



Glucocorticoids, metabolism and brain activity

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ABSTRACT

The review integrates different experimental approaches including biochemistry, c-Fos expression, microdialysis (glutamate, GABA, noradrenaline and serotonin), electrophysiology and fMRI to better understand the effect of elevated level of glucocorticoids on the brain activity and metabolism. The available data indicate that glucocorticoids alter the dynamics of neuronal activity leading to context-specific changes including both excitation and inhibition and these effects are expected to support the task-related responses. Glucocorticoids also lead to diversification of available sources of energy due to elevated levels of glucose, lactate, pyruvate, mannose and hydroxybutyrate (ketone bodies), which can be used to fuel brain, and facilitate storage and utilization of brain carbohydrate reserves formed by glycogen. However, the mismatch between carbohydrate supply and utilization that is most likely to occur in situations not requiring energy-consuming activities lead to metabolic stress due to elevated brain levels of glucose. Excessive doses of glucocorticoids also impair the production of energy (ATP) and mitochondrial oxidation. Therefore, glucocorticoids have both adaptive and maladaptive effects consistently with the concept of allostatic load and overload.

1. Introduction

Glucocorticosteroids (GCs) are involved in the regulation of many basic physiological functions both under basal conditions (Kalafatakis et al., 2019) and in response to stress (de Kloet et al., 2019). Furthermore, because of a potent effect on the immune system, GCs are also widely used in the treatment of inflammatory, autoimmune and lymphoproliferative diseases. Effects of endogenously released GCs are divided into three broad categories that is permissive/stimulating, suppressive and preparative actions (Sapolsky et al., 2000). The first category of effects primes defensive mechanisms in basal conditions (permissive) and enhances the first wave of hormonal responses to stress (stimulating). Suppressive effects, in turn, prevent defense reactions from overshooting (Sapolsky et al., 2000) and in this respect can be compared with actions preventing water damage at the time of fire-fighting (Tausk, 1951 as cited in Sapolsky et al., 2000). Suppressive effects are also the main reason for using GCs in pharmacology. Finally,

the last category of actions prepares an organism for subsequent stressors enabling, therefore, better responses in future (Sapolsky et al., 2000). All these actions of GCs participate in allostasis which is an active process of adaptation enabling maintaining physiological stability. However, when adaptation mechanisms are overused, they lead to so called allostatic overload causing adverse effects (Gray et al., 2017). This general classification of GC-mediated effects helps to place pharmacological effects in physiological perspective.

Although GCs affect many different physiological and cellular processes, they are in fact intimately connected with energy production because corticosterone and cortisol are mitochondria-derived hormones (mitokines) that mediate mitochondria-to-mitochondria communication among distant sites throughout the organism (Picard et al., 2018). Furthermore, the process of energy production is closely connected to many other cellular processes, even ones that are apparently not related such as gene methylation (Picard et al., 2018). Therefore, the regulation of metabolism is a key process in stress adaptation and contributes both

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to adaptive and maladaptive responses (Picard et al., 2018). The effect of glucocorticoids on metabolism of peripheral tissues received a lot of attention (Kuo et al., 2015; Magomedova and Cummins, 2016) but much less is known about the effect of glucocorticoids on brain metabolism. This issue is especially difficult because brain metabolism is highly dynamic due to changes in ongoing electrical signaling (Harris et al., 2012; Watts et al., 2018) and because it depends on the interaction between neurons and astrocytes which have a different metabolic profile (Watts et al., 2018). Furthermore, brain responses should be considered together with the time-course of peripheral metabolic changes to obtain a full picture of GC-induced changes in metabolism. Therefore, we decided to integrate different experimental approaches ranging from *in vitro* biochemical experiments to fMRI and electrophysiological studies to better understand the effect of an elevated level of glucocorticoids on the brain function. This integration also includes the discussion of limitations associated with different methodological approaches.

2. Limitations of the review

2.1. Neuronal activity

First, it should be noted that GCs exert a pleiotropic effect leading to changes in a multitude of cellular functions (Juszczak and Stankiewicz, 2018) and physiological processes ranging from immune responses (Sorrells and Sapolsky, 2007; Sorrells et al., 2009) to neuronal plasticity (Sapolsky et al., 2000; Joels et al., 2012; Gray et al., 2017). Therefore, we only tackle a relatively small aspect of a widespread bodily effect of glucocorticoids. Furthermore, we only focused on changes in activity ranging from the firing of single cells to a net effect observed at the population level. We chose the spiking activity as the lowest considered level because it constitutes the direct measure of changes in the neuronal activity. Obviously, spike generation depends on multiple local changes in membrane potentials that sum up to produce action potential or to block further signal transmission in the network. These processes depend in turn on multiple neurotransmitters and their receptors, ion channels and intracellular signaling pathways which are itself very complex and this complexity is even growing due to plastic changes. These mechanisms are very important but are beyond the scope of this review. Therefore, interested readers are referred to earlier reviews attempting to better understand the effect of GCs on local changes in membrane potentials that are responsible for spike generation (Joels et al., 2012).

2.2. Pharmacological effects

The second limitation results from the fact that most of the available pharmacological studies focused exclusively on the effects of an increased level of GCs without the consideration of interaction with other stress molecules. Such reductionism is a common approach in science because it helps to disentangle the contribution of separate factors to more complex phenomena. In the case of treatments with GCs, it has also a direct relevance for medicine because GCs are commonly used anti-inflammatory drugs. However, it should be stressed that the sum of separate parts studied in isolation is not always equal to the complex system from which they were derived and this issue applies also to glucocorticoids. For example, few available studies suggest that actions induced by GCs vary considerably depending on the presence or absence of noradrenergic stimulation and timing of this interaction (Allaman et al., 2004; van Stegeren et al., 2010; Schwabe et al., 2012; Karst and Joels, 2016). The distinction between treatment with GCs and stress response is also nicely shown by sensitization of the HPA axis to repeated stressful experiences in contrast to inhibition found after administration of exogenous corticosterone (Dallman and Jones, 1973). Another example is a beneficial effect of exercise in contrast to the detrimental effect of stress despite the fact that both of them increase the level of GCs (Chen et al., 2017). Therefore, disentangling the interaction

between GCs and other factors such as noradrenaline is crucial for understanding the role of glucocorticoids in more complex physiological phenomena. Furthermore, it can help to better understand the variability in psychiatric side effects associated both with administration of GCs and Cushing's disease. It has also been suggested that differences in experimental procedures leading to inadvertent sympathetic activation may be responsible for variability between studies (van Stegeren et al., 2010). However, due to the shortage of data, future experiments will be needed to properly understand interactions between GCs and other mediators of the stress response (Joels, 2018).

2.3. Adrenalectomy

The third major limitation of the review results from potentially confounding effects of adrenalectomy that was frequently performed before many experiments. The rationale for performing adrenalectomy was to create a situation in which mineralocorticoid (MR) and glucocorticoid (GR) receptors are unoccupied at the beginning of an experiment to enable testing a wide range of doses of glucocorticoids including also the small one (Karst and Joels, 1991). Additionally, this approach solves the problem of stress-induced changes in GCs that may occur during preparation of animals for the experiments. Therefore, the experiments performed on adrenalectomized animals advanced our understanding of the role of MRs and GRs in responses to GCs. However, the adrenalectomy also affects other hormones released by the adrenal gland (Rosol et al., 2001) and leads to a number of metabolic (Kadekaro et al., 1988; Freo et al., 1992; Doyle et al., 1994b; Plaschke et al., 1996) and electrophysiological changes (Rey et al., 1987; Kasai and Yamashita, 1988; Joels and de Kloet, 1989). A peculiar phenomenon observed after adrenalectomy is also translocation of glucocorticoid receptors to nuclei in the absence of corticosterone (Sarabdjitsingh et al., 2009). Importantly, problems associated with adrenalectomy cannot be completely overcome by corticosterone supplementation because a basal level of corticosterone in intact animals is not stable but instead displays ultradian and circadian rhythms (Qian et al., 2012), and there are data suggesting that these naturally occurring fluctuations have functional significance (den Boon et al., 2019). It has also been found that corticosterone supplementation (pellets) results in altered responsiveness of hippocampal neurons in adrenalectomized animals (Beck et al., 1994). Collectively, these data indicate that adrenalectomized animals are not fully representative for the general population of intact subjects. Therefore, we restricted our review to non-adrenalectomised animals as much as possible. However, in case of research topics with few available data, such studies were included with annotation about adrenalectomy as a potential confounding factor.

3. Permeability of the blood-brain barrier

3.1. Differences between glucocorticoids

Both endogenous and synthetic GCs differ in their ability to penetrate the blood-brain barrier because its permeability is high for corticosterone while low for cortisol (Pardridge and Mietus, 1979; Karssen et al., 2001), dexamethasone (De Kloet et al., 1975; Meijer et al., 1998) and prednisolone (Karssen et al., 2002). Cortisol administered to rats enters brain at a low rate that is stable across various brain areas (McEwen et al., 1976). As a result, when comparable doses of cortisol and corticosterone are applied, similar concentrations are found after an hour in brain areas with lower expression of receptors such as hypothalamus, cortex and cerebellum while especially huge differences are found in the hippocampus (McEwen et al., 1976; Karssen et al., 2001). Differences between cortisol and corticosterone are present also in the human brain indicating that preferential uptake of corticosterone is a common phenomenon found in different species (Karssen et al., 2001). Despite lower permeability of human blood-brain barrier for cortisol, its content in brain is comparable with that in plasma indicating that it enters the

brain (Karssen et al., 2001) although the time-course of this process is unknown.

Similarly, a restricted ability to penetrate the blood-brain barrier is found in the case of dexamethasone (De Kloet et al., 1975; Meijer et al., 1998). The threshold for its entry into the brain depends on the applied dose because 50 µg/kg had a negligible central effect after acute (Cole et al., 2000) and repeated treatments (Karssen et al., 2005) in contrast to 250–500 µg/kg (Reul et al., 1987; Karssen et al., 2005). Responses to lower doses of dexamethasone may also differ between various brain areas because regions with lower expression of glucocorticoid receptors such as hypothalamus are more likely to be saturated with dexamethasone than hippocampus (De Kloet et al., 1975). Similar properties in terms of the restricted ability to cross the blood-brain barrier poses prednisolone but despite clinical significance we have a very limited number of experimental data (Karssen et al., 2002). Low permeability of the blood-brain barrier for some GCs in combination with peripheral effects of GCs and differences in affinity to MRs and GRs (Section 4) may lead to indirect effects confounding interpretation of pharmacological data (Section 5, Fig. 1).

3.2. Corticosterone in rodent brain

3.2.1. Corticosterone - time course

The most precise information about the timing of GCs entrance into the brain has been collected in laboratory rodents subjected to stress or treated with corticosterone, and this knowledge is crucial for the proper interpretation of experimental data. Experiments performed with microdialysis showed that the total blood level of corticosterone, which is usually measured, may not provide an accurate reflection of glucocorticoid concentrations in the brain. It is because brain corticosterone peaks 20 min later than total corticosterone in blood under stress conditions (Droste et al., 2008). The duration of initial period when there are no significant changes in the brain level of corticosterone can only be assumed based on the previously reported data because they either lack a detailed statistical analysis of differences between each time point and the baseline (Venero and Borrell, 1999; Droste et al., 2008, 2009; Heinzmann et al., 2010; Qian et al., 2011) or present rather conservative estimates due to multiple comparisons (Thoerlinger et al., 2007). A comparison of means and SEM indicates that during the first 5–10 min the changes are negligible after subcutaneous administration of corticosterone (Droste et al., 2008) or stress exposure in rats while a clear-cut increase occurs after at least 10–15 min (Venero and Borrell, 1999; Droste et al., 2008, 2009; Qian et al., 2011). Microdialysis data are consistent with a finding that 10 min after i.v. injection of corticosterone there is increased nuclear translocation of glucocorticoid receptors (Conway-Campbell et al., 2007). This in turn indicates that such latency is sufficient for the penetration of the blood-brain barrier by the

hormone at least in adrenalectomized animals. Similarly, delayed changes in the brain level of corticosterone were also observed in mice after exposure to stress (Thoerlinger et al., 2007; Heinzmann et al., 2010) although some studies reported much faster changes (Yau et al., 2015a, b).

The maximum brain level of extracellular corticosterone is recorded 20–40 min after injection (Venero and Borrell, 1999; Droste et al., 2008; Bouchez et al., 2012) and usually 20–67 min after the beginning of the stress procedure in mice (Thoerlinger et al., 2007; Heinzmann et al., 2010) and rats (Droste et al., 2008, 2009; Bouchez et al., 2012). Occasionally, very short latencies (10 min) to reach the maximum brain level of corticosterone were also reported in mice after stress (Yau et al., 2015a, b). Available data additionally show that nuclear translocation of glucocorticoid receptors peaks from 15 to 120 min after treatment (Conway-Campbell et al., 2007; Sarabdjitsingh et al., 2009) depending on the route of administration, studied brain area and utilization of either intact or adrenalectomized animals. An alternative approach based on nuclear binding of radiolabeled corticosterone (De Kloet et al., 1975) showed a maximum hippocampal radioactivity in adrenalectomized animals one hour after i.v. injection of a tracer amount of the hormone which is retained in these conditions by the high affinity mineralocorticoid receptors. These scarce data give us a hint of the time-course of a direct interaction between genome and receptor-bound corticosterone with the caveat that there are multiple mechanisms regulating binding of the available receptors to glucocorticoid response elements existing within the DNA (Polman et al., 2013; Mifsud and Reul, 2018).

Elevated brain levels of GCs return to the baseline or are greatly diminished after approximately 60–120 min although in some cases full normalization occurs during the third hour (Venero and Borrell, 1999; Thoerlinger et al., 2007; Droste et al., 2008, 2009; Heinzmann et al., 2010; Bouchez et al., 2012; Yau et al., 2015a). A similar time course was observed in case of experiments assessing receptor occupation and nuclear translocation of glucocorticoid receptors in adrenalectomized (Conway-Campbell et al., 2007) and intact animals (Reul et al., 1987; Sarabdjitsingh et al., 2009) after injection of corticosterone or stressful experience. Summing up, available data indicate that the brain level of corticosterone is usually elevated 10–15 min after peripheral injection or stress exposure, peaks after 20–60 min and in most cases returns to baseline after 60–120 min.

3.2.2. Factors affecting brain entrance of corticosterone

The reviewed experiments show that the kinetics of the brain level of corticosterone depends on several factors such as genetic background, pre-exposure to mild stress (Thoerlinger et al., 2007), age of animals (Yau et al., 2015a) and the amount of injected or released hormone due to the stress exposure. Higher doses (Bouchez et al., 2012) and more severe

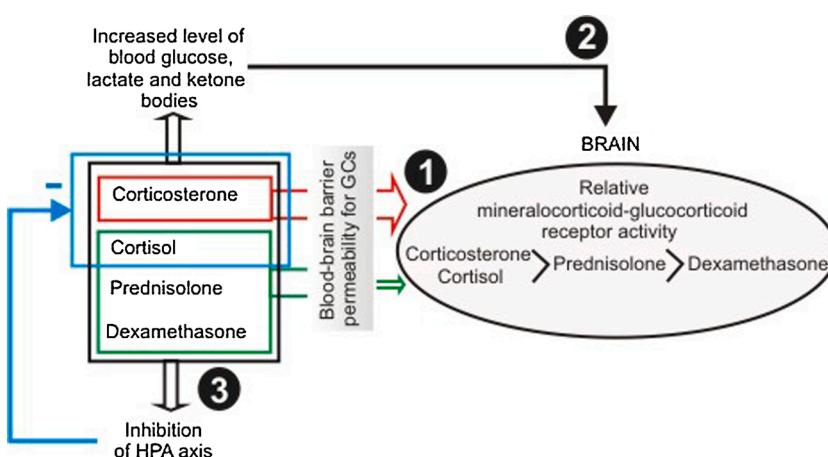


Fig. 1. First, GCs affect the nervous system directly by activation of brain mineralocorticoid and glucocorticoid receptors. These central effects are modulated by properties of GCs that affect their ability to penetrate the blood-brain barrier (Section 3.1) and ability to activate MRs and GRs (Section 4). Second, GCs affect the nervous system indirectly by changes in the blood level of glucose (Section 8.3.1) and other energetic substrates (Section 8.5) leading to altered gradient across the blood-brain barrier and ensuing changes in brain concentration of these substances (Section 8.3.2.4 and 8.5). Third, treatment with GCs inhibits the HPA axis leading to a decreased release of endogenous glucocorticoids during the sleep-waking cycle (Section 5). Therefore, the administration of GCs may also lead to periods of hypocortisolemia (Karssen et al., 2005) that will additionally depend on the properties of applied GCs and time-course of experiments. These three mechanisms complicate the functional interpretation of effects induced by peripheral administration of GCs.

stressors (Thoeringer et al., 2007; Droste et al., 2008, 2009; Qian et al., 2011) result in a more delayed peak level of corticosterone and longer time needed to normalize the level of the hormone. A physiological mechanism contributing to the delay of brain entrance of corticosterone is a concomitant release of Corticosteroid-Binding Globulin from the liver that is most pronounced during moderate and severe stress (Qian et al., 2011). A confounding factor that can also contribute to the variability of results is stress associated with preparation of animals for experiments, for example transport of animals between different rooms. Such inadvertent stress can initiate release of GCs before the start of the procedure intended for inducing the stress response. Finally, significant changes in the brain level of corticosterone are easier for detection in adrenalectomized animals (Venoro and Borrell, 1999; Conway-Campbell et al., 2007) because of a negligible basal level of GCs and smaller between-subject variability due to the absence of changes in the level of endogenously released hormone. Therefore, multiple factors affect the timing of elevated levels of GCs and resulting brain responses.

