel agents for the treatment of depression. The current review extends the utility of this paradigm by demonstrating several neurobiological effects of CMS exposure that are reliably produced across laboratories and parallel alterations that are seen in major depressive disorder. With this established, the CMS model may be more readily accepted as a model of the neurobiology of depression and employed both to identify novel neurobiological systems involved in depression and to allow for the reversal of established neurobiological and behavioral endpoints as markers of antidepressant efficacy.

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Table 1

5-HT.

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Whole brain							
	48	Mice/ICR	28–30 g	M	Single	↑ MAO-A and MAO-B activities	Chen et al. (2007)
	24	Mice/ICR	20–25 g	M	ns	↑ MAO-A and MAO-B activities	Mao et al. (2009b)
	21	Rat/W	200–250 g	F	ns	↑ MAO-A and MAO-B activities; ↓ 5-HT levels	Bhutani et al. (2009)
Frontal cortex							
	56	Mice/BALB/c	6 weeks	M	3–4/cage	↓ 5-HT levels	Vancassel et al. (2008)
	7	Rat/SD	180–200 g	M	4/cage	↓ 5-HT levels	Sheikh et al. (2007)
	28	Rat/W	250–300 g	M	Single	↓ 5-HT levels	Li et al. (2003)
	42	Mice/BALB/cByJ	8–9 weeks	M	Single	↓ 5-HT levels	Yalcin et al. (2008)
	56	Rat/W	220–250 g	M	Single	↓ 5-HT levels	Yi et al. (2008)
	56	Rat/W	220–250 g	M	Single	↓ 5-HT levels	Xu et al. (2008)
	7	Mice/Swiss albino	30–35 g	M	3–4/cage	↓ 5-HT levels	Rasheed et al. (2008)
	63	Rat/W	8 weeks	M	Single	↓ 5-HT levels; ↑ 5-HT1A receptor mRNA; ↔ 5-HT1B or 5-HT7 receptor mRNA	Li et al. (2009a)
	77	Rat/W	180–200 g	M	3–4/cage	↓ 5-HT levels	Vitale et al. (2009)
	7	Rat/SD	180–220 g	M	3/cage	↓ 5-HT levels	Ahmad et al. (2010)
	14	Mice/Kun-ming	18–22 g	M	5/cage	↓ 5-HT levels	Shi et al. (2010)
	42	Rat/SD and W	170–230 g (W); 280–340 g (SD)	M	Single	↔ 5-HT levels, but ↓ 5-HT turnover (SD not W)	Bekris et al. (2005)
	42	Rat/W	3 months	M and F	Single	↔ 5-HT levels (both M and F)	Dalla et al. (2005)
	35	Rat/W	260–390 g	M	Single	↔ 5-HT levels	Haidkind et al. (2003)
	60	Mice/BALB/cByJ and C57/Bl6ByJ	7 weeks	M	4/cage	↔ 5-HT levels	Tannenbaum and Anisman (2003)
	10	Rat/SD	175–250 g	M	3–4/cage	↔ 5-HT levels	Johnson and Yamamoto (2009)
	35	Rat/SD	190–250 g	M and F	Single	↔ 5-HT levels	Dang et al. (2009b)

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
	10	Rat/SD	175–250 g	M	3–4/cage	↔ 5-HT levels	Johnson and Yamamoto (2010)
	14	Mice/Mixed C57/Bl6 and DBA	2–4 months	M	Single	↔ 5-HT levels	Patterson et al. (2010)
	42	Mice/BALBc	2 months	M	Single	↔ 5-HT levels	Laugeray et al. (2010)
	56	Rat/W	300–320 g	M	Single	↑ 5-HT2A receptor binding	Papp et al. (1994a)
	16	Rat/W	200 g	M	Single	↑ 5-HT2A receptor binding	Ossowska et al. (2001)
	16	Rat/W	180–220 g	M	Single	↑ 5-HT2A receptor binding	Ossowska et al. (2002)
	56	Rat/W	6 weeks	M	ns	↓ 5-HT1A receptor binding	Jang et al. (2004)
	70	Rat/W	220–250 g	M	Single	↓ 5-HT1A receptor mRNA	Pan et al. (2010)
Hippocampus							
	56	Mice/BALB/c	6 weeks	M	3–4/cage	↓ 5-HT levels	Vancassel et al. (2008)
	7	Rat/SD	180–200 g	M	4/cage	↓ 5-HT levels	Sheikh et al. (2007)
	28	Rat/W	250–300 g	M	Single	↓ 5-HT levels	Li et al. (2003)
	56	Rat/W	220–250 g	M	Single	↓ 5-HT levels	Yi et al. (2008)
	56	Rat/W	220–250 g	M	Single	↓ 5-HT levels	Xu et al. (2008)
	7	Mice/Swiss albino	30–35 g	M	3–4/cage	↓ 5-HT levels	Rasheed et al. (2008)
	63	Rat/W	8 weeks	M	Single	↓ 5-HT levels; ↑ 5-HT1A and 5-HT7 receptor mRNA; ↔ 5-HT1B receptor mRNA	Li et al. (2009a)
	56	Rat/SD	220–250 g	M	Single	↓ 5-HT levels	Kang et al. (2005)
	28	Rat/SD	180–200 g	M	ns	↓ 5-HT levels	Chen et al. (2009)
	7	Rat/SD	180–220 g	M	3/cage	↓ 5-HT levels	Ahmad et al. (2010)
	14	Mice/Kun-ming	18–22 g	M	5/cage	↓ 5-HT levels	Shi et al. (2010)
	42	Rat/SD and W	170–230 g (W); 280–340 g (SD)	M	Single	↑ 5-HT turnover (both SD and W)	Bekris et al. (2005)
	42	Rat/W	3 months	M and F	Single	↔ 5-HT levels (both M and F), but ↓ 5-HT turnover (F only)	Dalla et al. (2005)
	60	Mice/BALB/cByJ and C57/Bl6ByJ	7 weeks	M	4/cage	↔ 5-HT levels	Tannenbaum and Anisman (2003)
	10	Rat/SD	175–250 g	M	3–4/cage	↔ 5-HT levels	Johnson and Yamamoto (2009)

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
	10	Rat/SD	175–250 g	M	3–4/cage	↔ 5-HT levels	Johnson and Yamamoto (2010)
	14	Mice/Mixed C57/Bl6 and DBA	2–4 months	M	Single	↔ 5-HT levels	Patterson et al. (2010)
	42	Mice/BALBc	2 months	M	Single	↔ 5-HT levels	Laugeray et al. (2010)
	35	Rat/SD	190–250 g	M	Single	↔ 5-HT levels	Dang et al. (2009a)
	35	Rat/SD	190–250 g	M and F	Single	↔ 5-HT levels	Dang et al. (2009b)
	42	Mice/BALB/cByJ	8–9 weeks	M	Single	↔ 5-HT levels	Yalcin et al. (2008)
	28	Rat/SD	11 weeks	M	Single	↔ 5-HT levels	Gronli et al. (2007)
	14	Rat/SD	250–300 g	M	6/cage	↓ 5-HT1A receptor mRNA and binding (CA1, CA3 and DG); ↔ 5-HT transporter binding	Lopez et al. (1998)
	10	Rat/SD	175–200 g	M	3–4/cage	↔ 5-HT transporter protein (whole hippocampus)	Cunningham et al. (2009)
	56	Rat/W	300–320 g	M	Single	↓ 5-HT1A receptor binding (whole hippocampus)	Papp et al. (1994a)
	35	Rat/W	260–390 g	M	Single	↔ 5-HT1A receptor binding (whole hippocampus)	Haidkind et al. (2003)
	56	Rat/W	6 weeks	M	ns	↓ 5-HT1A receptor binding (CA1, CA3 and DG)	Jang et al. (2004)
	19 and 28	Rat/SD	210–250 g	M	2/cage	↓ 5-HT1A receptor mRNA and protein (whole hippocampus)	Wang et al. (2009)
	70	Rat/W	220–250 g	M	Single	↓ 5-HT1A receptor mRNA (whole hippocampus)	Pan et al. (2010)
	20	Rat/SD	190–200 g	M	6/cage	↓ 5-HT1A receptor mRNA (CA1 and DG)	Xu et al. (2007)
	21	Rat/W	145–155 g	M	2/cage	↔ 5-HT1A receptor mRNA (CA1, CA3 and DG)	van Riel et al. (2003)
	7	Rat/W	250 g	M	3/cage	↑ 5-HT7 receptor mRNA (CA3 only)	Yau et al. (2001)
Hypothalamus							
	42	Rat/SD and W	170–230 g (W); 280–340 g (SD)	M	Single	↑ 5-HT turnover (W not SD)	Bekris et al. (2005)
	56	Rat/W	220–250 g	M	Single	↓ 5-HT levels	Yi et al. (2008)
	56	Rat/W	220–250 g	M	Single	↓ 5-HT levels	Xu et al. (2008)
	63	Rat/W	8 weeks	M	Single	↓ 5-HT levels; ↑ 5-HT1A, 5-HT1B and	Li et al. (2009a)