4. Contribution of mineralocorticoid and glucocorticoid receptors

Endogenous GCs (corticosterone/cortisol) bind both to mineralocorticoid (MR) and glucocorticoid (GR) receptors but with different affinity leading to variable contribution of these two types of receptors depending on the level of circulating hormones. Relatively low levels of GCs are released in basal conditions (Qian et al., 2012; Oster et al., 2017) which are additionally associated with circadian and ultradian fluctuations supporting daily activities, while high levels are present during stress response or after treatment with exogenous hormones (Section 3). In morning hours, when rodent HPA axis displays the lowest basal activity, brain MRs are occupied by hormones in about 80 % while GRs only in about 30 % (Reul et al., 1987). Therefore, effects observed after elevated levels of GCs due to stress exposure or pharmacological treatment were mostly attributed to activation of GRs. It should be noted, however, that the activity of MRs is also important. It creates not only a setpoint of the stress system (Joels et al., 2008) but also participates in effects induced by GCs released during the stress response (Joels and de Kloet, 2017; de Kloet et al., 2019). For example, MRs affect appraisal processes, behavioral reactivity, selection of coping style, encoding of new memories and retrieval of previously acquired information (Joels and de Kloet, 2017; de Kloet et al., 2019). Such a role is possible because there is a pool of membrane-associated MRs that has a lower affinity to corticosterone than intracellular receptors and, therefore, are activated at the time of elevated levels of glucocorticoids (Joels and de Kloet, 2017). Activation of GRs, in turn, facilitates behavioral adaptation and memory consolidation (de Kloet et al., 2019).

Taking into account the role of MRs and GRs is also crucial for the interpretation of effects induced by exogenous glucocorticoids that differ in ability to bind and activate these receptors. While different binding assays produced variable results (Lan et al., 1982; Rupprecht et al., 1993), the relative mineralocorticoid – glucocorticoid receptor activity is a most consistent determinant of physiological responses (Lan et al., 1982). Available data indicate that betamethasone and prednisolone that are commonly applied synthetic glucocorticoids have a lower relative mineralocorticoid activity than corticosterone and cortisol but higher than dexamethasone (Lan et al., 1982) which has a negligible effect on MRs in rodent brain after peripheral injections (Reul et al., 1987). These differences in affinity to MRs and GRs constitute an important factor contributing to the variability of results reported after administration of various glucocorticoids (Fig. 1).

5. Interaction between exogenous and endogenous GCs

Functional interpretation of effects induced by *in vivo* treatments with GCs is further complicated by inhibition of the HPA axis (Fig. 1) leading to a decreased release of endogenous GCs such as cortisol and

corticosterone (Reul et al., 1987; Juruena et al., 2006). Cortisol is the main glucocorticoid in most of mammals including humans while corticosterone is preferentially released in rodents and rabbits (Bush, 1953; Karssen et al., 2001; Koren et al., 2012; Gong et al., 2015). Importantly, endogenous GCs are released not only in response to stress but also in basal conditions, with the highest level around the time of the sleep-wake transition and the lowest level at the beginning of the sleep period (Qian et al., 2012; Oster et al. 2017). Therefore, the effect of treatment with exogenous GCs can be counterbalanced by a decreased release of endogenous GCs especially in the case of prolonged experiments. In the case of rodents the effect of disrupted circadian rhythm of corticosterone should be considered especially when experimental period extends into the evening period of rising level of corticosterone (Reul et al., 1987). This issue is further complicated by the selection of administered glucocorticoid, doses and investigated species. For example, some older studies applied cortisol in experiments performed in rodents. In such a case, even a restricted range of changes in the basal release of corticosterone can be relevant because of considerable differences in permeability of the blood-brain barrier for these two hormones (Section 3.1). The variability in penetration of the blood-brain barrier will also lead to dissociation between peripheral and central effects of treatment. Another important factor is a difference between endogenous and synthetic GCs in affinity for MRs and GRs (Section 4) in combination with applied doses. For example, lower doses of dexamethasone that are not crossing the blood-brain barrier are expected to produce central hypocorticosteroid state (insufficient activation of both MRs and GRs) while higher doses alter the balance between activation of these two types of receptors in favor of GRs (Karssen et al., 2005). A support for this hypothesis is given by observation of reduced occurrence of neuropsychological symptoms in patients receiving both dexamethasone and cortisol (Warris et al., 2016). Summing up, GCs can induce both direct and indirect effects (Fig. 1) that vary depending on applied drugs, administered doses, treatment durations and investigated species leading to difficulty in interpretation of experimental data.

6. Time-course of non-genomic and genomic effects

Considering latency of responses, GCs have two modes of action: rapid non-genomic and delayed genomic mechanism that depends on changes in gene expression. Both these modes of action involve MRs (Karst et al., 2005; Nasca et al., 2015; van Weert et al., 2017) and GRs (Morsink et al., 2007; Nahar et al., 2015; van Weert et al., 2017) coded by Nr3c2 and Nr3c1 genes, respectively. The non-genomic activity of GCs starts almost immediately after the entrance of GCs into the brain as indicated by changes in the firing rate of neurons (Table 3) and lasts for approximately 60 min (Joels et al., 2012). Because of various mechanisms involved in the non-genomic activity of GCs, there is an additional differentiation between rapid effects occurring almost immediately after the hormone reaches the brain and intermediate effects that peak after 20–60 min (Joels et al., 2012). In contrast, genomic effects start after a delay of about 1 h and last for many hours (Joels et al., 2012) involving a direct and indirect mechanism of gene regulation (Newton, 2000; Popoli et al., 2011). Some early indirect genomic effects rely on interference of GCs with signaling mediated by second messengers as indicated by experiments investigating a negative feedback regulation of HPA axis activity (van der Laan et al., 2009; Evans et al., 2013). In such a case, the effect depends on the level of cellular activation that triggers the second messenger signaling and timing of GC administration (van der Laan et al., 2009). In contrast, direct genomic mechanisms are mediated by cytoplasmic receptors that move to the nucleus after binding the hormone and act as transcription factors (Popoli et al., 2011). Importantly, numerous transcriptomic (Carter et al., 2012) and proteomic (Kamisoglu et al., 2015; Ayyar et al., 2017) effects induced by GCs occur with longer delays peaking at about 4 h–6 h in case of mRNA and 5 h–8 h in case of proteins or even later after treatment. These delays in transcription and translation of genetic information is consistent with the time-course of

changes in blood glucose (Section 8.3.1, Fig. 2) and with alternation in glucose uptake in neuronal and astrocytic cell culture (Horner et al., 1990; Virgin et al., 1991). Collectively, these data points to various mechanisms involved in responses to GCs and expand the time window for studying their effects from minutes to many hours.

7. Methods used to investigate brain metabolism and activity

7.1. Measures of brain metabolism

Brain metabolism is usually measured by the assessment of the local level of 2-deoxyglucose (2DG) which is labeled with isotopes allowing its detection by autoradiography (Sokoloff et al., 1977), scintillation (Delanoy and Dunn, 1978) or Positron Emission Tomography (PET) (Lameka et al., 2016). 2DG is incorporated into cells due to the structural similarity to glucose but cannot be oxidized leading to the cellular accumulation of the isotope (Sokoloff et al., 1977). It should be noted that in case of animal *in vivo* experiments the accumulation of 2DG is measured postmortem and, therefore, transient changes may not be

detected because of averaging the uptake over a longer period of time. Another method enabling tracing substances labeled with isotopes is magnetic resonance (MRS) spectroscopy detecting atoms of carbon-13 in various metabolites (Hyder and Rothman, 2017; Rothman et al., 2019). Importantly, this approach enables differentiation between neuronal and astrocytic metabolism but it was not applied to study effects of GCs, thus creating an important gap in available data. Other methods rely on measurement of metabolites such as lactate, energy-carrying molecules (ATP) and oxygen in animal tissues. These methods show a contribution of oxidative and non-oxidative metabolism (lactate) and provide information about the balance between production and utilization of energy (ATP). Together with the assessment of glucose utilization they provide basic information about metabolism of studied tissues.

7.2. Measures of brain activity

Metabolism is tightly coupled with neuronal activity that is responsible for most of the energy expenditures in the brain (Yu et al., 2018). The direct measure of neuronal activity relies on detection of electric

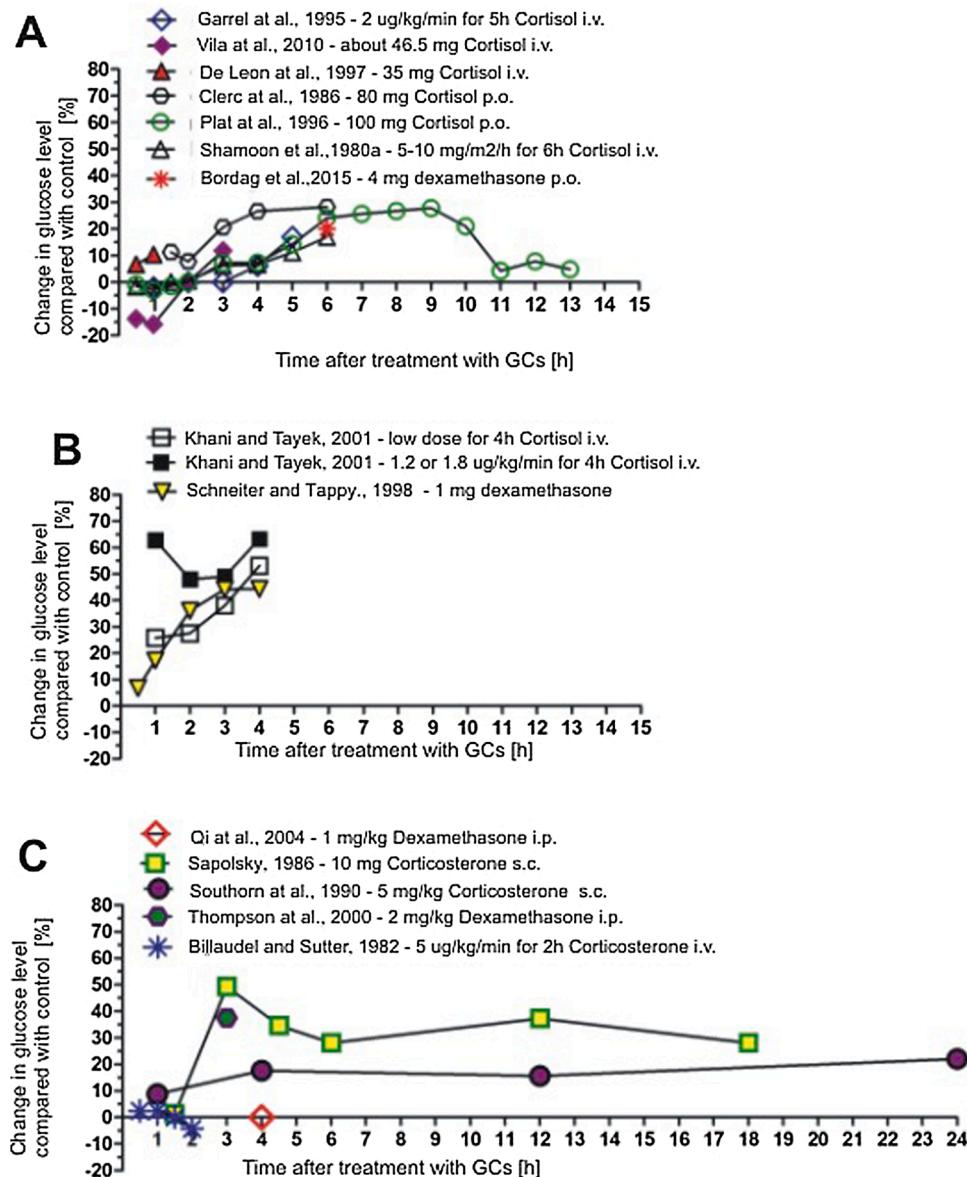


Fig. 2. Change in blood / serum glucose after treatment with GCs. A percentage change was assessed based on data reported in experimental studies. The comparison does not include data from one withdrawn study (Shamoon et al., 1980b).

currents generated by single neurons (single-unit recordings) or small groups of adjacent cells (multi-unit recordings). Such recordings can be performed with electrodes either *in vivo* or in simplified *in vitro* models such as brain slices or cell cultures. They also have the highest temporal resolution compared with other methods. Unfortunately, classical electrophysiological techniques used in the past to study the effect of GCs are restricted to a small number of neurons and brain areas.

An alternative method detects expression of c-Fos protein which is transiently expressed in neurons after synaptic stimulation and, therefore, constitutes an indirect marker of neuronal activity (Hudson, 2018). The advantage of c-Fos is that it allows detecting neuronal activity at cellular resolution in the entire brain. The main drawback of this method is that it has a very low temporal resolution because the expression of c-Fos protein peaks approximately 90–120 min poststimulus and is detected postmortem (Hudson, 2018). It is also less suitable for the detection of inhibited regions (Stark et al., 2006a).

A third method applicable in animal studies is microdialysis combined with HPLC enabling detection of neurotransmitters in extracellular space and, therefore, measuring a synaptic component of neuronal signaling (Linhorst and Reul, 2008). The advantage of microdialysis is that it allows performing experiments in freely moving animals with temporal resolution much better compared with c-fos expression. However, it is restricted to selected brain areas and is not allowing detection of changes at the level of single neurons.

Finally, an indirect method that can be easily applied in humans is functional magnetic resonance imaging (BOLD fMRI) which exploits differences in magnetic properties between oxygenated and deoxygenated hemoglobin (Magistretti and Allaman, 2015). An increased neuronal activity leads to dilation of vessels and increased local blood flow that surpasses the increase in oxygen utilization, resulting in locally increased oxygenation of hemoglobin (Kim and Ogawa, 2012). The main advantage of fMRI is that it is a non-invasive method enabling the analysis of the entire brain although its spatial and temporal resolution are very low compared to the direct measurement with electrodes (Heeger and Ress, 2002; Glover, 2011). This is because the changes in oxygenation of hemoglobin result from the pooled activity of a very large number of cells and are much slower than the spiking activity of neurons. It also means that fMRI is not able to detect changes neither in the activity of small subpopulations of neurons mixed with nonresponsive cells nor in structures composed of neurons displaying opposite responses.

These four methods assessing the brain activity (electrophysiology, c-Fos, microdialysis, and fMRI) together with the measurement of metabolism constitute complementary approaches that enable better understanding of the brain activity. Each method has some limitations and neither of them is able to detect all changes in the brain activity. For example, there is a considerable but not complete overlap between c-fos mapping and fMRI (Stark et al., 2006a) and between c-fos and 2-deoxyglucose uptake (Sharp et al., 1989; Komisaruk et al., 2000; Kaliszewska et al., 2012). Therefore, these data should be considered jointly.

7.3. Limitations of *in vitro* experiments

Finally, it is important to understand limitations associated with methods used to study brain metabolism and activity in *in vitro* preparations especially when neuronal or astrocytic cultures are used. First of all, they are obtained usually from embryos, pups or immortalized cell lines and, therefore, are not fully representative of an adult brain. Many concerns related to cell cultures and brain slices were expressed previously (Dienel, 2012; Joels et al., 2012) including differences in the rate of glucose metabolism during prenatal/early postnatal stages of development and adulthood (Nehlig, 1996; Dienel, 2012). Second, neurons in the intact brain do not function autonomously because they depend on metabolic cooperation with astrocytes. Therefore, any procedure that disrupts the structural and functional integrity of the network can lead to quantitative and qualitative changes in metabolism (Clarke and

Sokoloff, 1999). Finally, the constant and highly standardized milieu applied in *in vitro* experiments may not be representative of dynamic changes in the content of various metabolites and neurotransmitters found *in vivo*. This problem is especially important in the case of glucocorticoids as discussed in greater detail in section 8.3.2.4 and 8.5. Therefore, while *in vitro* experiments provide valuable information, their interpretation is difficult and should be done cautiously.

8. Metabolic effects of GCs

8.1. Overview of GC-induced metabolic effects in peripheral tissues

One of the most known effects of glucocorticoids is an increased level of blood glucose (Fig. 2, Section 8.3.1) due to a decreased uptake in some tissues (Sakoda et al., 2000; Su et al., 2014) and increased gluconeogenesis in the liver (McMahon et al., 1988; Khani and Tayek, 2001; Kuo et al., 2015). Additionally, GCs also stimulate the intake of food containing carbohydrates (Tataranni et al., 1996). Importantly, maintaining high levels of glucose is not feasible without a disabled negative feedback mediated by insulin (Fig. 3), which inhibits glucose production in the liver and stimulates the uptake of blood glucose by muscles and adipose tissue (Wilcox, 2005). This in turn necessitates the mobilization of fatty acids stored in adipose tissue to provide energy for muscles deprived of the carbohydrates (Fig. 3) (Ciaraldi et al., 1995; Hunter and Garvey, 1998). Therefore, although GCs are primarily linked with metabolism of glucose, they also have a profound effect on metabolism of lipids and affect the availability of numerous energetic substrates that are described in more detail in subsequent sections.

8.2.1. Blood insulin

GC-mediated interference with insulin signaling after activation of HPA axis is known as cerebral insulin suppression (Peters and McEwen, 2015). It depends on short-term inhibition of release (Billaudel and Sutter, 1982; Longano and Fletcher, 1983; Plat et al., 1996) that is followed by induction of insulin resistance in muscles (Su et al., 2014) and adipose tissue (Sakoda et al., 2000). The inhibition of release occurs with a delay of about 1 h and is manifested by either a decreased level of insulin or altered proportion between blood insulin and glucose (Billaudel and Sutter, 1982; Longano and Fletcher, 1983; Plat et al., 1996). A factor that modifies the effect of GCs on the insulin release is glucose availability indicating flexibility of the regulatory mechanism (Billaudel and Sutter, 1982; Longano and Fletcher, 1983). In humans the blood insulin concentration returns to the basal level after about 3–4 h and next increases following changes in the blood glucose (Plat et al., 1996). The increased levels of glucose despite an elevated level of insulin (Plat et al., 1996) indicates the development of insulin resistance that is observed as early as 4–6 h after treatment (Plat et al., 1996; Qi et al., 2004) and results from a decreased uptake of glucose in muscles (Weinstein et al., 1995, 1998; Su et al., 2014) and adipocytes (Sakoda et al., 2000). An elevated level of insulin may persist despite the return of the glucose level to the baseline after acute GC treatment (Plat et al., 1996). Insulin resistance is also observed after longer treatments (Doyle et al., 1994a; Chipkin et al., 1998; Severino et al., 2002; Piroli et al., 2007; Su et al., 2014). This indicates that changes in insulin signaling contributes to the effects induced by GCs.

8.2.2. Brain insulin

Because of the GC-induced changes in the level of insulin, we should consider a role of insulin in central effects mediated by glucocorticoids. Such effect is possible because insulin crosses the blood-brain barrier by a saturable transport system (Banks et al., 1997; Rhea et al., 2018) and activates specific receptors that are present in the brain and affect various processes including metabolism, apoptosis, neuronal plasticity and regulation of food intake (Arnold et al., 2018). Although insulin is not necessary for the neuronal uptake of glucose (Heidenreich et al., 1989; Uemura and Greenlee, 2006), it supports an increased uptake

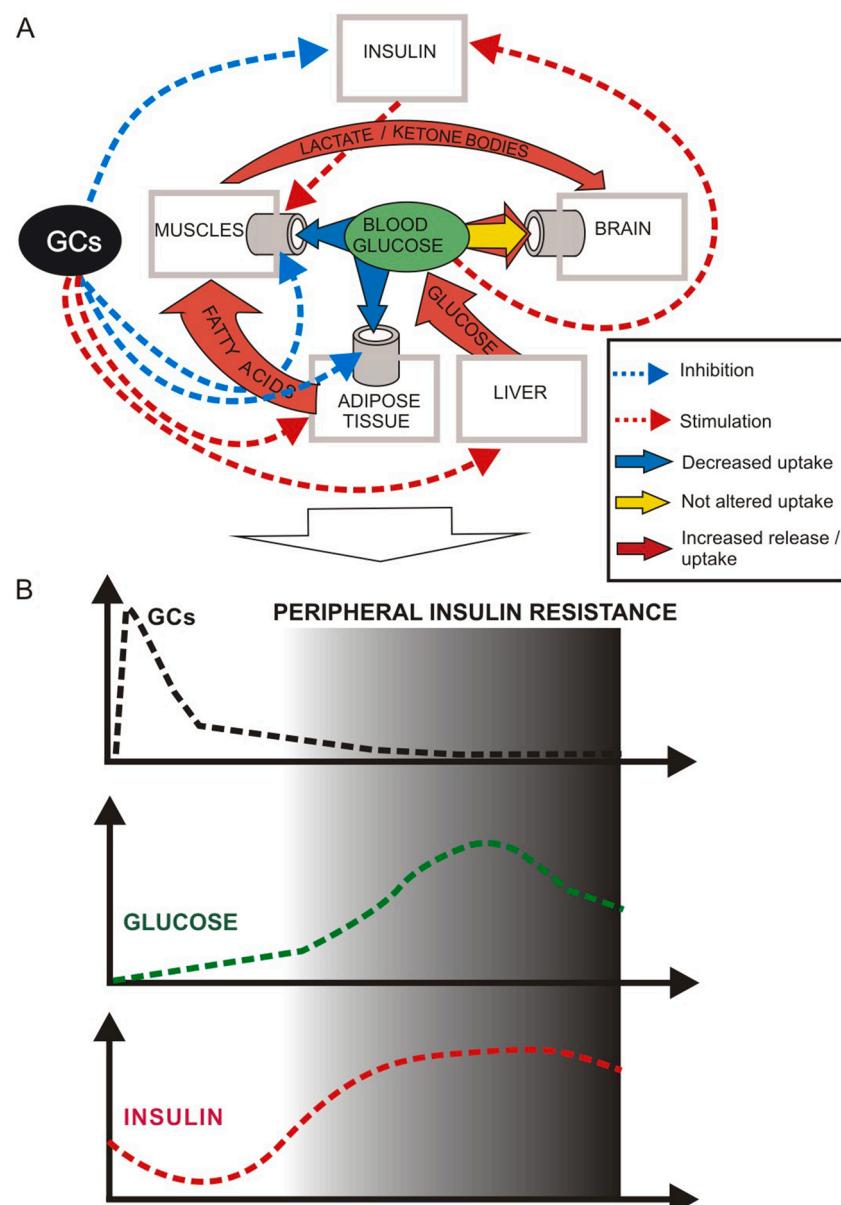


Fig. 3. Mechanisms responsible for GC-induced changes in the blood level of glucose and lipids. The gray color (B) indicated increasing insulin resistance. For more details see Section 8.1 (overview) and subsequent sections discussing in detail regulation of insulin (8.2), glucose (8.3) and other metabolites (8.5).

during periods of neuronal excitation (Uemura and Greenlee, 2006). Despite the importance of this topic, there are few experimental data showing involvement of insulin in brain metabolic effects mediated by GCs. First, acute treatment with dexamethasone impaired the insulin-stimulated glucose uptake in accumbal slices 35 min after treatment (Pinheiro et al., 2016). Second, repeated treatments with corticosterone (7 days) resulted in the impaired hippocampal signaling mediated by the insulin receptor, a decreased level of glucose transporter type 4 (GLUT4) and blocked translocation of GLUT4 to the plasma membrane in response to glucose bolus (Piroli et al., 2007). Third, treatment with dexamethasone for one week attenuated the actions of insulin in arcuate nucleus leading to a decreased sympathoexcitatory response to insulin (Steiner et al., 2014). This effect was specific for some brain areas since the same treatment schedule did not affect insulin signaling in ventral hypothalamus (Steiner et al., 2014). The whole brain insulin resistance was not either present after two days of treatment with dexamethasone (Su et al., 2014) but these data are difficult for interpretation because of specific properties of dexamethasone (Section 3.1,

4 and 5, Fig. 1). On the other hand, there are data showing that chronic hyperinsulinemia is important for induction of an increased brain uptake of glucose after the repeated treatment with dexamethasone (Chipkin et al., 1998) consistently with an increased brain/plasma glucose ratio after joint treatment with dexamethasone and insulin (Thompson et al., 2000). The picture is further complicated by the fact that dexamethasone also impairs the efficiency of brain insulin uptake as indicated by an experiment performed in dogs (Baura et al., 1996). Collectively, these data show that insulin contributes to effects mediated by GCs in brain although the extent of these actions and underlying mechanisms are still poorly understood.

8.3.1. Blood glucose

The time course of changes in blood glucose varies between studies and species. In humans most studies show that glucose does not increase during the first 2 h after treatment with cortisol (Shamoon et al., 1980a; Garrel et al., 1995; Plat et al., 1996; Vila et al., 2010) or changes are small because they are within an about 10 % range (Clerc et al., 1986; de

Leon et al., 1997). A clear increase starts at longer delays (Shamoon et al., 1980a; Clerc et al., 1986; Garrel et al., 1995; Plat et al., 1996; Vila et al., 2010) and plateau is achieved after 4–6 hours when the change in blood glucose is approaching 30 % (Clerc et al., 1986; Plat et al., 1996) (Fig. 2A). It should be noted, however, that much faster and higher increases in blood glucose were found in two studies (Fig. 2B). One of them applied dexamethasone (Schneiter and Tappy, 1998) which is a very potent synthetic glucocorticoid while the other study applied pituitary-pancreatic clamp infusion of somatostatin, insulin, growth hormone and glucagon to maintain all hormone concentrations in the fasting range, except for that of cortisol (Khani and Tayek, 2001). Therefore, both studies are not likely to represent physiological conditions associated with an increased level of endogenous GCs. In rats, the time course of blood glucose response to corticosterone (Sapolsky, 1986; Southorn et al., 1990) is similar to human studies applying cortisol (Fig. 2C). Lack of changes was observed during the first 2 h (Billaudel and Sutter, 1982; Sapolsky, 1986; Southorn et al., 1990) after corticosterone treatment while an increase occurred after 3–4 hours (Sapolsky, 1986; Southorn et al., 1990). An elevated level of glucose was still observed 12 (Sapolsky, 1986; Southorn et al., 1990) and 24 h (Southorn et al., 1990) after a single injection of corticosterone and after repeated treatments with dexamethasone (Thompson et al., 2000). In contrast, mice displayed changes in blood glucose much faster than humans and rats because significant hyperglycemia was observed 30, 60 (Longano and Fletcher, 1983) and 120 min after treatment with cortisol (Watanabe and Passonneau, 1973; Longano and Fletcher, 1983) although some researchers observed this effect only in fasted animals (Watanabe and Passonneau, 1973). It is possible that the time course of metabolic effects depends on the body weight and related rate of metabolism leading to differences between species. It also suggests that rats may be a better model of human metabolic responses to GCs than mice because of a stable blood level of glucose during the first two hours followed by hyperglycemia that develops 3–4 hours after treatment.

8.3.2. Brain glucose

8.3.2.1. First 2–3 hours after acute treatment. Glucose is especially important for the brain because it has a very limited ability to oxidize fatty acids and, therefore, requires a constant supply of glucose in contrast to other tissues (Yang et al., 1987; Schonfeld and Reiser, 2013). This severe dependence on glucose supply is demonstrated by the loss of consciousness triggered by a sudden drop of blood glucose due to insulin overdose (Cryer, 2007; Kalra et al., 2013). The only study that tested immediate effects of GCs (15 s) was performed in adrenalectomized and anaesthetized rats (Landgraf et al., 1978). This study reported a decreased incorporation of glucose in most brain areas but because of adrenalectomy and anesthesia these data are not comparable with normal physiological conditions (Section 2.3). Furthermore, very short latency after administration of corticosterone was not sufficient for penetration of the blood-brain barrier (Section 3.2.1). Other experiments applied much longer latencies between treatments and measurements of glucose utilization (Table 1). Most frequently, there were no changes in the brain glucose uptake during the first two hours after treatment with GCs (Table 1), that is at the time when changes in blood glucose are usually negligible or very small (Fig. 2). The lack of significant changes in the uptake of 2-deoxyglucose was found in basal conditions in slices derived from rat nucleus accumbens and treated with dexamethasone (35 min) (Pinheiro et al., 2016), mouse brain including hippocampus in response to corticosterone (55 min) (Delanoy and Dunn, 1978), most of the human brain with an exception of the hippocampus after administration of cortisol (55 min) (de Leon et al., 1997) and in hippocampal astrocytes treated with corticosterone (1 and 2 h) (Virgin et al., 1991). There were neither any changes in the level of glucose in the mouse brain 2 h after treatment with cortisol (Watanabe and Passonneau, 1973). Some studies reported the lack of significant changes

even at longer latencies, that is 3 h after administration of dexamethasone (total brain glucose) (Thompson et al., 2000) and after 4 h of corticosterone treatment (2DG in mixed neuronal/glial culture derived from the hippocampus) (Horner et al., 1990). The only positive finding during the first 3 h was a decreased uptake in the human hippocampus after administration of cortisol (55 min) (de Leon et al., 1997) and prevention of the insulin-stimulated glucose uptake in accumbal slices treated with dexamethasone (35 min) (Pinheiro et al., 2016). Collectively, these data indicate that during an initial period of 2–3 hours after treatment with GCs, the changes in the brain glucose level and its utilization are in most cases negligible. Although there is a problem of restricted penetration of the blood-brain by cortisol and dexamethasone (Section 3.1), negative results are confirmed with corticosterone *in vivo* (Delanoy and Dunn, 1978) and *in vitro* both in hippocampal astrocytes (Virgin et al., 1991) and in mixed culture derived from the hippocampus (Horner et al., 1990).

8.3.2.2. 4–12 hours after acute treatment. Longer latencies after a single treatment with GCs were associated with more variable effects that additionally depended on the studied brain area. Experiments performed on hippocampal cell cultures that contained various proportion of astrocytes (from 20 % to more than 95 %) revealed a decreased glucose uptake after treatment with corticosterone and dexamethasone (Horner et al., 1990; Virgin et al., 1991). A significant effect occurred after 4–8 hours (Horner et al., 1990; Virgin et al., 1991), achieving maximum values after 12 h (Virgin et al., 1991). Importantly, the reduced glucose uptake was not associated with a significant change in the level of intracellular glucose in hippocampal astrocytes after treatment with corticosterone (Tombaugh et al., 1992). A potential mechanism responsible for decreased utilization of glucose is increased expression of pyruvate dehydrogenase kinase (Pdk4) which suppresses the oxidation of glucose (Juszczak and Stankiewicz, 2018). The inhibition of glucose uptake depends, however, on the studied brain area because differences existed in hippocampal cells (astrocytes, mixed and neuron-enriched cultures) after corticosterone treatment lasting for 24 h but not in cortical and cerebellar astrocytes and mixed cell cultures derived from cortex, cerebellum and hypothalamus (Horner et al., 1990; Virgin et al., 1991). Other research groups testing dexamethasone found even increased glucose uptake in cortical astrocytes after 9 h (Allaman et al., 2004) and in astrocytes obtained from brain hemisphere after 24 h (Skupio et al., 2019). The significant effect after 9 h was visible only when dexamethasone was administered without the concomitant treatment with noradrenaline (Allaman et al., 2004). This indicates that the effects induced by GCs may vary greatly depending on interaction with other signaling molecules.

There is a question about functional significance of observed changes in the glucose uptake in cell cultures that are maintained in stable milieu because a decreased uptake detected *in vitro* coincides with increased glucose availability *in vivo* (Fig. 2). There is a possibility that a decreased rate of glucose uptake is compensated by increased glucose availability. Explaining this issue requires *in vivo* experiments but available data provided discrepant results. First, there is a study performed in rat pups (7 days old) that revealed a decreased uptake in several brain regions (including hippocampus) in basal conditions 6 h after treatment with dexamethasone (Tuor et al., 1997). In contrast, the experiment performed in older rats showed the lack of changes in the hippocampus and in most of other brain areas at comparable latency (5 h) after administration of dexamethasone (Kaderek et al., 1988) (Table 1). However, both studies suffer from methodological problems such as administration of dexamethasone (Kaderek et al., 1988; Tuor et al., 1997) characterized by restricted penetration of the blood-brain barrier and a different pattern of affinity to MRs and GRs compared with endogenously released corticosterone (Section 3.1 and 4, Fig. 1). There is also a problem of interaction with circadian release of corticosterone (Section 5, Fig. 1) although in this case it should play rather a minor role

Table 1
Effect of GCs on brain glucose uptake.