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
						5-HT7 receptor mRNA	
	42	Rat/W	3 months	M and F	Single	↔ 5-HT levels or 5-HT turnover (both M and F)	Dalla et al. (2005)
	35	Rat/W	260–390 g	M	Single	↔ 5-HT levels	Haidkind et al. (2003)
	60	Mice/BALB/cByJ and C57/Bl6ByJ	7 weeks	M	4/cage	↔ 5-HT levels (PVN); ↑ 5-HT utilization (ME)	Tannenbaum and Anisman (2003)
	14	Mice/CD1	90 days	M	Single	↔ 5-HT levels (PVN)	Sudom et al. (2004)
	54	Mice/CD1	10 weeks	M	4/cage	↔ 5-HT levels (PVN); ↑ 5-HT utilization (ME)	Tannenbaum et al. (2002)
	14	Mice/Mixed C57/Bl6 and DBA	2–4 months	M	Single	↔ 5-HT levels (PVN)	Patterson et al. (2010)
	56	Rat/W	6 weeks	M	ns	↓ 5-HT1A receptor binding	Jang et al. (2004)
Striatum							
	56	Mice/BALB/c	6 weeks	M	3–4/cage	↓ 5-HT levels	Vancassel et al. (2008)
	42	Mice/BALB/cByJ	8–9 weeks	M	Single	↓ 5-HT levels	Yalcin et al. (2008)
	56	Rat/W	220–250 g	M	Single	↓ 5-HT levels	Xu et al. (2008)
	56	Rat/W	220–250 g	M	Single	↔ 5-HT levels (whole striatum); ↓ 5-HT levels (nucleus accumbens)	Yi et al. (2008)
	7	Rat/SD	180–220 g	M	3/cage	↓ 5-HT levels	Ahmad et al. (2010)
	42	Rat/SD and W	170–230 g (W); 280–340 g (SD)	M	Single	↔ 5-HT levels or turnover (both SD and W)	Bekris et al. (2005)
	28	Rat/W	250–300 g	M	Single	↔ 5-HT levels	Li et al. (2003)
	10	Rat/SD	175–250 g	M	3–4/cage	↔ 5-HT levels	Johnson and Yamamoto (2009)
	10	Rat/SD	175–250 g	M	3–4/cage	↔ 5-HT levels	Johnson and Yamamoto (2010)
	10	Rat/SD	175–200 g	M	2/cage	↔ 5-HT levels	Tata and Yamamoto (2008)
	42	Mice/BALBc	2 months	M	Single	↔ 5-HT levels	Laugeray et al. (2010)
Amygdala							
	60	Mice/BALB/cByJ and C57/Bl6ByJ	7 weeks	M	4/cage	↑ 5-HT utilization	Tannenbaum and Anisman (2003)
	42	Mice/BALBc	2 months	M	Single	↔ 5-HT levels	Laugeray et al. (2010)

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
	14	Mice/Mixed C57/Bl6 and DBA	2–4 months	M	Single	↔ 5-HT levels	Patterson et al. (2010)
Raphe nucleus							
	42	Mice/BALB/cByJ	8–9 weeks	M	Single	↓ 5-HT levels	Yalcin et al. (2008)
	21	Rat/W	175–250 g	M	ns	↓ 5-HT levels	Yang et al. (2008)
	28	Mice/B6C3f1	10–12 weeks	F	6/cage	↓ Sensitivity of somatodendritic 5-HT1A receptors	Froger et al. (2004)
	42	Rat/W	250–260 g	M	2–3/cage	↓ Sensitivity of somatodendritic 5-HT1A receptors	Bambico et al. (2009)
Hindbrain							
	28	Rat/W	250–300 g	M	Single	↓ 5-HT levels (medulla oblongata)	Li et al. (2003)
	77	Rat/W	180–200 g	M	3–4/cage	↑ 5-HT levels (pons)	Vitale et al. (2009)
	42	Mice/BALB/cByJ	8–9 weeks	M	Single	↔ 5-HT levels (cerebellum)	Yalcin et al. (2008)

Table 2

NE.

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Whole brain							
	21	Rat/W	200–250 g	F	ns	↔ NE levels	Bhutani et al. (2009)
Frontal cortex							
	56	Mice/BALB/c	6 weeks	M	3–4/cage	↓ NE levels	Vancassel et al. (2008)
	7	Rat/SD	180–200 g	M	4/cage	↓ NE levels	Sheikh et al. (2007)
	42	Mice/BALB/cByJ	8–9 weeks	M	Single	↓ NE levels	Yalcin et al. (2008)
	7	Mice/Swiss albino	30–35 g	M	3–4/cage	↓ NE levels	Rasheed et al. (2008)
	35	Rat/SD	190–250 g	M and F	Single	↓ NE levels	Dang et al. (2009b)
	14	Mice/Kun-ming	18–22 g	M	5/cage	↓ NE levels	Shi et al. (2010)
	56	Rat/W	220–250 g	M	Single	↔ NE levels	Yi et al. (2008)
	60	Mice/BALB/cByJ and C57/Bl6ByJ	7 weeks	M	4/cage	↔ NE levels	Tannenbaum and Anisman (2003)
	14	Mice/Mixed C57/Bl6 and DBA	2–4 months	M	Single	↔ NE levels	Patterson et al. (2010)
	14	Rat/SD	200–250 g	M	Single	↔ NE levels	Bondi et al. (2010)
	14	Rat/W	286–360 g	M	Single	↔ NE levels	Harro et al. (2001)
	35	Rat/W	260–390 g	M	Single	↔ NE levels; ↑ β-adrenoceptor receptor binding; ↔ α-adrenoceptor binding	Haidkind et al. (2003)
	56	Rat/W	300–320 g	M	Single	↑ β-adrenoceptor receptor binding	Papp et al. (1994a)
	7	Rat/W	12 weeks	M	6/cage	↑ β-adrenoceptor receptor binding	Basso et al. (1993)
	14	Rat/W	280–350 g	M	4–6/cage	↑ β-adrenoceptor receptor binding	Molina et al. (1990)
	56	Rat/W	ns	M	Single	↑ β-adrenoceptor receptor binding and cAMP generation	Papp et al. (2002)
Hippocampus							
	35	Rat/SD	190–250 g	M	Single	↓ NE levels	Dang et al. (2009a)
	35	Rat/SD	190–250 g	M and F	Single	↓ NE levels	Dang et al. (2009b)
	42	Mice/BALB/cByJ	8–9 weeks	M	Single	↓ NE levels	Yalcin et al. (2008)
	7	Rat/SD	180–200 g	M	4/cage	↓ NE levels	Sheikh et al. (2007)