Author	Species	Experiment	Measurement	Brain area	Drug /dose	Latency	Effect
(Landgraf et al., 1978)	Rats (Adx)	<i>In vivo</i> Anaest.	[¹⁴ C]glucose	Most of the brain	Corticosterone 1–100 µg/mL	15 s	Decrease
(Pinheiro et al., 2016)	Rats	<i>In vitro</i> slices	[³ H]2-deoxyglucose	Nucleus accumbens	Dexamethasone 1–10 µM	35 min	No effect on basal glucose uptake
(Pinheiro et al., 2016)	Rats	<i>In vitro</i> slices	[³ H]2-deoxyglucose	Nucleus accumbens	Dexamethasone 1–10 µM	35 min	Prevents insulin-stimulated glucose uptake
(Delanoy and Dunn, 1978)	Mice	<i>In vivo</i>	[³ H]2-deoxyglucose in dissected brain regions	Whole brain and several regions analyzed separately	Corticosterone 2.5 mg/kg	55 min	No effect on basal glucose uptake.
(de Leon et al., 1997)	Human	<i>In vivo</i>	2-deoxy-2-[¹⁸ F]fluoro-D-glucose PET	Hippocampus	Cortisol 35 mg	55 min	Reduced brain glucose utilization
(de Leon et al., 1997)	Human	<i>In vivo</i>	2-deoxy-2-[¹⁸ F]fluoro-D-glucose PET	Brain with the exception of hippocampus	Cortisol 35 mg	55 min	No significant changes in brain glucose utilization
(Fishman and Reiner, 1972)	Rats	<i>In vivo</i>	3-O-methyl-D-[¹⁴ C] glucose	Pons, cerebellum, brain hemisphere	Cortisol 75 mg/kg	1 h	No effect
(Virgin et al., 1991)	Rats	<i>In vitro</i>	[¹⁴ C]2-deoxy-D-glucose	Hippocampal astrocytes	Corticosterone 1 µM	1–2 h	No effect
(Watanabe and Passonneau, 1973)	Mice	<i>In vivo</i>	Total glucose	Whole brain	Cortisol 25 mg/kg i.p.	2 h	No effect
(Horner et al., 1990)	Rats	<i>In vitro</i>	[¹⁴ C]2-deoxy-D-glucose	Mixed (neuronal/glial) hippocampal culture	Corticosterone 1 µM	4 h	No effect
(Virgin et al., 1991)	Rats	<i>In vitro</i>	[¹⁴ C]2-deoxy-D-glucose	Hippocampal astrocytes	Corticosterone 1 µM	4, 8, 12 and 24 h	Decreased glucose uptake
(Tuor et al., 1997)	Rats (pups)	<i>In vivo</i>	[¹⁴ C]2-deoxy-D-glucose	Hippocampus, ventrolateral thalamus, parietal cortex, mid caudate nucleus	Dexamethasone 0.1 mg/kg	6 h	Decreased glucose uptake
(Tuor et al., 1997)	Rats (pups)	<i>In vivo</i>	[¹⁴ C]2-deoxy-D-glucose	Corpus callosum, hippocampus, ventrolateral thalamus, hypothalamus, parietal cortex, mid caudate nucleus	Dexamethasone 0.1 mg/kg + hypoxia	7.5 h–9 h	Increased glucose uptake
(Kadekaro et al., 1988)	Rats (sham-operated)	<i>In vivo</i>	[¹⁴ C]2-deoxy-D-glucose in slices	Most of brain	Dexamethasone 0.25 mg/kg	5 h	No effect
(Kadekaro et al., 1988)	Rats (sham-operated)	<i>In vivo</i>	[¹⁴ C]2-deoxy-D-glucose in slices	Locus ceruleus	Dexamethasone 0.25 mg/kg	5 h	Increase
(Kadekaro et al., 1988)	Rats (sham-operated)	<i>In vivo</i>	[¹⁴ C]2-deoxy-D-glucose in slices	Median eminence, pituitary anterior lobe, superior cervical ganglion	Dexamethasone 0.25 mg/kg	5 h	Decrease
(Horner et al., 1990)	Rats	<i>In vitro</i>	[¹⁴ C]2-deoxy-D-glucose	Mixed (neuronal/glial) hippocampal culture	Corticosterone 1 µM	8, 12 and 24 h	Decreased glucose uptake
(Allaman et al., 2004)	Mice	<i>In vitro</i>	[¹⁴ C]2-deoxy-D-glucose	Cerebral cortical astrocytes	Dexamethasone 100 nM	9 h	Increased glucose uptake
(Allaman et al., 2004)	Mice	<i>In vitro</i>	[¹⁴ C]2-deoxy-D-glucose	Cerebral cortical astrocytes	Dexamethasone 100 nM + noradrenaline	9 h	No effect
(Horner et al., 1990)	Rats	<i>In vitro</i>	[¹⁴ C]2-deoxy-D-glucose	Mixed (neuronal/glial) hippocampal culture	Dexamethasone 10 nM–1 µM Corticosterone (100 nM–1 µM)	24 h	Decreased glucose uptake
(Virgin et al., 1991)	Rats	<i>In vitro</i>	[¹⁴ C]2-deoxy-D-glucose	Hippocampal astrocytes	Dexamethasone 100 nM–10 µM	24 h	Decreased glucose uptake
(Tombaugh et al., 1992)	Rats	<i>In vitro</i>	[¹⁴ C]2-deoxyglucose	Hippocampal Astrocytes	Corticosterone 100 nM	24 h	Decreased glucose uptake
(Virgin et al., 1991)	Rats	<i>In vitro</i>	[¹⁴ C]2-deoxy-D-glucose	Cortical and cerebellar astrocytes	Corticosterone 1 µM	24 h	No effect
(Horner et al., 1990)	Rats	<i>In vitro</i>	[¹⁴ C]2-deoxy-D-glucose	Mixed cortical, cerebellar/brainstem, hypothalamic (neuronal/glial) culture	Corticosterone 1 µM	24 h	No effect
(Horner et al., 1990)	Rats	<i>In vitro</i>	[¹⁴ C]2-deoxy-D-glucose	Neuronal (80 %) hippocampal culture	Corticosterone 1 µM	24 h	Decreased glucose uptake
(Skupio et al., 2019)	Mice	<i>In vitro</i>	2-deoxyglucose-6-phosphate	Cultured astrocytes from brain hemispheres	Dexamethasone 100 nM	24 h	Increased glucose uptake
(Thompson et al., 2000)	Rats	<i>In vivo</i>	Total glucose	Whole brain	Dexamethasone 2 mg/kg i.p.	1–4 days	Increased glucose content
(Doyle et al., 1994a)	Rats	<i>In vivo</i>	[¹⁴ C]2-deoxy-D-glucose	hippocampus, septal nuclei, caudate putamen, median eminence	Corticosterone pellets 70 mg	2 days	Increased brain glucose utilization
(Doyle et al., 1994a)	Rats	<i>In vivo</i>	[¹⁴ C]2-deoxy-D-glucose	Lateral habenula, mediodorsal thalamic nuclei, the dorsomedial and ventromedial hypothalamic nuclei	Corticosterone pellets 70 mg	2 days	Reduced brain glucose utilization
	Rats	<i>In vivo</i>	[¹⁴ C]2-deoxy-D-glucose			2 days	No change

(continued on next page)

Table 1 (continued)

Author	Species	Experiment	Measurement	Brain area	Drug /dose	Latency	Effect
(Doyle et al., 1994a)				Number of other brain areas and total cerebral utilization	Corticosterone pellets 70 mg		
(Fishman and Reiner, 1972)	Rats	In vivo	2-deoxy-D-[¹⁴ C]glucose or 3-O-methyl-D-[¹⁴ C]glucose	Pons, cerebellum, brain hemisphere	Cortisol 75 mg/kg	5–7 days	No effect
(Chipkin et al., 1998)	Rats	In vivo	[¹⁴ C]-D-glucose	Whole brain	Dexamethasone 1 mg/day + sucrose feeding	7 days	Increased uptake
(Chipkin et al., 1998)	Rats	In vivo	[¹⁴ C]-D-glucose	Whole brain	Dexamethasone 1 mg/day	7 days	Insignificant
(Thurston et al., 1980)	Mice	In vivo	Total glucose	Whole brain	Cortisol 50 mg/kg s.c.	10 days	Increased content
(Thurston et al., 1980)	Mice	In vivo	3-O-[¹⁴ C]methyl-D-glucose	Whole brain	Cortisol 50 mg/kg s.c.	10 days	Increased brain/plasma ratio
(Thurston and Pierce, 1969)	Mice	In vivo	Total glucose	Whole brain	Cortisol 50 mg/kg s.c.	10 days	Increased content
(Liu et al., 2018)	Human	In vivo	[¹⁸ F]-fluorodeoxyglucose positron emission tomography	Basal ganglia, limbic lobe, parahippocampal gyrus, hippocampus, amygdala, thalamus, precentral cortex, and cerebellum	Cushing's disease		Increased brain glucose utilization
(Liu et al., 2018)	Human	In vivo	[¹⁸ F]-fluorodeoxyglucose positron emission tomography	Medial and lateral frontal cortex, superior and inferior parietal lobule, medial occipital cortex, and insular cortex	Cushing's disease		Reduced brain glucose utilization
(Brunetti et al., 1998)	Human	In vivo	[¹⁸ F]-fluorodeoxyglucose PET	Entire brain with the exception of striatum	Cushing's disease		Reduced brain glucose utilization

* *in vitro* culture derived from fetuses derived from mothers that were either treated with corticosterone or adrenalectomized and treated with metyrapone to inhibit GC synthesis in fetuses (control).

considering the duration of experiments and the time course of circadian rhythm of corticosterone release (Reul et al., 1987). Finally, generalization of results is further compromised by utilization of pups (Tuor et al., 1997) that differ from mature animals in terms of brain metabolism (Nehlig, 1996; Dienel, 2012). Therefore, we still cannot unequivocally state what happens with the brain glucose uptake *in vivo* during the period ranging from approximately 4–12 hours after acute elevation of GCs when at least some genomic effects are expected to reach a maximum level (Section 6).

8.3.2.3. Repeated treatments with GCs. Repeated treatments with GCs are associated with an increased whole brain level of glucose as indicated by experiments performed in rats treated with dexamethasone for 1–4 days (Thompson et al., 2000) and young mice treated with cortisol for 10 days (Thurston and Pierce, 1969; Thurston et al., 1980). There are also some data showing an increased uptake of radiolabeled derivates of D-glucose although the results are more variable (Table 1). On the one hand, there was increased brain to plasma ratio of radiolabeled derivative of D-glucose after treatment with cortisol lasting for 10 days (Thurston et al., 1980), increased whole brain uptake in some conditions (high sugar intake) after 7 days of treatment with dexamethasone (Chipkin et al., 1998) and in some brain areas after two days of treatment with corticosterone (Doyle et al., 1994a). On the other hand, the same treatments did not affect the whole brain uptake in standard feeding conditions (Doyle et al., 1994a; Chipkin et al., 1998) while in some brain areas caused even a decrease in glucose uptake (Doyle et al., 1994a). Finally, there is one study that yielded negative results in the brain both after acute and repeated treatments (5–7 days) in mature and immature rats (Fishman and Reiner, 1972). However, this study also failed to find differences in the blood glucose level and glucose uptake in other tissues including muscles and liver even after repeated treatments with a high dose of cortisol (75 mg/kg) (Fishman and Reiner, 1972). Therefore, such unexpected negative results in all tissues suggest methodological problems.

Considering all available data, we can conclude that most experiments showed increases in uptake or the total brain level of glucose at least in some experimental conditions after repeated treatment with corticosterone, cortisol and dexamethasone (Thurston and Pierce, 1969;

Thurston et al., 1980; Doyle et al., 1994a; Chipkin et al., 1998; Thompson et al., 2000) while only one study showed concomitant local decreases after a relatively short period of treatment with corticosterone lasting for two days (Doyle et al., 1994a). To further disentangle these data, it is important to separate data concerning the total brain glucose from the uptake of its derivates marked with isotopes. The total brain glucose that was consistently increased by GCs (Thurston and Pierce, 1969; Thurston et al., 1980; Thompson et al., 2000) is informative on its own. In contrast, the uptake of radiolabeled derivates of glucose depends not only on brain metabolism but also on other factors such as route of injection, timing of measurements and concentration of blood glucose competing for transport across the blood-brain barrier. Therefore, the increased total brain glucose constitutes a basis for further consideration of the effects of repeated treatments with GCs on the whole brain metabolism (the next section).

8.3.2.4. Mechanism of increased brain glucose. Available data suggest two potential mechanisms responsible for the increased total brain glucose after repeated treatments with dexamethasone and cortisol (Thurston and Pierce, 1969; Thurston et al., 1980; Thompson et al., 2000). First, the transport of glucose across the blood-brain barrier is proportional to the blood level as indicated for example by diabetic animals (Gandhi et al., 2010). Therefore, the likely explanation is that an increased brain level of glucose results from peripheral effects of glucocorticoids triggering rise in blood glucose (Section 8.3.1, Fig. 2). Such a possibility is supported by observation that changes in the total brain glucose in rats treated with dexamethasone were indeed proportional to levels of blood glucose without significantly altered brain-to-plasma glucose ratio (Thompson et al., 2000).

Second, GCs can also affect efficiency of glucose transport across the blood-brain barrier because changes in brain glucose are not always associated with concomitant increases in blood glucose (Thurston and Pierce, 1969; Thurston et al., 1980). Changes in the brain up-take of 3-O-[¹⁴C]methyl-D-glucose after i.p. injection suggest increased transport in animals treated with cortisol but interpretation of these data is confounded by differences between groups in blood and the brain level of glucose (Thurston et al., 1980). However, experiments performed with [¹⁴C]deoxy-D-glucose confirmed that at least in some conditions

glucocorticoids may affect the transport of glucose across the blood-brain barrier. Chipkin et al. (1998) tested incorporation of radiolabeled D-glucose after single cerebral circulatory passage (5 s) in rats treated with dexamethasone for 3 and 7 days. All animals received a single dose of D-glucose together with $^3\text{H}_2\text{O}$ as an extraction marker and the solution was injected after transient interruption of the blood circulation in carotid artery. Therefore, detected brain uptake of the deoxy-D-glucose should not be affected by GC-induced changes in the level of blood glucose. The experiment showed that dexamethasone increased the uptake but only after longer treatments (7 days) combined with a high sugar intake (Chipkin et al., 1998). Changes in brain D-glucose uptake were associated with increased expression of glucose transporter GLUT1 in cerebral microvessels and required chronic hyperinsulinemia (Chipkin et al., 1998) consistently with the observation that joint treatment with dexamethasone and insulin increases the brain-to-plasma glucose ratio (Thompson et al., 2000). Therefore, prolonged treatment with GCs may affect the transport of glucose across the blood-brain barrier especially in cases when glucocorticoids are combined with elevated glucose consumption and chronic hyperinsulinemia.

Obviously, there is a question about benefits of an increased level of brain glucose. In fact brain has privileged access to glucose and even in most extreme conditions like starvation receives sufficient amount of nutrients to maintain its structure in contrast to other organs (Peters, 2011). Increased blood glucose facilitates entrance of glucose into the brain and this additional fuel can be used at the time of increased energy expenditures. However, unused glucose that accumulates in the brain due to its increased blood level or potentiated transport constitutes a metabolic stress and therefore is not beneficial (Gandhi et al., 2010; Rowan et al., 2018).

8.3.2.5. Cushing's disease. Previous studies were restricted to several days of treatment with GCs and, therefore, there are no experimental data concerning a chronic effect of glucocorticoids on brain glucose utilization and the only source of information comes from patients with Cushing's disease. PET experiments provided, however, inconsistent results because both widespread decrease (Brunetti et al., 1998) and mixed results including an increase in numerous brain areas such as hippocampus were reported (Liu et al., 2018) (Table 1). One of the possible explanation of discrepancies is a difference in number of tested subjects because Brunetti et al. (1998) tested only 13 patients while Liu et al. (2018) investigated 92 patients and, therefore, the later study is more representative. This is important because Cushing's disease is not homogenous in terms of glucose homeostasis. It is estimated that up to 70 % of patients with Cushing's disease have impaired glucose metabolism including diabetes mellitus (20–45 %) and defective glucose tolerance (10–30%) although in many cases these patients display normal fasting glucose levels (Scaroni et al., 2017). Previous PET studies indicated a normal level of glucose in tested patients but the measurement procedure was not clearly described and probably was restricted to standard fasting condition (Brunetti et al., 1998; Liu et al., 2018) that is not sufficient to unequivocally identify abnormalities in glucose metabolism found in Cushing's disease (Scaroni et al., 2017). These data indicate that chronic exposure to cortisol affects both peripheral and brain metabolism of glucose although there is a considerable variability between patients and studies. Identification of subgroups displaying comparable glucose impairments in blood constitute a potential avenue for understanding variability between patients in brain glucose utilization.

8.4. Brain glycogen

Glucose entering the brain can be either catabolized or stored in the form of glycogen which is accumulated by astrocytes (Brown and Ransom, 2007, 2015). There is a growing body of evidence that

astrocytic glycogen is not only an energy storage activated in pathological conditions but also has an important function in normal brain physiology. It is stored in astrocytic processes contacting neurons and, therefore, can be quickly mobilized to provide 'fast' ATP at times of locally increased energy demand over intervals too short to be met by changes in delivery of blood glucose (Dienel and Carlson, 2019; Wu et al., 2019). Therefore, the blood-born glucose is used to replenish the local pools of glycogen during periods of lower activity (glycogen shunt) and the glycogenolysis is activated during bursts of neuronal activity to buffer against rapid changes in energy demands (Dienel and Rothman, 2019).

Administration of radiolabeled glucose in fasted mice showed that acute cortisol increases both synthesis and utilization of brain glycogen (Watanabe and Passonneau, 1973). This explains the variability of results that showed both an increased level of brain glycogen after acute (0.5–5 h) and repeated (6–10 days) administration of cortisol in mice, rats and rabbits (Timiras et al., 1956; Coxon et al., 1965; Watanabe and Passonneau, 1973; Thurston et al., 1980), an insignificant effect of cortisol (Thurston and Pierce, 1969; Watanabe and Passonneau, 1973) and dexamethasone (Klepac, 1985; Thompson et al., 2000) after acute and repeated treatments and, finally, a decreased level of glycogen in astrocytic cultures treated with corticosterone and dexamethasone for 9–24 h (Tombaugh et al., 1992; Allaman et al., 2004; Skupio et al., 2019). Differences between *in vivo* (Timiras et al., 1956; Coxon et al., 1965; Thurston and Pierce, 1969; Watanabe and Passonneau, 1973; Thurston et al., 1980) and *in vitro* (Tombaugh et al., 1992; Allaman et al., 2004; Skupio et al., 2019) experiments also suggest that there are metabolic differences between these conditions that preferentially uncover one component of responses to GCs in astrocytic cultures. A potential mechanism supporting accumulation of glycogen is increased expression of glycogenin (Gyg1) after treatment with GCs (Juszczak and Stankiewicz, 2018). This effect can be further potentiated by increased availability of ketone bodies derived from lipid catabolism that constitute an alternative source of energy for brain (Thurston et al. 1980). Finally, increased brain synthesis of glycogen can also result from increased availability of blood glucose. In the experiment performed by Watanabe and Passonneau (1973), increased brain glycogen was associated with increased blood glucose in fasted animals in contrast to negative effects of cortisol in normally fed animals that displayed both insignificant changes in brain glycogen and blood glucose. Therefore, an increased level of brain glycogen can result both from peripheral effects of GCs leading to an increased level of blood glucose and central effects facilitating synthesis of glycogen. In contrast, there are no clues suggesting the mechanism responsible for facilitated utilization of glycogen. Nonetheless, it is clear that the double effect of GCs, which both increase synthesis and utilization of brain glycogen (Watanabe and Passonneau, 1973), clearly supports a metabolic flexibility of neuronal networks.

8.5. Other metabolites

An increased blood level of glucose is associated with an increased level of lactate (Thompson et al., 2000; Bordag et al., 2015), pyruvate (Bordag et al., 2015), mannose, 3-hydroxybutyrate (ketone bodies) and other metabolites (Thurston et al., 1980; Dardzinski et al., 2000; Bordag et al., 2015). These effects occur usually as early as 6 h after treatment with dexamethasone (Bordag et al., 2015). Importantly, mentioned metabolites cross the blood-brain barrier (Oldendorf, 1971; Fuglsang et al., 1986; Miller and Oldendorf, 1986; Bhattacharya and Boje, 2004; Knudsen, 2012) and are used by the brain as an alternative source of energy (Dringen et al., 1994; Smith et al., 2003; Zielke et al., 2009; Wyss et al., 2011; Achanta and Rae, 2017; Achanta et al., 2017; Rastedt et al., 2017).

Ketone bodies are produced mainly in the liver from free-fatty acids (Evans et al., 2017) while the source of glucocorticoid-induced mannose is not clear. It is known that the blood level of mannose is closely correlated with glucose and that it is increased in diabetic subjects (Sone

et al., 2003; Mori et al., 2009). Therefore, it is not surprising that mannose is also increased at the time of GC-induced insulin resistance.

The precise source of increased blood lactate and pyruvate found after treatment with dexamethasone is also not well defined (Thompson et al., 2000; Bordag et al., 2015). One of the involved mechanisms is probably increased expression of pyruvate dehydrogenase kinase (Pdk4) in muscles (Salehzadeh et al., 2009) and brain astrocytes (Juszczak and Stankiewicz, 2018) consistently with local changes in levels of these metabolites in muscles and cultured astrocytes in response to dexamethasone (Ardawi and Jamal, 1990; Allaman et al., 2004; Skupio et al., 2019). The activity of Pdk4 suppresses the influx of glycolytic metabolites into mitochondria leading to decreased incorporation of pyruvate into Krebs cycle and increased production of lactate (Liu et al., 2017; Juszczak and Stankiewicz, 2018). This in turn constitutes a part of mechanism responsible for the switch from utilization of glucose to fatty acids as an energy source (Connaughton et al., 2010). Increased production of lactate is present after acute treatment with dexamethasone in astrocytic cell culture in basal conditions (Allaman et al., 2004; Skupio et al., 2019) or can be unmasked in brain by special conditions such as hypoxic-ischemic insult occurring 24 h after a single dose of dexamethasone *in vivo* (Tuor et al., 1997). Although the interpretation of actions triggered by dexamethasone is complicated (Section 5, Fig. 1), the simplest explanation for these delayed brain effects is increased availability of blood glucose that was also unmasked by injury (Tuor et al., 1997). While acute treatments with dexamethasone increased production of lactate, such effect was not observed in the brain after repeated treatment with cortisol *in vivo* (Thurston and Pierce, 1969; Thurston et al., 1980). It is not clear, however, whether the negative data result from adaptation to elevated levels of GCs, different properties of dexamethasone and cortisol (Section 4, Fig. 1) or from disrupted release of endogenous corticosterone counterbalancing the effects of administered cortisol (Section 5, Fig. 1).

Acute changes in blood levels of lactate that were found after treatment with dexamethasone (Thompson et al., 2000; Bordag et al., 2015) can significantly affect brain metabolism. First, there are data showing that lactate is preferred over glucose when both substrates are available (Wyss et al., 2011) and, therefore, intravenous infusion of lactate leads to decreased glucose brain uptake (Smith et al., 2003). Second, according to the model of astrocyte-neuron lactate shuttle, astrocytes release lactate at the time of increased brain activity to provide fuel for neurons (Belanger et al., 2011). While there is an ongoing controversy regarding the fate of lactate released during brain activation (Dienel and Cruz, 2016), it is also known that brain oxidation of lactate increases at the time of altered concentration gradient due to an elevated blood level of this metabolite (Quistorff et al., 2008; van Hall et al., 2009; Rasmussen et al., 2011). Therefore, GC-induced rise in blood level of lactate due to peripheral effects in muscles is expected to increase the utilization of lactate in brain.

Summing up, available data show that GCs increase blood level of a number of metabolites such as 3-hydroxybutyrate (ketone bodies), mannose, pyruvate, and lactate that can be used by the brain to produce energy. These changes together with increased blood glucose constitute a metabolic context that is important for interpretation of brain effects of GCs especially in *in vitro* preparations that are maintained in a standard milieu.

8.6. Oxygen consumption

It is estimated that neurons produce about 80 % of total brain oxidative ATP (Hyder et al., 2006) while astrocytes rely largely but not exclusively on glycolysis (Bolanos, 2016). Although neurons and glial cells differ in metabolism, there is paucity of studies testing the effect of GCs on oxygen utilization in different cell types that are present in the nervous system. Only one study tested neuronal mitochondria (Du et al., 2009) while the remaining experiments used either anaesthetized animals (Liu and Zhou, 2012) or mitochondria obtained from a

homogenized brain tissue containing all types of cells (Bottoms and Goetsch, 1968; Morin et al., 2000; Katyare et al., 2003; Pandya et al., 2007).

Available data obtained in rats indicate that GCs induce a biphasic or even triphasic response. Shortly after treatment (15 min - 2 h) with various GCs (cortisol, corticosterone, dexamethasone, and prednisolone), a decrease in mitochondrial oxygen consumption was reported (Morin et al., 2000; Katyare et al., 2003). After 5 h there were no differences in adrenalectomized rats (see also Section 2.3) treated with corticosterone (Bottoms and Goetsch, 1968) while longer treatments lasting for 1–3 (Du et al., 2009) or 40 days (Liu and Zhou, 2012) resulted in increased mitochondrial oxidation in cortical neurons (Du et al., 2009) and reduced oxygen partial pressure in the rat brain suggesting increased *in vivo* oxygen utilization (Liu and Zhou, 2012). Finally, high doses of corticosterone (1 μM) decreased mitochondrial oxidation after 3 days, indicating the occurrence of toxic effect (Du et al., 2009). Mechanisms responsible for these effects are not well understood. Considering the time-course of responses ranging from minutes to days, both non-genomic and genomic actions of GCs should be considered (Section 6) including direct regulation of mitochondrial genes (Picard et al., 2018).

Presence of triphasic response may explain variable results obtained after repeated subcutaneous treatments (Katyare et al., 2003; Pandya et al., 2007) that involved different drugs (corticosterone vs dexamethasone), treatment schedules (consecutive days vs every second day), time of analysis after the last treatment (24 h vs 48 H), age of animals and metabolic substrates added to mitochondrial preparations (Katyare et al., 2003; Pandya et al., 2007). However, because of the large number of variables, these data are difficult to interpret.

Although the short-term (15 min–2 h) decrease in oxygen consumption following treatment with GCs may seem maladaptive, it can be easily understood considering a metabolic response to an increased neuronal activity observed for example during intense sensory stimulation or mental effort. Such activation is associated with highly increased nonoxidative glycolytic metabolism despite an excessive supply of oxygen due to locally increased blood flow (Dienel, 2012; Dienel and Cruz, 2016). Therefore, the biphasic effect consisting of initially decreased and then increased oxygen consumption in response to GCs may constitute an adaptation for initial increase in glycolytic metabolism associated with task-related brain activation followed by delayed compensation for a metabolic debt. On the other hand, delayed disruption of mitochondrial oxidation contributes to toxic effects induced by prolonged exposition to high doses of GCs.

8.7. Synthesis of ATP

8.7.1. Basal conditions

ATP is a molecule responsible for the transfer of energy needed for various processes taking place in cells. Medium doses of GCs applied for a restricted period of time (from 1 h to 10 days) usually did not affect the brain level of ATP or less frequently increase it. Lack of effect was observed *in vitro* after administration of corticosterone (100 nM) to astrocytes and mixed hippocampal cultures maintained in standard milieu (Tombaugh and Sapolsky, 1992; Brooke et al., 1998) and *in vivo* after treatment with cortisol (25–50 mg/kg) (Watanabe and Passonneau, 1973; Thurston et al., 1980). The same doses of cortisol occasionally increased the brain level of ATP *in vivo* (Thurston and Pierce, 1969; Watanabe and Passonneau, 1973) and in some cases the effect depended on the feeding status with lack of changes in fasted animals and an increased ATP level in fed mice (Watanabe and Passonneau, 1973). Lack of changes in the total pool of ATP was also reported *in vivo* after treatment with dexamethasone in basal conditions (Adlard and De Souza, 1974; Tuor et al., 1997; Adachi et al., 2001; Namba et al., 2002; Yorozuya et al., 2015). However, interpretation of results obtained with cortisol and dexamethasone is complicated by restricted entrance into the brain, differences in affinity to MRs and GRs and interaction with

endogenous release of glucocorticoids (Section 3.1, 4 and 5, Fig. 1). Nonetheless, negative results obtained with corticosterone in standard *in vitro* conditions (Tombaugh and Sapolsky, 1992; Brooke et al., 1998) support the notion that medium doses of GCs applied for a restricted period of time do not impair synthesis of ATP while some *in vivo* data obtained after cortisol treatment suggest that at least in some situations GCs may even increase the production of ATP (Thurston and Pierce, 1969; Watanabe and Passonneau, 1973).

8.7.2. Brain ischemia

Another common finding is that pretreatment with dexamethasone and cortisol slows ATP loss during severe but short-term brain ischemia lasting for 30 s–60 s after decapitation (Thurston et al., 1980; Adachi et al., 2001; Namba et al., 2002) or during more prolonged but gradual asphyxia leading almost to death (Adlard and De Souza, 1974). Such effect was found in mice (3 h and 10 days) (Thurston et al., 1980; Namba et al., 2002), mongolian gerbils (1 h) (Adachi et al., 2001) and rats (2 h) (Adlard and De Souza, 1974) while one study showed insignificant suppression of the ATP loss (3 h) (Yorozuya et al., 2015). Additionally, one study showed that dexamethasone (24 h) significantly slowed the loss of ATP during locally induced hypoxia (Tuor et al., 1997). Comparable results were also obtained after dexamethasone treatment (22 h) in the experiment applying ^{31}P magnetic resonance spectroscopy that allows for *in vivo* measurement of the total pools of inorganic phosphate and nucleoside triphosphate that includes ATP (Dardzinski et al., 2000). The limitation of these results is that they are based on treatment with dexamethasone (Adlard and De Souza, 1974; Tuor et al., 1997; Dardzinski et al., 2000; Adachi et al., 2001; Namba et al., 2002) and cortisol (Thurston et al., 1980), which penetrate the blood-brain barrier much less effectively than corticosterone and, therefore, may lead even to central hypocorticosteroid state (Section 3.1 and 5, Fig. 1). Therefore, interpretation of these results in terms of underlying mechanism is difficult, especially in the case of longer latencies between drug administration and metabolic testing (section 5). In contrast to short-term ischemia, the prolonged oxygen/glucose deprivation combined with corticosterone treatment leads to an opposed effect in cortical astrocytes (Tombaugh and Sapolsky, 1992). However, relevance of this *in vitro* finding for *in vivo* conditions has not been proven (see also Section 7.3). Collectively, available data show that pretreatment with GCs has a beneficial effect in case of short-term ischemia resembling a situation that can be found during strangling although significance of these findings for endogenously released GCs is not clear due to methodological limitations of performed experiments.

8.7.3. Toxic doses of GCs

A decreased level of ATP was observed in basal conditions after application of very high doses of corticosterone *in vitro* (10 μM) (Zheng et al., 2015; Zhao et al., 2018) or after prolonged *in vivo* treatments with corticosterone lasting for 7–21 days in mice (Zhao et al., 2008) and 40 days in rats (cortex and hippocampus) (Hoyer and Lannert, 2008). These data are consistent with the finding that longer treatments and high doses of corticosterone (1 μM) impair mitochondrial oxidation (Du et al., 2009). It should be noted, however, that the level of ATP returned to the baseline after 5 weeks of treatment with corticosterone (Zhao et al., 2008). Therefore, this study shows that there is an adaptation process counteracting toxic effects of prolonged treatment with corticosterone. Collectively, available data show that excessive doses of GCs disrupt production of energy in the brain.

8.7.4. Contribution of mitochondrial and glycolytic metabolism

ATP is synthesized both during cytosolic glycolysis and mitochondrial oxidative metabolism. In case of glycolysis that is increased by GCs at least in some conditions (Tuor et al., 1997; Allaman et al., 2004; Skupio et al., 2019) we can only assume the increased production of ATP but there are no studies quantifying contribution of glycolytic metabolism to total production of energy after treatment with GCs. In

contrast, we have some reports testing contribution of mitochondrial metabolism but the data are anyway fragmentary. The most consistent data show that mitochondrial synthesis of ATP is decreased 10 min - 2 h after treatment with corticosterone (Katyare et al., 2003; Fujita et al., 2009) consistently with decreased oxygen utilization at this period of time (Morin et al., 2000; Katyare et al., 2003). Other data are less consistent and more difficult for interpretation. For example, after repeated treatments (3 days) there were frequently reported decreases in mitochondrial synthesis of ATP but the results were variable because in some groups no changes or even increases were found (Katyare et al., 2003; Pandya et al., 2007). The mitochondrial synthesis of ATP varied depending on the treatment schedule (consecutive days vs every second day), time of analysis after the last treatment (24 h vs 48 H), injected drug (corticosterone vs dexamethasone), age of animals and metabolic substrates added to mitochondrial preparations (Katyare et al., 2003; Pandya et al., 2007). Because of the large number of variables, these data are difficult for interpretation. Finally, there is a study that found no effect 5 h after treatment with corticosterone (Bottoms and Goetsch, 1968) but the experiment was performed on adrenalectomized animals which restricts our ability to draw firm conclusions (section 2.3). Therefore, we still have very limited information about contribution of oxidative and nonoxidative metabolism to energy production in conditions of elevated levels of GCs and the most consistent data are restricted to first two hours after administration of corticosterone that results in decreased production of mitochondrial ATP.