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
	7	Mice/Swiss albino	30–35 g	M	3–4/cage	↓ NE levels	Rasheed et al. (2008)
	14	Mice/Kun-ming	18–22 g	M	5/cage	↓ NE levels	Shi et al. (2010)
	56	Mice/BALB/c	6 weeks	M	3–4/cage	↔ NE levels	Vancassel et al. (2008)
	56	Rat/W	220–250 g	M	Single	↔ NE levels	Yi et al. (2008)
	60	Mice/BALB/cByJ and C57/Bl6ByJ	7 weeks	M	4/cage	↔ NE levels	Tannenbaum and Anisman (2003)
	14	Mice/Mixed C57/Bl6 and DBA	2–4 months	M	Single	↔ NE levels	Patterson et al. (2010)
	14	Rat/W	286–360 g	M	Single	↔ NE levels	Harro et al. (2001)
	14	Rat/SD	250–320 g	M	4/cage	↑ NE levels	Prieto et al. (2003)
	15	Rat/W	ns	M	Single	↔ β-adrenoceptor receptor binding	Harro et al. (1999)
Hypothalamus							
	56	Rat/W	220–250 g	M	Single	↔ NE levels	Yi et al. (2008)
	35	Rat/W	260–390 g	M	Single	↔ NE levels	Haidkind et al. (2003)
	60	Mice/BALB/cByJ and C57/Bl6ByJ	7 weeks	M	4/cage	↔ NE levels (PVN and ME)	Tannenbaum and Anisman (2003)
	54	Mice/CD1	10 weeks	M	4/cage	↔ NE levels (PVN, ME and ARC)	Tannenbaum et al. (2002)
	14	Mice/Mixed C57/Bl6 and DBA	2–4 months	M	Single	↔ NE levels (ARC); ↑ NE utilization (PVN)	Patterson et al. (2010)
	14	Mice/CD1	90 days	M	Single	↑ NE utilization (PVN)	Sudom et al. (2004)
	14	Rat/SD	250–320 g	M	4/cage	↑ NE levels	Prieto et al. (2003)
Striatum							
	56	Mice/BALB/c	6 weeks	M	3–4/cage	↓ NE levels	Vancassel et al. (2008)
	42	Mice/BALB/cByJ	8–9 weeks	M	Single	↓ NE levels	Yalcin et al. (2008)
	56	Rat/W	220–250 g	M	Single	↔ NE levels (whole striatum and nucleus accumbens)	Yi et al. (2008)
Amygdala							
	60	Mice/BALB/cByJ and C57/Bl6ByJ	7 weeks	M	4/cage	↔ NE levels	Tannenbaum and Anisman (2003)
	14	Mice/Mixed C57/Bl6 and DBA	2–4 months	M	Single	↑ NE utilization	Patterson et al. (2010)
Septum							

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
	14	Rat/W	286–360 g	M	Single	↔ NE levels	Harro et al. (2001)
Hindbrain							
	15	Rat/W	ns	M	Single	↔ NE levels (cerebellum)	Harro et al. (1999)
Locus coeruleus							
	14	Mice/Mixed C57/Bl6 and DBA	2–4 months	M	Single	↔ NE levels or utilization	Patterson et al. (2010)
	21	Rat/SD	320–380 g (M); 210–250 (F)	M and F	Single	↓ mRNA levels of tyrosine hydroxylase	Duncko et al. (2001)

Table 3

Dopamine.

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Whole brain							
	21	Rat/W	200–250 g	F	ns	↓ DA levels	Bhutani et al. (2009)
Limbic forebrain							
	56	Rat/W	350–370 g	M	Single	↓ D2 receptor binding	Papp et al. (1994b)
	16	Rat/W	200 g	M	Single	↑ D1 receptor binding	Ossowska et al. (2001)
	16	Rat/W	180–220 g	M	Single	↑ D1 receptor binding	Ossowska et al. (2002)
Frontal cortex							
	7	Rat/SD	180–200 g	M	4/cage	↓ DA levels	Sheikh et al. (2007)
	42	Rat/SD and W	170–230 g (W); 280–340 g (SD)	M	Single	↓ DA levels (W); ↑ DA levels (SD)	Bekris et al. (2005)
	7	Mice/Swiss albino	30–35 g	M	3–4/cage	↓ DA levels	Rasheed et al. (2008)
	35	Rat/SD	190–250 g	M	Single	↓ DA levels	Dang et al. (2009a)
	35	Rat/SD	190–250 g	M and F	Single	↓ DA levels	Dang et al. (2009b)
	7	Rat/SD	180–220 g	M	3/cage	↓ DA levels	Ahmad et al. (2010)
	14	Mice/Kun-ming	18–22 g	M	5/cage	↓ DA levels	Shi et al. (2010)
	7	Rat/SD	180–200 g	M	3–4/cage	↓ DA levels; ↓ D1 receptor binding; ↔ D2 receptor binding	Rasheed et al. (2010)
	42	Rat/W	3 months	M and F	Single	↓ DA turnover (F not M)	Dalla et al. (2008)
	14	Rat/W	286–360 g	M	Single	↔ DA levels	Harro et al. (2001)
	35	Rat/W	260–390 g	M	Single	↔ DA levels	Haidkind et al. (2003)
	60	Mice/BALB/cByJ and C57/Bl6ByJ	7 weeks	M	4/cage	↔ DA levels	Tannenbaum and Anisman (2003)
	10	Rat/SD	175–250 g	M	3–4/cage	↔ DA levels	Johnson and Yamamoto (2009)
	10	Rat/SD	175–250 g	M	3–4/cage	↔ DA levels	Johnson and Yamamoto (2010)
	14	Mice/Mixed C57/Bl6 and DBA	2–4 months	M	Single	↔ DA levels	Patterson et al. (2010)
	28	Rat/SD	250–280 g	M	Single	↔ DA levels (basal); ↑ DA release in response to stress	Di Chiara et al. (1999)

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
	7	Rat/W	280–300 g	M	4/cage	↔ DA levels (basal); ↑ DA release in response to stress	Cuadra et al. (2001)
	56	Rat/W	220–250 g	M	Single	↑ DA levels	Yi et al. (2008)
Striatum							
	7	Mice/Swiss albino	30–35 g	M	3–4/cage	↓ DA levels (nucleus accumbens)	Rasheed et al. (2008)
	7	Rat/SD	180–200 g	M	3–4/cage	↓ DA levels; ↑ D1 receptor binding; ↔ D2 receptor binding	Rasheed et al. (2010)
	7	Rat/SD	180–220 g	M	3/cage	↓ DA levels	Ahmad et al. (2010)
	42	Rat/W	3 months	M and F	Single	↔ DA turnover	Dalla et al. (2008)
	10	Rat/SD	175–250 g	M	3–4/cage	↔ DA levels (nucleus accumbens)	Johnson and Yamamoto (2009)
	10	Rat/SD	175–250 g	M	3–4/cage	↔ DA levels (nucleus accumbens)	Johnson and Yamamoto (2010)
	28	Rat/SD	250–280 g	M	Single	↔ DA levels (basal); ↑ DA release in response to stress; ↓ DA release in response to reward (nucleus accumbens)	Di Chiara et al. (1999)
	10	Rat/SD	175–200 g	M	2/cage	↔ DA levels (nucleus accumbens)	Tata and Yamamoto (2008)
	10	Rat/SD	175–200 g	M	2/cage	↔ DA levels (nucleus accumbens)	Raudensky and Yamamoto (2007a)
	14	Mice/Mixed C57/Bl6 and DBA	2–4 months	M	Single	↑ DA utilization (nucleus accumbens)	Patterson et al. (2010)
	60	Mice/BALB/cByJ and C57/Bl6ByJ	7 weeks	M	4/cage	↑ DA utilization (BALBc only, not C57; nucleus accumbens)	Tannenbaum and Anisman (2003)
	56	Rat/W	220–250 g	M	Single	↑ DA levels (nucleus accumbens)	Yi et al. (2008)
	42	Rat/SD and W	170–230 g (W); 280–340 g (SD)	M	Single	↓ DA levels (W); ↑ DA levels (SD)	Bekris et al. (2005)
	35	Rat/W	260–390 g	M	Single	↔ D2 receptor binding	Haidkind et al. (2003)
	56	Rat/W	350–370 g	M	Single	↑ D1 receptor binding; ↔ D2 receptor binding	Papp et al. (1994b)
	56	Rat/W	300–350 g	M	Single	↓ D2 receptor mRNA expression (nucleus accumbens)	Dziedzicka-Wasylewska et al. (1997)
	28	Rat/W	350 g	M	Single	↔ D1 or D2 receptor mRNA expression (nucleus accumbens)	Bergstrom et al. (2008)
Hypothalamus							