8.8. Summary: the most consistent finding and existing gaps

Acute metabolic responses to GCs can be divided into early (first 2 h) and delayed (≥ 4 h) effects based on the time-course of concomitant changes in blood glucose (section 8.3.1, Fig. 2). During the first two hours after administration of GCs there is a decrease in oxidative production of energy (Morin et al., 2000; Katyare et al., 2003; Fujita et al., 2009) without concomitant decreases in total energy production (ATP) (Watanabe and Passonneau, 1973) and glucose utilization (section 8.3.2.1, Fig. 4). Unimpaired production of energy suggests that decreased oxidative metabolism is probably compensated by increased glycolysis but there are no data confirming this assumption. However, glycolysis is known to be increased by GCs at longer delays (Allaman et al., 2004; Skupio et al., 2019). GCs also promote syntheses and utilization of glycogen (Coxon et al., 1965; Watanabe and Passonneau, 1973) supporting metabolic flexibility (Fig. 4). The delayed phase starting after about 4 h is poorly understood. It is associated with increased blood availability of glucose (Section 8.3.1, Fig. 2) and other metabolic substrates (Section 8.5) that can be used to diversify sources of energy but the fate of these substances is unknown. Their utilization in brain metabolism can be assessed with MR spectroscopy after injection of substrates labeled with carbon-13 (Hyder and Rothman, 2017) but no such studies concerning GCs are available. *In vitro* experiments indicate changes in brain glucose utilization but there is a paucity of *in vivo* data that can be unequivocally interpreted (Section 8.3.2.2). Nonetheless, we can assume that during the delayed phase there is an increase in total blood glucose because its transport is proportional to blood levels (Gandhi et al., 2010) that achieve maximum concentration 4–6 hours after treatment with glucocorticoids (Section 8.3.1, Fig. 2). Although there are no data for this time window, it is known that the increased total brain level of glucose is present after repeated treatments (Thurston and Pierce, 1969; Thurston et al., 1980; Thompson et al., 2000). Longer treatments with GCs are also known to increase mitochondrial oxidative metabolism (Du et al., 2009) although excessive doses and prolonged treatments can lead to toxic effects disrupting mitochondrial oxidation (Du et al., 2009) and energy production (Section 8.7.3, Fig. 4). Available *in vivo* data also indicate that metabolic effects of GCs are affected by feeding status of animals (Watanabe and Passonneau, 1973; Chipkin et al., 1998) indicating flexibility of responses. One of the main weakness of available data is that they are

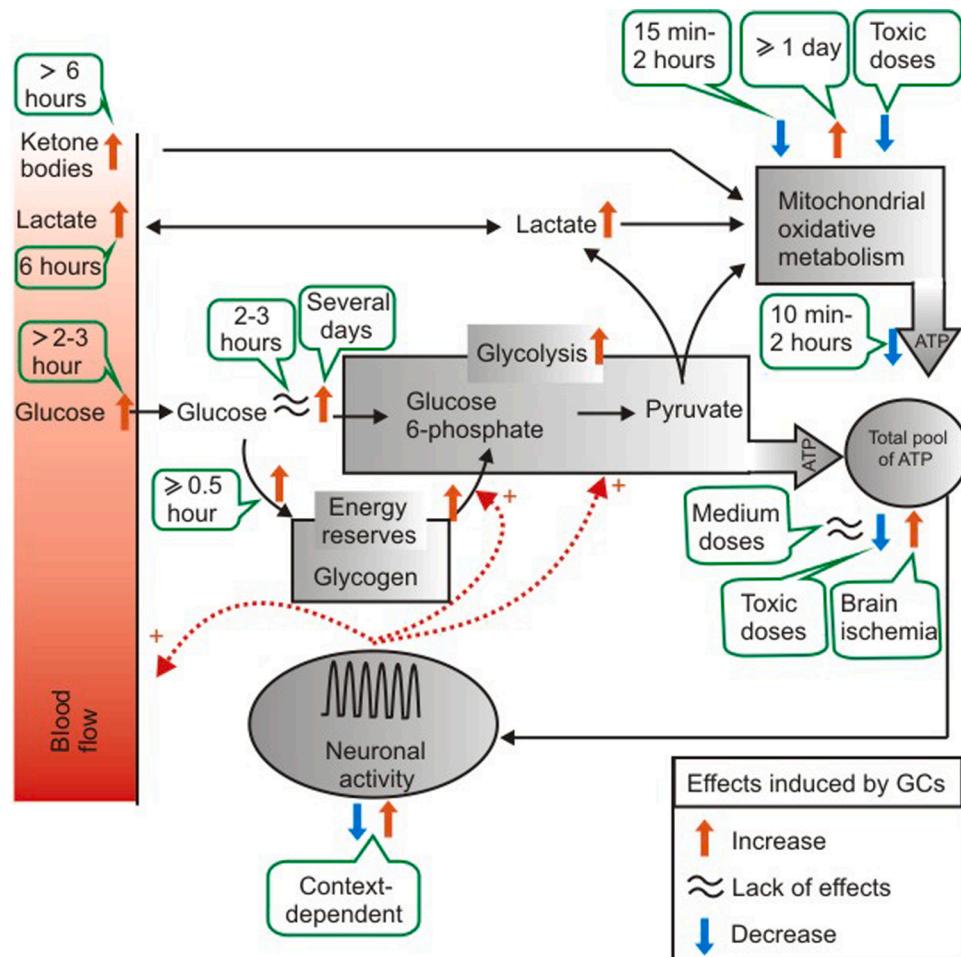


Fig. 4. Summary of the most important effects of GCs (Section 10) on brain metabolism and activity. Comments with green frames indicate time of occurrence of the effect after treatment with GCs or modifying factors. Metabolic effects of GCs include increased availability of energetic substrates in blood, facilitated synthesis and utilization of glycogen, increased glycolysis and time-dependent changes in oxidative metabolism. The total pool of energy (ATP) is not decreased by GCs in standard conditions, indicating maintained balance between energy production and utilization. However, prolonged treatments with excessive doses of GCs disrupt the production of energy, leading to toxic effects. A crucial limitation of available data is that metabolic experiments are restricted to resting or ischemic conditions and, therefore, have no behavioral relevance (Section 11). This is important because the brain activity varies considerably depending on the state of the organism and is regulated in a context-dependent manner by GCs (Section 10.3). Furthermore, the brain activity is intimately connected with metabolism because most of brain energy is consumed by neuronal signaling which in turn regulates regional blood flow, glycogen utilization and glycolysis.

restricted to resting conditions and often were performed in *in vitro* conditions with stable milieu. This is an important gap because brain metabolism is dynamic and depends on the neuronal activity that regulates blood flow leading to local changes in availability of metabolic substrates that are additionally modulated by peripheral effects of GCs (Section 8.3.1 and 8.5, Fig. 2). Additionally, available data contains many gaps concerning the time-course of observed effects and are frequently difficult for interpretation because of usage of exogenous GCs (Section 5, Fig. 1).

9. Brain activity

9.1. Electrophysiology

9.1.1. Activation vs inhibition of neuronal activity

First observations of altered brain excitability after treatment with glucocorticoids come from experiments investigating mechanisms of epilepsy (Hall, 1982). This line of research showed that GCs increase brain excitability as indicated by an increased propensity for occurrence of seizures after treatments with cortisol and corticosterone (Feldman and Davidson, 1966; Conforti and Feldman, 1975; Reddy, 2013). Similar conclusions were drawn from a number of experiments that found a cortisol-induced increase in the amplitude of evoked potentials (Table 2) which represent a summated activity of large populations of neurons. These observations indicate increased excitability leading to the lowering of the threshold for synaptic transmission (Feldman et al., 1961). However, the later experiment showed that cortisol affected the brain in two opposite ways because they both increased ascending activation of the brain stem in response to peripheral stimulation shortly

after treatment and facilitated forebrain inhibitory influence on the brain stem activating system that developed during the second hour (Endroczi et al., 1968). These early observations made with crude electrophysiological methods are consistent with a modern concept of the brain response to stress emphasizing biphasic and reciprocal regulation of brain salience and executive control networks leading to initial hypervigilant state facilitating detection of sensory stimuli (Hermans et al., 2014). Furthermore, the dual effect characterized by induction of facilitatory and inhibitory effects should be considered as a hallmark of actions induced by GCs because it is visible with different recording tools at different levels of brain circuitry.

First, both inhibitory and excitatory effects were observed in single-unit recordings when neurons were treated individually using microelectrophoresis (Table 3). Importantly, opposite effects were triggered with short latency after application of the same doses of GCs and with the same experimental set-up as indicated by experiments reporting both excitatory and inhibitory responses after administration of cortisol and corticosterone (for example Kelly et al. 1977; Papir-Kricheli and Feldman, 1981, 1982) (see also Table 3). This indicates that the opposite effects were not resulting from different doses, variable time of recording or other procedural and technical differences between studies. Similarly, both excitatory and inhibitory responses to GCs were also frequently reported by *in vivo* studies which additionally showed some percentage of cells with biphasic responses to cortisol indicating time-related changes (for example Slusher et al., 1966; Phillips and Dafny, 1971; Nagler et al., 1973) (see also Table 5).

Although the variability in responses is clearly cell type specific as indicated by microelectrophoresis (Table 3), it also results from altered signal transmission within the neural network. Zeise et al. (1992)

Table 2

Effect of GCs on brain evoked potentials.

Author	Species	Experiment	Drug	dose	Brain area	Measurement	Effect	Additional information
(Feldman et al., 1961)	Cats	<i>In vivo</i> anaest	Cortisol	25 mg i.v.	Hypothalamus, intralaminar nuclei of thalamus, midbrain reticular formation	Amplitude of evoked potentials triggered by stimulation of sciatic nerve.	↑	
(Endroczi et al., 1968)	Rats	<i>In vivo</i> anaest	Cortisol	5–10 mg i.p.	Brain stem reticular formation, ventromedial hypothalamic nucleus	Amplitude of evoked potentials triggered by stimulation of sciatic nerve.	↑	Detected after 30–45 min
(Endroczi et al., 1968)	Rats	<i>In vivo</i> anaest	Cortisol	5–10 mg i.p.	Brain stem reticular formation, ventromedial hypothalamic nucleus	Amplitude of evoked potentials triggered by stimulation of sciatic nerve.	↓	Detected after 90–150 min
(Endroczi et al., 1968)	Rats	<i>In vivo</i> anaest	Cortisol	5–10 mg i.p.	Specific sensory pathways (lemniscus)	Amplitude of evoked potentials triggered by stimulation of sciatic nerve.	≈	
(Endroczi et al., 1968)	Rats	<i>In vivo</i> anaest	Cortisol	100 ug i.v.	Brain stem reticular formation, ventromedial hypothalamic nucleus	Amplitude of evoked potentials triggered by stimulation of sciatic nerve combined with conditioning stimulation of the medial forebrain bundle.	↓	Developed in the second hour after treatment
(Feldman et al., 1973)	Rats	<i>In vivo</i> anaest	Cortisol	5 mg i.p.	Hypothalamus	Amplitude of evoked potentials triggered by photic stimulation, stimulation of sciatic nerve, reticular formation, septum, and hippocampus	↑/≈	
(Kavushansky and Richter-Levin, 2006)	Rats	<i>In vivo</i> anaest	Corticosterone	10–25 mg/kg	Basolateral amygdala	Amplitude of evoked potentials triggered by stimulation of the entorhinal cortex	↑	
(Feldman and Davidson, 1966)	Rabbits	<i>In vivo</i>	Cortisol	25 mg i.v.	Septum, hippocampus	Amplitude of evoked potentials obtained by stimulating the midbrain reticular formation	↑	
(Feldman and Davidson, 1966)	Rabbits	<i>In vivo</i>	Cortisol	25 mg i.v.	Hypothalamus	Amplitude of evoked potentials obtained by photic stimulation or stimulation of septum and midbrain reticular formation	↑	
(Marcus et al., 1966)	Cats	<i>In vivo</i> Paralysed	Cortisol	1% topical	Lateral gyrus	Amplitude of evoked potentials induced by photic stimulation	↑	
(Covian et al., 1963)	Cats	<i>In vivo</i> anaest	Cortisol	topical	Cortex (gyrus marginalis)	Amplitude of evoked potentials induced by photic stimulation	↑	

≈ - lack of effect; ↑ - increased amplitude; ↓ - decreased amplitude.

showed that corticosterone reduces both GABAergic inhibition and excitability of hippocampal pyramidal neurons (Zeise et al., 1992). This pattern of changes suggests that corticosterone inhibits hippocampal responses to single stimulation but increases activity in response to repetitive excitatory stimulations (Zeise et al., 1992). The importance of the input signals on responsiveness of neurons to GCs (cortisol, corticosterone, dexamethasone) is also visible in experiments testing effects of glucocorticoids on resting and sensory-evoked activity (Feldman and Dafny, 1970b, a; Nagler et al., 1973; Mandelbrod et al., 1981; Feldman et al., 1983; Lei et al., 2014). For example, hypothalamic neurons that are not sensitive to locally applied cortisol (with background stimulation with glutamate) become sensitive at the time of distal (sensory and hippocampal) stimulation (Mandelbrod et al., 1981). Even more strikingly, some hypothalamic neurons may even change the direction of responses to corticosterone and cortisol (inhibition / excitation) depending on the presence or absence of sensory stimulation (Feldman and Dafny, 1970a; Feldman et al., 1983). Similarly, a more recent study found that locally applied dexamethasone both increase and decrease neuronal activity in resting conditions but induce a general increase in the firing of auditory neurons at the time of sensory stimulation (Lei et al., 2014).

Summing up, these data indicate that in normal nonepileptic brain GCs alter dynamics of the neuronal activity instead of inducing exclusively inhibitory or excitatory effects. Therefore, depending on interaction with other factors, GCs may lead to variable neuronal responses including both excitation and inhibition. This, in turn, is expected to support task-related activity in responses to environmental challenges. These conclusions are consistent with variable responses observed after treatment with cortisol (Henckens et al., 2010, 2012b; Sudheimer et al.,

2013; Bos et al., 2014; Montoya et al., 2015) and prednisolone (Bua-des-Rotger et al., 2016) in humans. For example, differential responses were reported by fMRI studies depending on the threat escapability (Montoya et al., 2015) and emotional valence of presented stimuli (Henckens et al., 2010, 2012b; Sudheimer et al., 2013; Bos et al., 2014; Bua-des-Rotger et al., 2016). These observations also indicate that it is important to consider the effect of GCs both on resting and task-evoked activity. This is especially important for interpretation of metabolic studies that were performed mainly in resting conditions or less frequently during severe brain ischemia but not during a task-related activity.

9.1.2. Responses of single cells and networks

Pharmacologically-induced changes in the neuronal activity can result from altered responsiveness of individual neurons, altered interaction between neurons composing local networks and from interaction between distant brain areas. Responsiveness of individual neurons can be studied using microelectrophoresis (Table 3) while local networks are studied after topical administration *in vivo* or in *in vitro* preparation (Table 4). In contrast, effects observed after systemic administrations (Table 5) represent a net effect of individual responses and interactions between neurons composing local and distal networks.

Microelectrophoresis applies micropipettes to release small amounts of drugs in the direct vicinity of selected neurons. A number of studies using this technique showed that at least some neurons scattered across the brain respond within seconds to corticosterone, cortisol and dexamethasone (Table 3). The responses include both GC-induced excitation and inhibition of firing during a spontaneous or glutamate facilitated activity in anesthetized animals (Table 3). Furthermore, the short-term

Table 3

Changes in the neuronal activity after local administration of GCs in direct vicinity of individual neurons (microelectrophoresis).

Author	Species	Drug	Dose [M]	Brain area	n	Neuronal activity			Latency of response
						≈	↓	↑	
(Barak et al., 1977)	Rats	Cortisol	0.05	Dorsal hippocampus	236	100 %	0%	0%	
(Barak et al., 1977)	Rats	Corticosterone	0.05	Dorsal hippocampus	125	100 %	0%	0%	
(Barak et al., 1977)	Cats	Cortisol	0.05	Dorsal hippocampus	142	100 %	0%	0%	
(Ruf and Steiner, 1967)	Rats	Dexamethasone	0.5	Hippocampus	?	100 %	0%	0%	
(Steiner et al., 1969)	Rats	Dexamethasone	0.5	Dorsal hippocampus	17	100 %	0%	0%	
(Segal, 1976)	Rats	Dexamethasone	0.5	Dorsal hippocampus (CA1-CA3)	24	42 %	58 %	0%	
(Ruf and Steiner, 1967)	Rats	Dexamethasone	0.5	Cortex	?	100 %	0%	0%	
(Steiner et al., 1969)	Rats	Dexamethasone	0.5	Cortex	26	100 %	0%	0%	
(Ruf and Steiner, 1967)	Rats	Dexamethasone	0.5	Thalamus	?	100 %	0%	0%	
(Steiner et al., 1969)	Rats	Dexamethasone	0.5	Thalamus	75	100 %	0%	0%	
(Saphier and Feldman, 1988)	Rats	Corticosterone	0.025	Paraventricular nucleus	102	36 %	36 %	27 %	Almost immediate
(Saphier and Feldman, 1988)	Rats	Cortisol	0.025	Paraventricular nucleus	143	32 %	36 %	32 %	Almost immediate
(Saphier and Feldman, 1990)	Rats	Cortisol	0.025	Paraventricular nucleus	24	33 %	67 %	0%	Usually within a few seconds
(Kasai et al., 1988)	Rats	Cortisol	0.0001	Paraventricular nucleus	83	65%	5%	30 %	Excitatory effects appeared rapidly
(Chen et al., 1991)	Rats	Cortisol	0.15	Paraventricular nucleus	97	22 %	70 %	8%	Several seconds
(Chen et al., 1991)	Rats	Dexamethasone	0.2	Paraventricular nucleus	100	63%	7%	30 %	
(Kasai et al., 1988)	Rats	Cortisol	0.0001	Periventricular hypothalamic nucleus	13	69 %	31 %	0%	
(Barak et al., 1977)	Rats	Cortisol or Corticosterone	0.05	Hypothalamus	17	76%	24 %	0%	
(Papir-Kricheli and Feldman, 1981)	Rats	Cortisol	0.05	Mediobasal hypothalamus	30	37 %	50 %	13 %	
(Mandelbrod et al., 1974)	Rats	Cortisol	0.05	Mediobasal hypothalamus	356	50 %	41 %	9%	Usually within 1–5 sec.
(Steiner et al., 1968)	Rats	Dexamethasone	0.5	Medial and anterior basal hypothalamus	49	76%	18 %	6%	Inhibition present after 2–20 sec or more
(Steiner et al., 1969)	Rats	Dexamethasone	0.5	Midline hypothalamus and midbrain	337	82%	17 %	1%	Some neurons responded almost instantaneously, others after 15–20 sec or even later.
(Ruf and Steiner, 1967)	Rats	Dexamethasone	0.5	Periventricular gray (hypothalamus and mesencephalon)	115	87%	13 %	0%	Inhibition of hypothalamic neurons was almost instantaneous. Inhibition of mesencephalic neurons was somewhat more delayed.
(Papir-Kricheli and Feldman, 1983)	Rats	Cortisol	0.05	Central gray	16	25 %	50 %	25 %	5–10 sec.
(Papir-Kricheli and Feldman, 1983)	Rats	Cortisol	0.05	Midbrain reticular formation	15	40%	47 %	13 %	5–10 sec.
(Avanzino et al., 1983)	Rats	Corticosterone	0.013	Brainstem reticular formation	98	59%	17 %	23 %	Excitatory effects were usually maximum by 10–40 sec. Inhibitory effects appeared with a slightly longer delay.
(Avanzino et al., 1983)	Rats	Cortisol	0.025	Brainstem reticular formation	169	59%	15 %	26 %	
(Avanzino et al., 1987b)	Rats	Corticosterone	0.013	Rostral part of reticular formation	74	55%	38 %	7%	Excitatory effects were maximum after 10–30 sec. Inhibitory effects appeared after 15–40 sec.
(Avanzino et al., 1987b)	Rats	Corticosterone	0.013	Caudal part of reticular formation	78	59%	4%	37 %	
(Avanzino et al., 1984)	Rats	Corticosterone	0.013	Raphe nuclei	54	39%	0%	61 %	Usually the excitatory effect was maximum within 20–30 sec. In some cases the effect appeared within 60–70 sec.
(Avanzino et al., 1987a)	Rats	Corticosterone	0.013	Locus coeruleus	48	27 %	0%	73 %	Maximum excitation within 1–5 sec.
(Papir-Kricheli and Feldman, 1981)	Rats	Cortisol	0.05	Medial septal nucleus	48	48%	21 %	31 %	5–10 sec.
(Papir-Kricheli and Feldman, 1981)	Rats	Corticosterone	0.05	Medial septal nucleus	29	38 %	34 %	28 %	5–10 sec.
(Papir-Kricheli and Feldman, 1982)	Rats	Cortisol	0.05	Medial preoptic Area	64	42 %	30 %	28 %	5–10 sec.
(Kelly et al., 1977)	Rats	Cortisol	0.05	Preoptic-septal area	166	73 %	19 %	8%	

\approx - nonresponsive cells; \downarrow - cells displaying a decreased activity; \uparrow - cells displaying an increased activity. Some results obtained after exposure to GCs and sensory stimuli are not summarized in this table because of too complex pattern of responses (Mandelbrod et al., 1981).

response to GCs (cortisol, corticosterone and dexamethasone) is cell-type specific in terms of the direction of change (Table 3, Fig. 5) and firing mode (Papir-Kricheli and Feldman, 1981, 1982). It should be noted, however, that these experiments cannot identify all neurons

responsive to glucocorticoids. First, microelectrophoresis is associated with sampling bias. Some neurons may not be detectable due to their slow rate of discharge, whereas others may be detected preferentially because of a high rate of firing induced by experimental conditions

Table 4

Changes in neuronal activity after administration of GCs affecting only restricted region of brain (*in vitro* preparations or topical administration in *in vivo* experiments).