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
	42	Rat/SD and W	170–230 g (W); 280–340 g (SD)	M	Single	↓ DA levels (W); ↔ DA levels (SD)	Bekris et al. (2005)
	42	Rat/W	3 months	M and F	Single	↔ DA levels or turnover	Dalla et al. (2008)
	56	Rat/W	220–250 g	M	Single	↔ DA levels	Yi et al. (2008)
	35	Rat/W	260–390 g	M	Single	↔ DA levels	Haidkind et al. (2003)
	54	Mice/CD1	10 weeks	M	4/cage	↔ DA levels (PVN, ME and ARC)	Tannenbaum et al. (2002)
	14	Mice/Mixed C57/Bl6 and DBA	2–4 months	M	Single	↔ DA levels (PVN)	Patterson et al. (2010)
Hippocampus							
	7	Rat/SD	180–200 g	M	4/cage	↓ DA levels	Sheikh et al. (2007)
	7	Mice/Swiss albino	30–35 g	M	3–4/cage	↓ DA levels	Rasheed et al. (2008)
	7	Rat/SD	180–200 g	M	3–4/cage	↓ DA levels; ↑ D1 receptor binding; ↔ D2 receptor binding	Rasheed et al. (2010)
	35	Rat/SD	190–250 g	M	Single	↓ DA levels	Dang et al. (2009a)
	35	Rat/SD	190–250 g	M and F	Single	↓ DA levels	Dang et al. (2009b)
	7	Rat/SD	180–220 g	M	3/cage	↓ DA levels	Ahmad et al. (2010)
	14	Mice/Kun-ming	18–22 g	M	5/cage	↓ DA levels	Shi et al. (2010)
	14	Rat/W	286–360 g	M	Single	↔ DA levels	Harro et al. (2001)
	42	Rat/W	3 months	M and F	Single	↔ DA levels	Dalla et al. (2008)
Amygdala							
	7	Rat/SD	180–200 g	M	3–4/cage	↓ DA levels, D1 or D2 receptor binding	Rasheed et al. (2010)
Septum							
	14	Rat/W	286–360 g	M	Single	↔ DA levels	Harro et al. (2001)
Orbitofrontal cortex							
	7	Rat/SD	180–200 g	M	3–4/cage	↔ DA levels, D1 or D2 receptor binding	Rasheed et al. (2010)
Midbrain							
	56	Rat/W	300–350 g	M	Single	↓ D2 receptor mRNA expression (VTA and SN)	Dziedzicka-Wasylewska et al. (1997)
	10	Rat/SD, F and L	170–185 g	M	3/cage	↑ tyrosine hydroxylase protein (VTA in SD, F, not L); ↔ tyrosine hydroxylase (SN)	Ortiz et al. (1996)

Table 4

GABA.

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Hippocampus							
	28	Rat/SD	9 weeks	M	Single	↓ GABA levels	Gronli et al. (2007)
	42	Mice/C57Bl/6	ns	M	ns	↓ GABA levels; ↓ protein expression of vGAT and GAD65	Garcia-Garcia et al. (2009)
	42	Mice/C57Bl/6	8–10 weeks	M	Single	↓ GABA levels; ↓ protein expression of GAD65 (only in ventral, not dorsal, hippocampus)	Elizalde et al. (2010a)
	15	Rat/SD	240–320 g	M	3/cage	↑ GAD67 mRNA expression (CA3 and DG, not CA1); ↔ GAD65 mRNA	Bowers et al. (1998)
	7	Rat/SD	250–300 g	M	3/cage	↔ GAD65 or GAD67 mRNA expression (CA1 and DG)	Herman et al. (2003)
	21	Rat/SD	300–350 g	M	2/cage	↑ β2 subunit, ↔ β1 or β3 subunit, of GABA-A receptor (CA1, CA3, DG) mRNA expression	Cullinan and Wolfe (2000)
Frontal cortex							
	42	Mice/C57Bl/6	ns	M	ns	↓ GABA levels; ↓ protein expression of vGAT and GAD65	Garcia-Garcia et al. (2009)
	7	Rat/SD	250–300 g	M	3/cage	↔ GAD65 or GAD67 mRNA expression	Herman et al. (2003)
	14	Rat/F	3, 15 and 30 months	M	3/cage	↔ GAD65 or GAD67 mRNA expression (all ages)	Herman and Larson (2001)
Hypothalamus							
	15	Rat/SD	240–320 g	M	3/cage	↑ GAD67 mRNA (MPOA); ↑ GAD65 mRNA (AHA, DMN, MPOA, SCN, PVN)	Bowers et al. (1998)
	14	Rat/F	3, 15 and 30 months	M	3/cage	↓ GAD65 mRNA (only 30 months old; MPOA, not AHA); ↔ GAD67 mRNA (all ages; MPOA and AHA)	Herman and Larson (2001)
	7	Rat/SD	250–300 g	M	3/cage	↔ GAD65 or GAD67 mRNA expression (DMH)	Herman et al. (2003)
	21	Rat/SD	300–350 g	M	2/cage	↑ β1 and β2 subunit, ↔ β3 subunit, of GABA-A receptor (PVN) mRNA expression	Cullinan and Wolfe (2000)
	21	Rat/W	120–140 g	M	2/cage	↑ GABA-A α5 subunit mRNA; ↓ GABA-A δ subunit mRNA (PVN)	Verkuyl et al. (2004)
Amygdala							
	7	Rat/SD	250–300 g	M	3/cage	↔ GAD65 or GAD67 mRNA expression (CeA and MeA)	Herman et al. (2003)
Septum							
	7	Rat/SD	250–300 g	M	3/cage	↔ GAD65 or GAD67 mRNA expression	Herman et al. (2003)
BNST							

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
	15	Rat/SD	240–320 g	M	3/cage	↑ GAD67 and GAD65 mRNA (anterior but not posterior regions)	Bowers et al. (1998)
	14	Rat/F	3, 15 and 30 months	M	3/cage	↓ GAD65 mRNA (only 30 months old; anterior but not posterior regions); ↔ GAD67 mRNA (all ages)	Herman and Larson (2001)
	7	Rat/SD	250–300 g	M	3/cage	↔ GAD65 or GAD67 mRNA expression (all regions)	Herman et al. (2003)

Table 5

Glutamate.

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Hippocampus							
	10	Rat/SD	175–200 g	M	3/cage	↑ Vesicular glutamate levels, EAAT-2 and vGLUT1 expression	Gronli et al. (2007)
	42	Mice/C57Bl/6	ns	M	ns	↑ Glutamate levels and EAAT-1; ↔ vGLUT1 or vGLUT2 expression	Garcia-Garcia et al. (2009)
	42	Mice/C57Bl/6	8–10 weeks	M	Single	↓ vGLUT1 protein (ventral, not dorsal, hippocampus); ↔ glutamate levels (measured 4 weeks following end of CMS)	Elizalde et al. (2010a)
	42	Mice/C57Bl/6	8–10 weeks	M	Single	↓ vGLUT1 mRNA (CA1, but not CA3 or DG) and vGLUT1 protein (whole hippocampus)	Elizalde et al. (2010b)
	15	Rat/SD	240–320 g	M	3/cage	↑ GAD67 mRNA expression (CA3 and DG, not CA1); ↔ GAD65 mRNA	Bowers et al. (1998)
	32	Rat/W	230–270 g	M	ns	↑ Glutamate levels; ↓ NR2A and NR2B expression; ↔ NR1 expression	Lou et al. (2010)
	28	Rat/SD	30 and 60 days old	M	Single	↓ GluR1 protein expression (dorsal, not ventral, DG, 60 days old only)	Toth et al. (2008)
	63	Rat/W	ns	M	Single	↑ mGluR5 protein (CA1); ↓ mGluR5 protein (CA3); ↔ mGluR5 protein (DG)	Wieronska et al. (2001)
Frontal cortex							
	42	Mice/C57Bl/6	ns	M	ns	↑ Glutamate levels; ↔ vGLUT1, vGLUT2, EAAT-1 or EAAT-2 expression	Garcia-Garcia et al. (2009)
	42	Mice/C57Bl/6	8–10 weeks	M	Single	↔ Glutamate levels (measured 4 weeks following end of CMS)	Elizalde et al. (2010a)
	42	Mice/C57Bl/6	8–10 weeks	M	Single	↓ vGLUT1 mRNA, but ↔ vGLUT1 protein	Elizalde et al. (2010b)
	35	Rat/SD	25–300 g	M	ns	↓ Glial glutamate metabolism; ↔ EAAT-1 and EAAT-2 expression	Banasr et al. (2010)
	32	Rat/W	230–270 g	M	ns	↑ Glutamate levels; ↓ NR2A and NR2B expression; ↔ NR1 expression	Lou et al. (2010)
	56	Rat/W	200 g	M	Single	↓ NMDA/glycine receptor binding	Nowak et al. (1998)
	28	Rat/SD	30 and 60 days old	M	Single	↓ GluR1 protein expression (both ages)	Toth et al. (2008)
Striatum							
	10	Rat/SD	175–200 g	M	2/cage	↔ Glutamate levels	Tata and Yamamoto (2008)
	28	Rat/SD	30 and 60 days old	M	Single	↑ GluR1 protein expression (anterior nucleus accumbens; 60 days old only)	Toth et al. (2008)

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Hypothalamus							
	28	Rat/SD	285–385 g	M	3/cage	↓ NR2B mRNA, ↔ NR2A or NR1 mRNA (PVN)	Ziegler et al. (2005)
VTA							
	28	Rat/SD	30 and 60 days old	M	Single	↔ GluR1 protein expression (both ages)	Toth et al. (2008)
	10	Rat/SD	200–250 g	M	3–4/cage	↑ NR1 and GluR1 protein expression	Fitzgerald et al. (1996)

Table 6

Acetylcholine.

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Hippocampus							
	35	Rat/SD	190–250 g	M and F	Single	↑ Cholinesterase expression	Dang et al. (2009b)
	21	Mice/Kun-ming	18–22 g	M	5/cage	↓ Muscarinic cholinergic receptor binding	Zhang et al. (2007)
	5	Rat/SD	3–4 months	M	ns	↔ Acetylcholinesterase activity	Das et al. (2005)
Frontal cortex							
	21	Mice/Kun-ming	18–22 g	M	5/cage	↓ Muscarinic cholinergic receptor binding	Zhang et al. (2007)
	5	Rat/SD	3–4 months	M	ns	↓ Acetylcholinesterase activity	Das et al. (2005)
Hypothalamus							
	21	Mice/Kun-ming	18–22 g	M	5/cage	↔ Muscarinic cholinergic receptor binding	Zhang et al. (2007)
	5	Rat/SD	3–4 months	M	ns	↓ Acetylcholinesterase activity	Das et al. (2005)
Striatum							
	5	Rat/SD	3–4 months	M	ns	↓ Acetylcholinesterase activity	Das et al. (2005)

Table 7

Mineralocorticoid and glucocorticoid receptors.

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Hippocampus							
	70	Rat/W	220–250 g	M	Single	↓ GR mRNA (whole hippocampus)	Pan et al. (2010)
	28	Rat/SD	150–200 g	M	Single	↓ GR mRNA (whole hippocampus)	Zheng et al. (2006)
	20	Rat/SD	190–200 g	M	6/cage	↓ GR mRNA (whole hippocampus)	Xu et al. (2006)
	42	Mice/ICR	20–25 g	M	ns	↓ GR mRNA (whole hippocampus)	Mao et al. (2009a)
	21	Rat/SD	8 weeks	M	Single	↓ GR and MR mRNA (whole hippocampus)	Yin et al. (2007)
	28	Mice/B6C3f1	10–12 weeks	F	6/cage	↓ GR mRNA and cytosolic binding (whole hippocampus)	Froger et al. (2004)
	18	Rat/SD	10 weeks	M and F	Single	↓ GR and MR cytosolic binding (whole hippocampus; M, not F)	Kim et al. (1999)
	30	Rat/SD	250–300 g	M	3/cage	↓ GR mRNA (CA1 and DG, not CA3); ↓ MR mRNA (CA1, CA3 and DG)	Herman et al. (1995)
	7	Rat/W	250 g	M	3/cage	↓ GR mRNA (DG, not CA1 or CA3); ↓ MR mRNA (CA1, CA3 and DG)	Yau et al. (2001)
	28	Rat/SD	250–300 g	M	6/cage	↔ GR mRNA (CA1–4, DG); ↓ MR mRNA (CA2, CA3–4, not CA1 or DG)	Lopez et al. (1998)
	21	Rat/W	145–155 g	M	2/cage	↔ GR mRNA (CA1, CA3 and DG); ↑ MR mRNA (DG, no effect in CA1 or CA3)	van Riel et al. (2003)
Frontal cortex							
	28	Mice/B6C3f1	10–12 weeks	F	6/cage	↓ GR mRNA and cytosolic binding	Froger et al. (2004)
	30	Rat/SD	250–300 g	M	3/cage	↓ GR mRNA; ↔ MR mRNA	Herman et al. (1995)
	70	Rat/W	220–250 g	M	Single	↔ GR mRNA	Pan et al. (2010)
Raphe							
	28	Mice/B6C3f1	10–12 weeks	F	6/cage	↑ GR mRNA	Froger et al. (2004)
Hypothalamus							
	70	Rat/W	220–250 g	M	Single	↔ GR mRNA	Pan et al. (2010)

Table 8

CRH and AVP.