Author	Species	Experiment	Drug	Dose	Brain area	Activity	N (cells)	Neuronal activity		
								\approx	\downarrow (%)	\uparrow (%)
(Chen et al., 1991)	Rats	<i>In vitro</i>	Corticosterone	0.01–1 μ M	Paraventricular nucleus of the Hypothalamus	Spontaneous	104	66%	27%	7%
(Kasai and Yamashita, 1988)	Rats	<i>In vitro</i>	Cortisol	0.1–1 μ M	Paraventricular nucleus of the Hypothalamus	Spontaneous	43	100%	0%	0%
(Kasai and Yamashita, 1988)	Rats	<i>In vitro</i>	Cortisol	10–100 μ M	Paraventricular nucleus of the Hypothalamus	Spontaneous	69	91%	3%	6%
(Liebmann et al., 2008)	Mice	<i>In vitro</i>	Corticosterone	100 nM	Basolateral Amygdala	Spikes elicited by depolarizing pulse	11–12	\approx		
(Liebmann et al., 2008)	Mice	<i>In vitro</i>	Corticosterone	100 nM	Hippocampus (CA1)	Spikes elicited by depolarizing pulse	11–12	\approx		
(Duvarci and Pare, 2007)	Rats	<i>In vitro</i>	Corticosterone	100 nM	Basolateral amygdala	Neuronal activity evoked by depolarizing current	10			\uparrow
(Duvarci and Pare, 2007)	Rats	<i>In vitro</i>	Corticosterone	100 nM	Basolateral amygdala	Neuronal activity evoked by depolarizing current	6	\approx		
(Maggio and Segal, 2009)	Rats	<i>In vitro</i>	Corticosterone	100 nM	Dorsal hippocampus	Neuronal activity evoked by depolarizing current	12	\approx		
(Maggio and Segal, 2009)	Rats	<i>In vitro</i>	Corticosterone	100 nM	Ventral hippocampus	Neuronal activity evoked by depolarizing current	12			\uparrow
(Lei et al., 2014)	Rats	<i>In vivo</i> anaest	Dexamethasone	1–10 μ M	Auditory cortex	Sound-evoked single-unit activity	103			\uparrow
(Lei et al., 2014)	Rats	<i>In vivo</i> anaest	Dexamethasone	1–10 μ M	Auditory cortex	Spontaneous single-unit activity	103	\approx		
(Vidal et al., 1986)	Rats	<i>In vitro</i>	Corticosterone	1–10 μ M	Hippocampus (CA1)	Amplitude of evoked population spikes (stimulation of Schaffer collaterals)	6–9			\downarrow
(Vidal et al., 1986)	Rats	<i>In vitro</i>	Dexamethasone	10 μ M	Hippocampus (CA1)	Amplitude of evoked population spikes (stimulation of Schaffer collaterals)		\approx		
(Rey et al., 1987)	Mice	<i>In vitro</i>	Corticosterone	0.2 nM	Hippocampus (CA1)	Amplitude of evoked population spikes (stimulation of Schaffer collaterals)	4–6			\uparrow
(Rey et al., 1987)	Mice	<i>In vitro</i>	Corticosterone	5–10 nM	Hippocampus (CA1)	Amplitude of evoked population spikes (stimulation of Schaffer collaterals)	4–6			\downarrow
(Doi et al., 1991)	Rats	<i>In vitro</i>	Corticosterone	1 μ M	Hippocampus (CA1)	Amplitude of evoked population spikes triggered by stimulation of CA3		\approx		
(Doi et al., 1991)	Rats	<i>In vitro</i>	Corticosterone	1 μ M	Hippocampus (CA3)	Amplitude of evoked population spikes triggered by stimulation of DG		\approx		
(Doi et al., 1991)	Rats	<i>In vitro</i>	Corticosterone	1 μ M	Hippocampus (DG)	Amplitude of evoked population spikes triggered by stimulation of perforant pathway		\approx		
(Cho and Little, 1999)	Rats	<i>In vitro</i>	Corticosterone	50 nM-2 μ M	Ventral tegmental area	Spontaneous single-unit activity	4–7	\approx		
(Cho and Little, 1999)	Rats	<i>In vitro</i>	Corticosterone	50 nM-2 μ M	Ventral tegmental area	Dopamine-induced single-unit activity	4–7	\approx		
(Cho and Little, 1999)	Rats	<i>In vitro</i>	Corticosterone	100 nM-1 μ M	Ventral tegmental area	NMDA-induced single-unit activity	4–7			\uparrow
(Cho and Little, 1999)	Rats	<i>In vitro</i>	Corticosterone	2 μ M	Ventral tegmental area	NMDA-induced single-unit activity	4–7			\downarrow
(Cho and Little, 1999)	Rats	<i>In vitro</i>	Corticosterone	100 nM	Ventral tegmental area	AMPA-induced single-unit activity	4–7			\downarrow
(Cho and Little, 1999)	Rats	<i>In vitro</i>	Corticosterone	500 nM-2 μ M	Ventral tegmental area	AMPA-induced single-unit activity	4–7			\uparrow
(Cho and Little, 1999)	Rats	<i>In vitro</i>	Corticosterone	100 nM and 2 μ M	Ventral tegmental area	Kainic acid-induced single-unit activity	4–7			\downarrow
(Cho and Little, 1999)	Rats	<i>In vitro</i>	Corticosterone	500 nM-1 μ M	Ventral tegmental area	Kainic acid-induced single-unit activity	4–7			\uparrow
(Michal, 1974)	Rats	<i>In vivo</i> anaest	Dexamethasone	0.01–1 nM	Dorsal hippocampus	Multi-unit activity	3–9			\downarrow

\approx - lack of effect; \downarrow - decreased activity; \uparrow - increased activity.

(Steiner, 1970). Second, most studies recorded a spontaneous activity that can be supported with background application of glutamate. However, there are data showing that some neurons are not affected by locally applied cortisol at such conditions but respond to glucocorticoids at the time of additional sensory or electric stimulation (Mandelbrod et al., 1981).

Data obtained with microelectrophoresis can be further extended by experiments applying peripheral treatments and longer periods of recording that detected an additional population of neurons displaying a biphasic response to cortisol during the first hour after treatment (Slusher et al., 1966; Phillips and Dafny, 1971; Nagler et al., 1973). Peripheral treatments with cortisol (Feldman and Dafny, 1970a) also trigger different patterns of firing (regular vs burst activity) (Fig. 6) consistently with studies using microelectrophoresis (Papir-Kricheli and Feldman, 1981, 1982). Recordings made in freely moving rats also revealed that more than 80 % of hypothalamic and midbrain neurons are responsive to cortisol (Phillips and Dafny, 1971).

An important observation derived from electrophysiological experiments is that changes in the activity of single cells after acute administration of GCs do not always result in significant changes in the firing rate at the level of local population of neurons due to the heterogeneity of responses. Such situation was found in auditory cortex in resting conditions after local treatment with dexamethasone (Lei et al., 2014) and in hypothalamus after peripheral administered cortisol (Nagler et al., 1973). Additionally, the reanalysis of data provided by (Feldman et al., 1983) and (Feldman and Dafny, 1970a) also shows the lack of changes at the population level of studied neurons at least in some experimental conditions (Supplementary file 1) despite changes in the activity of single cells detected in original studies. These observations are important for interpretation of fMRI imaging studies which usually show rather small and restricted changes in the brain activity after acute treatments (see Section 9.2.1.2). Furthermore, the detected brain activity is not always consistent with behavioral output. This issue can be exemplified by an fMRI study that found a propensity for striatal-dependent behavior without concomitant changes in activity in striatum after joint treatment with cortisol and yohimbine (Schwabe et al., 2012). Collectively, these data show limitations of brain imaging methods and indicate that some responses to GCs are detectable at the level of single cells but not at the level of averaged responses of larger populations of cells.

9.1.3. Latency of responses

Although GCs affect the neuronal activity almost immediately as evidenced by direct application, the effects observed after peripheral administration are rather much more delayed. The shortest responses of individual neurons to peripheral treatments were reported immediately in some neurons after i.p. injection of cortisol (Nagler et al., 1973), 1–2 min after i.v. injection of corticosterone (Avanzino et al., 1987b) and 1–5 min in some neurons after i.v. administration of cortisol (Slusher et al., 1966; Feldman and Dafny, 1970a) with mean latencies ranging, however, from almost 6–9.5 min depending on the analyzed brain area (Feldman and Dafny, 1970a). Importantly, all fast responses occurring during the initial 5 min after peripheral administration of GCs were obtained in acute preparations. In such cases, recording was performed shortly after surgical implantation of electrodes which inevitably leads to disruption of the blood-brain barrier due to physical injuries. Other studies including experiments performed several days after surgery (Pfaff et al., 1971; Dafny et al., 1973) reported neuronal responses to GCs (corticosterone, cortisol and dexamethasone) that occurred within 10 min (Kasai et al., 1988) or that started 10–15 min after drug administration (Pfaff et al., 1971; Ondo and Kitay, 1972; Dafny et al., 1973; Zhang et al., 2013). Such latencies are consistent with data concerning the permeability of the blood-brain barrier for corticosterone (Section 3.2.1). Comparable time-course was also reported in case of evoked potentials recorded in acute preparations. First effects were noticeable 5–15 min after i.v. injection of cortisol while a maximum

effect occurred after 30–60 min (Feldman et al., 1961). Collectively, these data indicate that neuronal responses usually occur with a delay of about 10 min after peripheral administration of GCs.

9.1.4. Gaps in electrophysiological data

Although the electrophysiological experiments provided indispensable information about effects induced by GCs, there are still large gaps in the available data. First, almost all experiments were performed in *in vitro* preparations or in anaesthetized/paralyzed animals and the only modification of experimental conditions relied on administration of sensory or electric stimulation. It means that we do not have electrophysiological data about the effect of GCs during real life situations requiring escape, problem solving etc. Furthermore, the available information is restricted to a short time window after administration of GCs. For example, most studies investigating the firing rate after local administration of cortisol, corticosterone and dexamethasone (Table 4) were performed during the first hour and only one study (Liebmann et al., 2008) recorded the activity during a period longer than two hours. Similarly, effects induced by peripheral treatments with corticosterone, cortisol and dexamethasone (Table 5) were usually reported for the first or second hour and in some cases an available description is not sufficient to precisely determine the total duration of recording in groups of interest. Although some researchers performed prolonged recordings (Phillips and Dafny, 1971) or used longer delays such as 3 h (Hesen and Joels, 1996) or 24 h (Koranyi et al., 1971b), the data are scarce and there is no systematic comparison of short-term non genomic effects and delayed genomic effects on neuronal firing especially after the first 2 h. This is important because a number of transcriptomic, proteomic and metabolic processes develop over the course of several hours after treatment (see Section 6 for more details).

Finally, some older *in vivo* studies applied cortisol and dexamethasone for peripheral treatments administered to rodents (Table 5), which utilize corticosterone as a main endogenous glucocorticoid (Section 5). Positive results occurring with short latencies (Section 9.1.3) indicate effectiveness of these treatments consistently with data showing that cortisol and dexamethasone enter the brain at a constant rate leading to concentrations comparable with corticosterone in some brain areas (McEwen et al., 1976). However, because of differences in concentration of these GCs in brain areas containing high levels of GRs (Section 3.1) and variability in affinity to MRs and GRs (Section 4), the data obtained after peripheral administration of cortisol and dexamethasone may differ from effects induced by corticosterone. Further complications are present when effects of cortisol or dexamethasone are tested after longer intervals (Section 5, Fig. 1) but this issue is less relevant for available electrophysiological experiments that usually applied short recording periods. Overall, these data indicate that there is a need for testing the effects of corticosterone, which is more relevant for physiological conditions in rodents than cortisol and dexamethasone, and the analysis of the neuronal activity should be extended to enable detection of delayed genomic effects (Section 6). Finally, it is important to study the effects of corticosterone in conditions allowing the collection of behaviourally relevant data. Such a possibility is offered by recent advancements in imaging methods and virtual reality (Aronov and Tank, 2014; Weisenburger and Vaziri, 2018; Piatkevich et al., 2019).

9.2. Functional magnetic resonance imaging (fMRI)

Magnetic resonance imaging is the most important source of information about the effects of GCs on the human brain activity. In case of most commonly applied BOLD fMRI, the level of activity is inferred from changes in oxygenation of blood hemoglobin resulting from altered blood flow that is in principle coupled with changes in the firing rate of local populations of neurons (Section 7.2). In this section we also included a PET study that applied H¹⁵O as a tracer (de Quervain et al., 2003) and a continuous arterial spin labelling MRI study (Strelzyk et al., 2012). Both these studies tested changes in cerebral blood flow and,

Table 5Effect of peripheral administration of GCs on single and multi-unit activity in *in vivo* experiments.