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Hypothalamus							
	28	Rat/SD	285–385 g	M	3/cage	↑ CRH mRNA (PVN)	Ziegler et al. (1999)
	30	Rat/SD	250–300 g	M	3/cage	↑ CRH and AVP mRNA (PVN)	Herman et al. (1995)
	7	Rat/SD	175–200 g	M	3/cage	↑ CRH mRNA (PVN; effect gone by 4 days after CMS); ↔ AVP mRNA (PVN)	Ostrander et al. (2006)
	14	Rat/SD	275–300 g	M	3/cage	↑ CRH mRNA and ↔ AVP mRNA (PVN)	Choi et al. (2008a)
	14	Rat/SD	275–300 g	M	3/cage	↑ CRH mRNA and ↔ AVP mRNA (PVN)	Choi et al. (2008b)
	30	Rat/SD	275–325 g	M	3/cage	↑ CRH mRNA and ↔ AVP mRNA (PVN)	Prewitt and Herman (1997)
	21	Rat/SD	320–380 g (M); 210–250 (F)	M and F	Single	↑ CRH mRNA (PVN; M not F)	Duncko et al. (2001)
	28	Rat/W	350 g	M	Single	↑ CRH mRNA and ↔ AVP mRNA (PVN)	Bergstrom et al. (2008)
	13	Rat/SD	150–250 g	M	2/cage	↑ CRH protein (periventricular nucleus); ↔ CRH protein (MPOA, VMN, DMH); ↓ CRH protein (ME/ARC)	Chappell et al. (1986)
	19	Rat/W	350 g	M	Single	↔ CRH mRNA (PVN)	Stout et al. (2000)
	19	Rat/SD	200–220 g	M	Single	↔ CRH mRNA (PVN)	Kim et al. (2006)
	21	Rat/SD	240–260 g	M	6/cage	↑ CRH immunoreactive neurons (PVN)	Wang et al. (2010b)
	21	Rat/SD	8 weeks	M	Single	↑ CRH mRNA (whole hypothalamus)	Yin et al. (2007)
	70	Rat/W	220–250 g	M	Single	↑ CRH mRNA and protein (whole hypothalamus); ↔ CRHR1 mRNA or protein (whole hypothalamus)	Pan et al. (2010)
	70	Rat/W	220–250 g	M	Single	↑ CRH protein (whole hypothalamus)	Pan et al. (2007)
	21	Rat/SD	200–220 g	M	Single	↑ CRH mRNA (whole hypothalamus)	Guo et al. (2009a)
	49	Mice/C57Bl/6 and BALB/cByJ	9 weeks	M	Single	↑ CRH protein (ME; C57 only); ↔ AVP protein (ME)	Anisman et al. (2007)
BNST							
	19	Rat/W	350 g	M	Single	↑ CRH protein	Stout et al. (2000)

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
	19	Rat/SD	200–220 g	M	Single	↑ CRH mRNA (dorsal, not ventral BNST)	Kim et al. (2006)
	13	Rat/SD	150–250 g	M	2/cage	↔ CRH protein	Chappell et al. (1986)
Amygdala							
	19	Rat/W	350 g	M	Single	↔ CRH protein or receptor binding	Stout et al. (2000)
	19	Rat/SD	200–220 g	M	Single	↔ CRH mRNA (CeA)	Kim et al. (2006)
	21	Rat/SD	240–260 g	M	6/cage	↑ CRH immunoreactive neurons (CeA)	Wang et al. (2010b)
	21	Rat/SD	ns	M	Single	↔ CRH mRNA (CeA)	Sandi et al. (2008)
Hippocampus							
	70	Rat/W	220–250 g	M	Single	↑ CRH mRNA and protein; ↔ CRHR1 mRNA or protein	Pan et al. (2010)
	70	Rat/W	220–250 g	M	Single	↑ CRH protein (whole hypothalamus)	Pan et al. (2007)
	13	Rat/SD	150–250 g	M	2/cage	↔ CRH protein	Chappell et al. (1986)
	10	Rat/SD	150–170 g	M	ns	↑ CRHR1 mRNA	Iredale et al. (1996)
Frontal cortex							
	70	Rat/W	220–250 g	M	Single	↑ CRH protein; ↔ CRHR1 mRNA or protein or CRH mRNA	Pan et al. (2010)
	70	Rat/W	220–250 g	M	Single	↑ CRH protein	Pan et al. (2007)
	13	Rat/SD	150–250 g	M	2/cage	↔ CRH protein	Chappell et al. (1986)
	19	Rat/W	350 g	M	Single	↔ CRH protein or CRHR1 protein or receptor binding	Stout et al. (2000)
	10	Rat/SD	150–170 g	M	ns	↓ CRHR1 mRNA	Iredale et al. (1996)
	49	Mice/C57Bl/6 and BALB/cByJ	9 weeks	M	Single	↓ CRHR1 mRNA and protein; ↔ CRHR2 mRNA (in orbitofrontal cortex)	Anisman et al. (2007)

Table 9

Opioids.

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Nucleus accumbens							
	21	Rat/LE	ns	M	Single	↔ Basal met-enkephalin levels, but no increase following social interaction	Bertrand et al. (1997)
	56	Rat/W	300–350 g	M	Single	↑ Met-enkephalin levels	Dziedzicka-Wasylewska and Papp (1996)
	28	Rat/W	350 g	M	Single	↔ Enkephalin and dynorphin mRNA levels	Bergstrom et al. (2008)
VTA							
	56	Rat/W	300–350 g	M	Single	↔ Met-enkephalin levels	Dziedzicka-Wasylewska and Papp (1996)

Table 10

Neuropeptides.

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Whole brain							
	35	Mice/C57Bl/6	2–3 months	M	3–5/cage	↔ MCHR1 mRNA	Roy et al. (2007)
Frontal cortex							
	35	Mice/C57Bl/6	2–3 months	M	3–5/cage	↔ MCHR1 mRNA	Roy et al. (2007)
	10	Rat/SD	260–300 g	M	2/cage	↔ NOFQ protein levels	Devine et al. (2003)
	15	Rat/W	ns	M	Single	↔ CCK receptor binding	Harro et al. (1999)
Hippocampus							
	35	Mice/C57Bl/6	2–3 months	M	3–5/cage	↑ MCHR1 mRNA (whole hippocampus)	Roy et al. (2007)
	25	Rat/W	350 g	M	Single	↓ NPY mRNA (DG)	Sergeyev et al. (2005)
	10	Rat/SD	260–300 g	M	2/cage	↔ NOFQ protein levels	Devine et al. (2003)
Hypothalamus							
	56	Rat/SD	200–220 g	M	Single	↓ NPY immunoreactivity (PVN and ARC) and ↑ CCK immunoreactivity (PVN)	Kim et al. (2003)
	25	Rat/W	350 g	M	Single	↑ NPY mRNA (ARC); ↑ substance P mRNA (VMH, DMH, LH); ↓ galanin mRNA (DMH, LH), ↔ (ARC)	Sergeyev et al. (2005)
	10	Rat/SD	260–300 g	M	2/cage	↔ NOFQ protein levels	Devine et al. (2003)
Amygdala							
	25	Rat/W	350 g	M	Single	↑ Substance P mRNA (MeA); ↔ galanin mRNA (CeA)	Sergeyev et al. (2005)
Thalamus							
	56	Rat/SD	200–220 g	M	Single	↓ NPY immunoreactivity (PVT); ↑ CCK immunoreactivity (PVT)	Kim et al. (2003)
	10	Rat/SD	260–300 g	M	2/cage	↔ NOFQ protein levels	Devine et al. (2003)
Septum							
	10	Rat/SD	260–300 g	M	2/cage	↔ NOFQ protein levels	Devine et al. (2003)
Midbrain							
	25	Rat/W	350 g	M	Single	↔ galanin mRNA (DR and LC); ↔ NPY mRNA (LC)	Sergeyev et al. (2005)
	10	Rat/SD	260–300 g	M	2/cage	↔ NOFQ protein levels	Devine et al. (2003)
Cerebellum							

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
	10	Rat/SD	260–300 g	M	2/cage	↔ NOFQ protein levels	Devine et al. (2003)
	15	Rat/W	ns	M	Single	↔ CCK receptor binding	Harro et al. (1999)

Table 11

Endocannabinoids.

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Limbic forebrain							
	21	Rat/LE	70 days	M	3/cage	↔ CB1 receptor binding or AEA and 2-AG levels	Hill et al. (2005)
Frontal cortex							
	70	Rat/W	200 g	M	Single	↑ CB1 receptor mRNA; ↔ AEA or 2-AG levels	Bortolato et al. (2007)
	21	Rat/LE	70 days	M	3/cage	↑ CB1 receptor binding; ↓ AEA levels; ↔ 2-AG levels	Hill et al. (2008)
Hippocampus							
	21	Rat/LE	70 days	M	3/cage	↓ CB1 receptor binding and protein levels; ↓ 2-AG levels; ↔ AEA levels	Hill et al. (2005)
	70	Rat/W	200 g	M	Single	↔ CB1 receptor mRNA or AEA or 2-AG levels	Bortolato et al. (2007)
	21	Rat/LE	70 days	M	3/cage	↓ CB1 receptor binding; ↓ AEA levels; ↔ 2-AG levels	Hill et al. (2008)
	21	Rat/SD	7–8 weeks	M and F	3/cage	↓ CB1 receptor protein levels (M); ↑ CB1 receptor protein levels (F); ↑ FAAH expression (M and F)	Reich et al. (2009)
Nucleus accumbens							
	21	Rat/LE	70 days	M	3/cage	↓ CB1 receptor binding; ↓ AEA levels; ↔ 2-AG levels	Hill et al. (2008)
	70	Rat/W	200 g	M	Single	↔ AEA or 2-AG levels	Bortolato et al. (2007)
	42	Mice/C57Bl/6	8–10 weeks	M	5/cage	↓ CB1 receptor mediated suppression of glutamate release; ↔ AEA or 2-AG levels	Wang et al. (2010a)
Hypothalamus							
	21	Rat/LE	70 days	M	3/cage	↓ CB1 receptor binding; ↓ AEA levels; ↑ 2-AG levels	Hill et al. (2008)
Amygdala							
	21	Rat/LE	70 days	M	3/cage	↔ CB1 receptor binding; ↓ AEA levels; ↔ 2-AG levels	Hill et al. (2008)
Thalamus							
	70	Rat/W	200 g	M	Single	↑ 2-AG levels; ↔ AEA levels	Bortolato et al. (2007)
Midbrain							
	21	Rat/LE	70 days	M	3/cage	↔ CB1 receptor binding; ↓ AEA levels; ↑ 2-AG levels	Hill et al. (2008)
	70	Rat/W	200 g	M	Single	↓ CB1 receptor mRNA; ↔ AEA or 2-AG levels	Bortolato et al. (2007)

Table 12

Neurotrophins.

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Hippocampus							
	42	Mice/ICR	20–25 g	M	ns	↓ BDNF mRNA (whole hippocampus)	Mao et al. (2009a)
	10	Rat/SD	150–200 g	M	Group	↓ BDNF mRNA and ↑ catalytic TrkB mRNA (whole hippocampus)	Nibuya et al. (1999)
	28	Mice/ICR	7 weeks	M	Group	↓ BDNF mRNA (whole hippocampus)	Song et al. (2006)
	28	Rat/SD	150–200 g	M	Single	↓ BDNF mRNA and protein (whole hippocampus)	Hu et al. (2010a)
	28	Rat/SD	150–200 g	M	Single	↓ BDNF mRNA (whole hippocampus)	Hu et al. (2010a)
	35	Rat/SD	200–220 g	M	ns	↓ BDNF mRNA and protein (whole hippocampus)	Mao et al. (2010b)
	28	Rat/SD	180–220 g	M	ns	↓ BDNF mRNA and protein (whole hippocampus)	Mao et al. (2010a)
	42	Mice/C57Bl/6	8–10 weeks	M	Single	↓ BDNF mRNA (CA1, but not CA3 or DG); ↓ BDNF protein (whole hippocampus, four after end ofCMS)	Elizalde et al. (2010b)
	28	Rat/SD	150–200 g	M	Single	↓ BDNF mRNA (whole hippocampus)	Zheng et al. (2006)
	35	Rat/SD	190–250 g	M	Single	↓ BDNF protein (whole hippocampus)	Dang et al. (2009a)
	28	Mice/Kun-ming	18–22 g	M	Group	↓ BDNF protein (whole hippocampus)	Li et al. (2007)
	35	Mice/Swiss Albino	18–22 g	M	5/cage	↓ BDNF protein (whole hippocampus)	Li et al. (2008)
	20	Rat/SD	190–200 g	M	6/cage	↓ BDNF protein (whole hippocampus)	Xu et al. (2006)
	28	Rat/SD	30 and 60 days old	M	Single	↓ BDNF protein (dorsal hippocampus; 60 days old); ↑ BDNF protein (ventral hippocampus; 30 days old)	Toth et al. (2008)
	38	Rat/SD	60 days old	M	Single	↓ BDNF protein (dorsal, not ventral, hippocampus)	Gersner et al. (2010)
	20	Rat/SD	190–200 g	M	6/cage	↓ BDNF protein (CA1, CA3 and DG)	Xu et al. (2007)
	42	Rat/W	200–220 g	M	ns	↓ BDNF protein (CA1, CA3 and DG)	Zhang et al. (2010)
	35	Rat/SD	11 weeks	M	Single	↓ BDNF protein (DG, not CA1 and CA3)	Gronli et al. (2006)
	40	Rat/W	3–4 months	M	5/cage	↔ BDNF protein (whole hippocampus)	Lucca et al. (2008)
	40	Rat/W	3–4 months	M	5/cage	↔ BDNF protein (whole hippocampus)	Garcia et al. (2009)

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
	19	Rat/SD	150–180 g	M	Single	↔ BDNF mRNA (GCL of DG)	Lee et al. (2006)
	49	Rat/W	ns	M	ns	↔ BDNF mRNA (CA1, CA3 and DG)	Allaman et al. (2008)
	28	Rat/SD	200–250 g	M	2/cage	↑ BDNF mRNA (DG in dorsal hippocampus and CA3 in ventral hippocampus)	Larsen et al. (2010)
	28	Rat/W	350 g	M	Single	↑ BDNF mRNA (CA3 and DG of ventral hippocampus)	Bergstrom et al. (2008)
	40	Rat/W	60 days	M	5/cage	↑ BDNF protein (whole hippocampus)	Fortunato et al. (2010)
	22	Rat/SD	7 weeks	M	3/cage	↑ BDNF protein (whole hippocampus)	Luo et al. (2010)
Frontal cortex							
	42	Mice/ICR	20–25 g	M	ns	↓ BDNF mRNA	Mao et al. (2009a)
	35	Rat/SD	200–220 g	M	ns	↓ BDNF mRNAand protein	Mao et al. (2010b)
	28	Rat/SD	180–220 g	M	ns	↓ BDNF mRNAand protein	Mao et al. (2010a)
	20	Rat/SD	190–200 g	M	6/cage	↓ BDNF protein	Xu et al. (2006)
	42	Rat/W	200–220 g	M	ns	↔ BDNF protein	Zhang et al. (2010)
	22	Rat/SD	7 weeks	M	3/cage	↔ BDNF protein	Luo et al. (2010)
Striatum							
	28	Rat/SD	30 and 60 days old	M	Single	↓ BDNF protein (60 days old only)	Toth et al. (2008)
	38	Rat/SD	60 days old	M	Single	↓ BDNF protein (whole striatum, but not in nucleus accumbens)	Gersner et al. (2010)
VTA							
	28	Rat/SD	30 and 60 days old	M	Single	↔ BDNF protein	Toth et al. (2008)
	38	Rat/SD	60 days old	M	Single	↔ BDNF protein	Gersner et al. (2010)
Amygdala							
	49	Rat/W	ns	M	ns	↔ BDNF mRNA	Allaman et al. (2008)

Table 13

Signal transduction cascades.

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Hippocampus							
	70	Rat/W	220–250 g	M	Single	↓ pCREB expression; ↔ CREB mRNA (whole hippocampus)	Pan et al. (2010)
	63	Rat/W	8 weeks	M	Single	↓ AC activity, cAMP levels and AC subunit 2 and CREB mRNA (whole hippocampus)	Li et al. (2009a)
	35	Rat/SD	11 weeks	M	Single	↓ pCREB expression (DG, not CA1 or CA3); ↔ CREB expression	Gronli et al. (2006)
	28	Mice/ICR	7 weeks	M	Group	↓ CREB mRNA (whole hippocampus)	Song et al. (2006)
	20	Rat/SD	190–200 g	M	6/cage	↓ pCREB expression	Xu et al. (2006)
	42	Mice/CD1	2 months	M	Single	↓ pCREB, pERK1/2 and pCaMKIV expression; ↓ PKA activity; ↔ PKC activity (whole hippocampus)	Kong et al. (2009)
	28	Rat/SD	150–200 g	M	Single	↓ pCREB expression (whole hippocampus)	Hu et al. (2010a)
	21	Rat/SD	150–200 g	M	Single	↓ pCREB and pJNK expression; ↔ CREB, JNK, ERK1/2, pERK1/2, p38 (whole hippocampus)	Li et al. (2009b)
	42	Mice/BALBc	60 days	F	Single	↓ nNOS activity; ↔ PKC activity; ↑ PKCζ and PKCγ isoform expression (whole hippocampus)	Palumbo et al. (2007)
	21	Mice/ICR	4–5 weeks	M	ns	↑ nNOS activity (whole hippocampus)	Zhou et al. (2007)
Frontal cortex							
	70	Rat/W	220–250 g	M	Single	↓ pCREB expression; ↔ CREB mRNA	Pan et al. (2010)
	63	Rat/W	8 weeks	M	Single	↓ AC activity, cAMP levels and CREB mRNA; ↔ AC subunit 2 mRNA	Li et al. (2009a)
	20	Rat/SD	190–200 g	M	6/cage	↓ pCREB expression	Xu et al. (2006)
Hypothalamus							
	70	Rat/W	220–250 g	M	Single	↔ CREB mRNA or pCREB expression;	Pan et al. (2010)
	63	Rat/W	8 weeks	M	Single	↓ CREB mRNA; ↔ AC activity; ↑ cAMP levels and AC subunit 2 mRNA	Li et al. (2009a)
	10	Rat/SD	190–240 g	M	2/cage	↓ RGS4 mRNA (PVN)	Ni et al. (1999)
Striatum							
	10	Rat/SD, F and L	170–185 g	M	3/cage	↑ PKA expression and ↓ Giα expression (nucleus accumbens, not caudate putamen)	Ortiz et al. (1996)

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
	14	Rat/W	ns	M	3–4/cage	↑ PKA activity (nucleus accumbens)	Araujo et al. (2003)
Midbrain							
	28	Rat/SD	275–300 g	M	2/cage	↑ pERK1/2 levels (VTA)	Iniguez et al. (2010)
	10	Rat/SD	190–240 g	M	2/cage	↑ RGS4 mRNA (LC)	Ni et al. (1999)

Table 14

Neurogenesis.

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
Hippocampus							
	35	Rat/SD	180–200 g	M	ns	↓ Cell proliferation (DG)	Chen et al. (2009)
	20	Rat/SD	190–200 g	M	6/cage	↓ Cell proliferation (SGZ and hilus)	Xu et al. (2007)
	28	Rat/SD	30 and 60 days old	M	Single	↓ Cell proliferation and neurogenesis (DG; 60 days old); ↑ cell proliferation (DG; 30 days old)	Toth et al. (2008)
	21	Rat/SD	ns	M	Single	↓ Cell proliferation (DG)	Sandi et al. (2008)
	28	Mice/Kun-ming	18–22 g	M	Group	↓ Cell proliferation (DG)	Li et al. (2007)
	35	Mice/Swiss Albino	18–22 g	M	5/cage	↓ Cell proliferation and survival (DG)	Li et al. (2008)
	42	Mice/CD1	2 months	M	Single	↓ Cell proliferation and survival (DG)	Kong et al. (2009)
	21	Mice/ICR	4–5 weeks	M	ns	↓ Cell proliferation and neurogenesis (DG)	Zhou et al. (2007)
	49	Mice/BALBc	17–32 g	M	Single	↓ Cell proliferation (DG)	Alonso et al. (2004)
	35	Mice/C57Bl/6	ns	M	ns	↓ Cell proliferation and neurogenesis (DG)	Goshen et al. (2008)
	35	Rat/SD	4 months	M	ns	↓ Cell proliferation (DG)	Liu et al. (2008)
	14	Rat/W	4 weeks and 2 months	M	3/cage	↓ Cell proliferation and neurogenesis (DG, but not SVZ; both age groups)	Silva et al. (2008)
	42	Rat/W	3 months	M	3/cage	↓ Cell proliferation and neurogenesis (DG)	Bessa et al. (2009)
	28	Rat/W	200–300 g	M	Single	↓ Cell proliferation (only in ventral DG)	Jayatissa et al. (2006)
	56	Rat/W	350 g	M	Single	↓ Cell proliferation (only in ventral DG)	Jayatissa et al. (2009)
	28 and 56	Rat/W	350 g	M	Single	↓ Cell proliferation (only in ventral DG, after 56 days but not 28)	Jayatissa et al. (2010)
	42	Mice/C57Bl/6	8–10 weeks	M	Single	↓ Cell proliferation (DG); ↓ neurogenesis (in ventral, but not dorsal, DG)	Elizalde et al. (2010b)
	24	Mice/Kun-ming	16–20 g	M	ns	↓ Cell proliferation (DG)	Li et al. (2006)
	21	Rat/SD	210–250 g	M	2/cage	↓ Cell survival (DG); ↔ cell proliferation (DG)	Wang et al. (2008)
	19	Rat/SD	150–180 g	M	3/cage	↓ Cell survival (DG and GCL, but not hilus); ↔ cell proliferation (GCL, hilus or DG)	Lee et al. (2006)

Region	Duration (days)	Species/Strain	Age/Weight	Sex	Housing condition	Summary of findings	Reference
	21	Rat/W	2–3 months	M	Single	↓ Neurogenesis and cell survivial (DG)	Holderbach et al. (2006)
	14	Mice/C57Bl/6, DBA/2J and BALB/cJ	2 months	M and F	ns	↓ Neurogenesis (DG; except in F C57Bl/6)	Mineur et al. (2007)
	21	Rat/W	10 weeks	M	2/cage	↓ Neurogenesis and cell survival (DG)	Oomen et al. (2007)
	32	Mice/ICR	18–22 g	M	ns	↓ Neurogenesis and cell survival (DG)	Hua et al. (2008)
	35	Rat/SD	ns	M	ns	↓ GFAP mRNA and protein (hippocampus)	Liu et al. (2009)
	28	Rat/W	350 g	M	Single	↔ Cell proliferation (DG and hilus)	Sousa et al. (1998)
	42	Rat/SD, L and F	6 weeks	M	Single	↔ Cell proliferation and neurogenesis (DG; SD and F); ↑ cell proliferation and neurogenesis (DG; L only)	Wu and Wang (2010)
	16	Rat/W	250–270 g	M	Single	↔ Cell proliferation (SGZ)	Nowak et al. (2010)
	28	Mice/C57Bl/6	28 weeks	F	5–6/cage	↔ Cell proliferation (DG)	Lagunas et al. (2010)
	14	Mice/Kun-ming	18–22 g	M	5/cage	↔ Cell proliferation (SGZ)	Shi et al. (2010)
PFC							
	15	Rat/SD	300–350 g	M	2/cage	↓ Cell proliferation and gliogenesis (PFC)	Banasr et al. (2007)
	35	Rat/SD	25–300 g	M	ns	↓ GFAP mRNA (PFC)	Banasr et al. (2010)