Author	Species	Animals	Drug	Dose	Brain area	Activity	N (cells)	Neuronal activity			
								≈	↓(%)	↑(%)	↑(%)
(Phillips and Dafny, 1971)	Rats	Freely moving	Cortisol	8 mg/kg	Hippocampus (CA3)	Spontaneous single-unit	18	44%	22 %	28 %	6%
(Pfaff et al., 1971)	Rats	Freely moving/ Anaesthetized	Corticosterone	0.5–1 mg	Dorsal hippocampus	Spontaneous single-unit	?		↓		
(Dafny et al., 1973)	Rats	Freely moving	Cortisol	1–64 mg/kg	Dorsal hippocampus	Spontaneous single-unit	28	57 %	18 %	25 %	0%
(Slusher et al., 1966)	Cats	Paralyzed	Cortisol	25 mg	Hypothalamus	Spontaneous single-unit	11	0%	18 %	64 %	18 %
(Nagler et al., 1973)	Rats	Anaesthetized	Cortisol	5 mg	Tuberal Hypothalamus	Spontaneous single-unit	39	2,5%	205%	28 %	49 %
(Feldman and Dafny, 1970a)	Cats	Anaesthetized	Cortisol	5 mg/kg	Anterior-tuberal hypothalamus	Spontaneous single-unit	19	42 %	0%	58 %	
(Feldman and Dafny, 1970b)	Rats	Anaesthetized	Cortisol	5 mg	Anterior-tuberal hypothalamus	Spontaneous single-unit	54			↑	
(Phillips and Dafny, 1971)	Rats	Freely moving	Cortisol	8 mg/kg	Anterior hypothalamus	Spontaneous single-unit	18	17 %	11 %	61 %	11 %
(Dafny et al., 1973)	Rats	Freely moving	Cortisol	1–64 mg/kg	Anterior hypothalamus	Spontaneous single-unit	35	14 %	17 %	69 %	11 %
(Ondo and Kitay, 1972)	Rats	Anaesthetized	Dexamethasone	200ug/kg	Basal hypothalamus	Spontaneous single-unit	22	23 %	41 %	36 %	
(Ondo and Kitay, 1972)	Rats	Anaesthetized	Dexamethasone	200ug/kg	Basal hypothalamus island	Spontaneous single-unit	22	41 %	50 %	9%	
(Kasai et al., 1988)	Rats	Anaesthetized	Cortisol	0.5 mg	Paraventricular nucleus of the hypothalamus	Spontaneous single-unit	11	55%	9%	36 %	0%
(Feldman and Dafny, 1970a)	Cats	Anaesthetized	Cortisol	5 mg/kg	Posterior hypothalamus	Spontaneous single-unit	21	38 %	5%	57 %	
(Feldman and Dafny, 1970b)	Rats	Anaesthetized	Cortisol	5 mg	Posterior hypothalamus near the midline.	Spontaneous single-unit	44			↑	
(Phillips and Dafny, 1971)	Rats	Freely moving	Cortisol	8 mg/kg	Ventromedial hypothalamus	Spontaneous single-unit	18	17 %	61 %	22 %	0%
(Dafny et al., 1973)	Rats	Freely moving	Cortisol	1–64 mg/kg	Ventromedial hypothalamus	Spontaneous single-unit	28	18 %	50 %	32 %	0%
(Slusher et al., 1966)	Cats	Paralyzed	Cortisol	25 mg	Zona incerta	Spontaneous single-unit	6	17 %	33 %	50 %	0%
(Dafny et al., 1973)	Rats	Freely moving	Cortisol	1–64 mg/kg	Midbrain reticular formation	Spontaneous single-unit	31	13 %	19 %	68 %	26 %
(Phillips and Dafny, 1971)	Rats	Freely moving	Cortisol	8 mg/kg	Midbrain reticular formation	Spontaneous single-unit	18	11 %	28 %	56 %	6%
(Avanzino et al., 1987b)	Rats	Anaesthetized	Corticosterone	0.05 mg/kg	Brain stem reticular formation	Spontaneous single-unit	27	26 %	37 %	37 %	0%
(Feldman et al., 1983)	Rats	Freely moving	Corticosterone	5 mg	Medial hypothalamus	Spontaneous multi-unit	15	13 %	27 %	60 %	0%
(Feldman et al., 1983)	Rats	Freely moving	Corticosterone	5 mg	Lateral hypothalamus	Spontaneous multi-unit	12	25 %	0%	75 %	0%
(Feldman et al., 1983)	Rats	Freely moving	Corticosterone	5 mg	Midbrain reticular formation	Spontaneous multi-unit	17	24 %	24 %	53 %	0%
(Feldman et al., 1983)	Rats	Freely moving	Corticosterone	5 mg	Amygdala	Spontaneous multi-unit	19	32 %	26 %	42 %	0%
(Feldman et al., 1983)	Rats	Freely moving	Corticosterone	5 mg	Hypothalamus	Spontaneous single-unit	23	35%	4%	61 %	0%
(Koranyi et al., 1971b)	Cats	Freely moving	Cortisol	10 mg/kg	Medial forebrain Bundle	Multi-unit activity			↓		
	Cats	Freely moving	Cortisol		Medial preoptic area	Multi-unit activity			↓		

(continued on next page)

Table 5 (continued)

Author	Species	Animals	Drug	Dose	Brain area	Activity	N (cells)	Neuronal activity		
							≈	↓(%)	↑(%)	‡(%)
(Koranyi et al., 1971b)				10 mg/kg						
(Koranyi et al., 1971b)	Cats	Freely moving	Cortisol	10 mg/kg	Mesencephalic reticular formation	Multi-unit activity		↓		
(Mor et al., 1986)	Rats	Freely moving	Corticosterone	0.5–5 mg/kg	Hypothalamic paraventricular nucleus	Multi-unit activity triggered by photic and acoustic stimulation		↓		
(Koranyi et al., 1971a)	Cats	Slow-wave sleep	Cortisol	10 mg/kg	Mesencephalic reticular formation	Multi-unit activity (spontaneous and induced by electrical stimulation)	6	↓		
(Koranyi et al., 1971a)	Cats	Slow-wave sleep	Cortisol	10 mg/kg	Medial forebrain Bundle	Multi-unit activity (spontaneous and induced by electrical stimulation)	6	↓		
(Koranyi et al., 1971a)	Cats	Slow-wave sleep	Cortisol	10 mg/kg	Medial preoptic area	Multi-unit activity (spontaneous and induced by electrical stimulation)	6	↓		
(Koranyi et al., 1971a)	Cats	Slow-wave sleep	Cortisol	10 mg/kg	Nucleus centromedianus of the thalamus	Multi-unit activity (spontaneous and induced by electrical stimulation)	6	↓		
(Zhang et al., 2013)	Rats	Anaesthetized	Dexamethasone	10 mg/kg	Lateral habenula, cocaine-up neurons	Spontaneous single-unit activity	9		↑	
(Zhang et al., 2013)	Rats	Anaesthetized	Dexamethasone	10 mg/kg	Lateral habenula, cocaine-down neurons	Spontaneous single-unit activity	6	≈		
(Hesen and Joels, 1996)	Rats	Slices	Corticosterone	1–10 mg/kg	Dorsal hippocampus	Percentage of neuron showing activity during carbachol perfusion			↑	

≈ - nonresponsive cells; ↓ - cells displaying decreased activity; ↑ - cells displaying increased activity; ‡ - cells displaying biphasic response. Some results obtained after exposition to GCs and sensory stimuli (Nagler et al., 1973) are not summarized in this table because of a too complex pattern of responses.

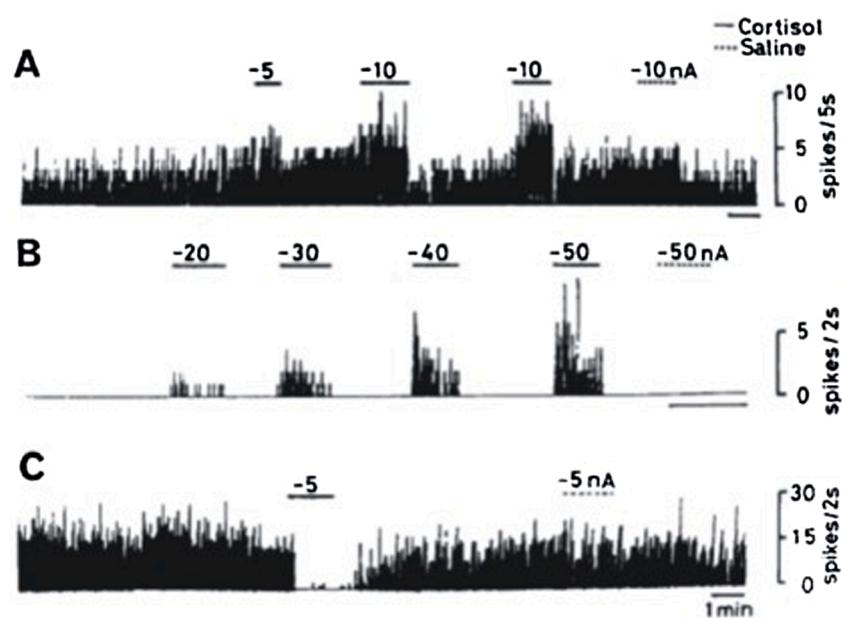


Fig. 5. Examples of excitatory and inhibitory effects induced by cortisol administered with iontophoresis in vicinity of TI-neurons in the PVN and the periventricular hypothalamic neurons. A - a spontaneously firing TI neuron which was excited by cortisol. B - a silent TI neuron which was excited by cortisol in a current dependent manner. C - spontaneously firing neuron in the periventricular hypothalamic nucleus which was inhibited by cortisol. Black bars and broken bars indicate the period of application of cortisol and saline, respectively. Numbers show the amount of ejection currents (nA). Reprinted with permission from Kasai et al. (1988).

therefore, detected the same physiological response as BOLD fMRI. Due to the number of limitations (Section 7.2), human brain imaging data should be considered jointly with other sources of information including biochemical and electrophysiological studies to obtain a more comprehensive picture of GC-induced changes in the brain activity (Section 10). Human studies investigating the effects of GCs on the brain activity

applied two approaches. First, the acute effect of cortisol (hydrocortisone), cortisone or prednisolone (Supplementary file 2) were studied mainly in healthy volunteers although there are also data collected in depressed patients (Abercrombie et al., 2011) and spider phobic patients (Nakataki et al., 2017). Second, chronic effects of GCs were studied in patients with Cushing's disease that is caused by tumors triggering a

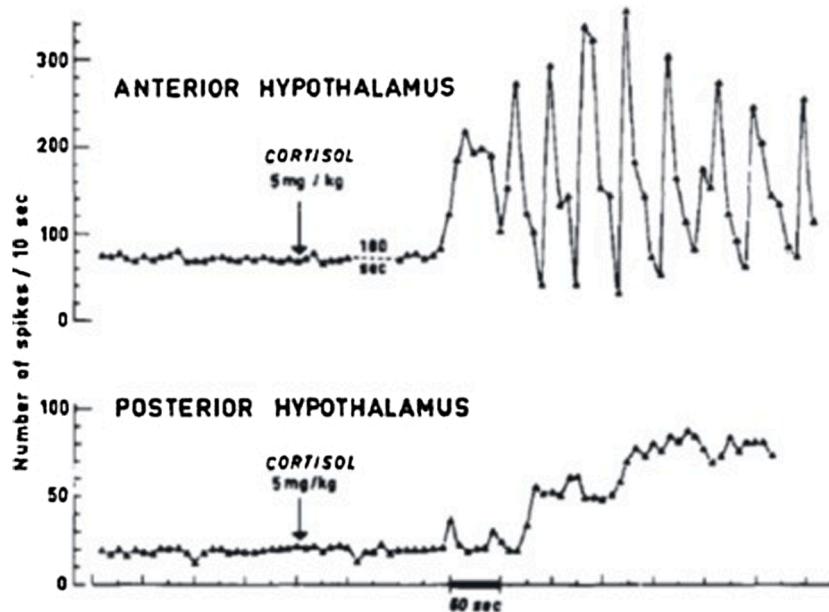


Fig. 6. Example of burst and regular activity induced by cortisol in cat hypothalamus after i.v. injection. Reprinted with permission from Feldman and Dafny (1970a).

continuous release of cortisol (Andela et al., 2015; van der Werff et al., 2015). These two lines of research are discussed in more detail in subsequent Sections 9.2.1 and 9.2.2.

9.2.1. Pharmacological fMRI experiments

9.2.1.1. General characteristic. GCs were administered usually within 80 min (de Quervain et al., 2003; Stark et al., 2006b; Oei et al., 2007; Henckens et al., 2010; Lovallo et al., 2010; Merz et al., 2010; Tabbert et al., 2010; van Stegeren et al., 2010; Abercrombie et al., 2011; Henckens et al., 2011, 2012a; Henckens et al., 2012b; Merz et al., 2012; Schwabe et al., 2012; Strelzyk et al., 2012; Symonds et al., 2012; Merz et al., 2013; Bos et al., 2014; Merz et al., 2014; Montoya et al., 2014, 2015; Kinner et al., 2016; Nakataki et al., 2017; Kinner et al., 2018; Merz et al., 2018; Fleischer et al., 2019) or two hours (Sudheimer et al., 2013; Ma et al., 2017) before the beginning of brain scanning while the minority of studies applied longer latencies such as 3 h (Henckens et al., 2012a), 4 h (Henckens et al., 2011; Buades-Rotger et al., 2016; Serfling et al., 2019), 4.5–4.75 h (Henckens et al., 2010, 2012b), 16 h (van Marle et al., 2013), 2.5 days (Brown et al., 2013) and one week (Merz et al., 2018) (for more details see Supplementary file 2). Considering the delayed penetration of the blood-brain barrier (Section 3) and the time-course of gene expression (Section 6), it should be assumed that most of the brain imaging studies investigated mostly non-genomic and early genomic effects of GCs. In contrast, effects occurring at longer latencies that are associated with the number of transcriptomic, proteomic and metabolic changes (Section 6) were rarely tested in fMRI experiments.

Almost all reviewed studies tested a single dose of GCs (Supplementary file 2) with an exception of two studies that applied treatments repeated for 2.5 and 4 days (Brown et al., 2013; Sudheimer et al., 2013). The most frequently used glucocorticoid was cortisol that was administered usually at a dose of 30 mg (Supplementary file 2) although the doses ranged from 10 (Henckens et al., 2010, 2011; Henckens et al., 2012b; Fleischer et al., 2019) to 100 mg (Sudheimer et al., 2013; Ma et al., 2017) in case of oral administration and from 4 (Strelzyk et al., 2012) to 100 mg (Symonds et al., 2012) in case of i.v. injections. Some brain imaging studies investigated the basal/resting activity in humans (Lovallo et al., 2010; Strelzyk et al., 2012; Symonds et al., 2012) and rats (Ferris and Stolberg, 2010) but most of the published experiments tested

exclusively an effect of GCs on the task-related activity. Experimental protocols at the time of brain scanning included a working memory task (Henckens et al., 2011; Symonds et al., 2012), memory encoding (Henckens et al., 2012a) and retrieval (de Quervain et al., 2003; Oei et al., 2007; Brown et al., 2013; van Marle et al., 2013; Fleischer et al., 2019), fear conditioning (Stark et al., 2006b; Merz et al., 2010; Tabbert et al., 2010; Merz et al., 2012, 2013; Merz et al., 2014; Kinner et al., 2018; Merz et al., 2018), instrumental learning task (Schwabe et al., 2012), emotional distraction task (Henckens et al., 2012b), exposition to neutral and emotional stimuli such as infant crying (Bos et al., 2014), pictures (Henckens et al., 2010; van Stegeren et al., 2010; Sudheimer et al., 2013; Buades-Rotger et al., 2016; Ma et al., 2017; Nakataki et al., 2017) and words (Abercrombie et al., 2011), anticipation of reward (Montoya et al., 2014; Kinner et al., 2016) or threat (Montoya et al., 2015) and finally the Go/NoGo task with food and neutral targets (Serfling et al., 2019). In some experiments the exposure to stimuli was intended as a part of a memory test (van Stegeren et al., 2010; Abercrombie et al., 2011). Summing up, the fMRI studies were focused on acute effects occurring within 80 min after administration of cortisol and usually involved tasks relevant for mechanisms of declarative memory, fear conditioning and responses to emotion-charged stimuli. In contrast, underrepresented aspects include longer treatments, measurement latencies extending beyond the first 2 h after treatment and assessments of the resting brain activity.

9.2.1.2. Magnitude of acute effects. In many cases cortisol-induced changes in the brain activity were not associated with significant cognitive and emotional effects at the time of scanning (Oei et al., 2007; Henckens et al., 2012a, b; Symonds et al., 2012; Bos et al., 2014; Montoya et al., 2015; Fleischer et al., 2019). Henckens et al. (2012b) showed that this dissociation between the brain activity and cognition at least in some cases is time-dependent because the lack of significant cognitive effects was observed at longer latencies (4 h) but not one hour after administration of cortisol. Changes in the brain activity detected by fMRI after acute treatment are rather subtle. In fact, the only study that revealed widespread changes in the brain activity after administration of GCs was performed in rats treated with corticosterone (Ferris and Stolberg, 2010) but this experiment differs from all other reviewed studies due to the specificity of animal fMRI procedures as discussed in Section 9.2.1.4. In contrast, human fMRI experiments detected less pronounced

effects of cortisol in terms of magnitude of responses (Symonds et al., 2012) and size of affected brain areas (for example (Oei et al., 2007; Henckens et al., 2011; Montoya et al., 2014; Ma et al., 2017; Nakataki et al., 2017) or even failed to detect a significant effect (Schwabe et al., 2012). The change in the resting activity of human hippocampus, that is the most frequently studied brain area after administration of GCs, was reported to be within 5% (Symonds et al., 2012), indicating a small range of changes during the first 20 min after administration of cortisol. The restricted effect of acute treatments with cortisol is also visible when we compare stimulus/task related changes with drug effects (for example (Oei et al., 2007; Merz et al., 2010; van Stegeren et al., 2010; Montoya et al., 2014; Ma et al., 2017)). These studies show that experimental procedures usually including exposure to various stimuli induce much more widespread changes in the brain activity than the acute elevation of the stress hormone. It has also been found that the ability to detect the effect of cortisol at least in some cases depends on the applied method of data analysis (Henckens et al., 2012a). For example, changes in the hippocampal activity were below the detection threshold of the voxel-wise analysis that was used specifically to test this brain area but were detected when BOLD signal from the entire area was averaged (Henckens et al., 2012a). This is probably because an altered activity was widely distributed across the entire hippocampus and, therefore, was not detected by a method that is most suitable for identification of focal effects (Henckens et al., 2012a). It is also symptomatic that almost all reviewed human studies applied a ROI (Region Of Interest) approach in addition to the whole brain analysis or as the exclusive method of data analysis. The comparison between a priori selected regions of interest increases sensitivity of a statistical analysis because it avoids the problem of multiple comparisons and about half of the reviewed fMRI studies provided only information about GC-induced changes in the activity of declared ROIs even if the whole brain analysis was performed (for example: (Henckens et al., 2010, 2011; Bos et al., 2014; Fleischer et al., 2019)). This restricted effect of cortisol detected in fMRI experiments can be easily reconciled with electrophysiological data (Table 3 and 5) because GCs both increase and decrease the activity of some subpopulations of neurons and, therefore, the net effect may be small or even absent (Sections 9.1.1 and 9.1.2).

9.2.1.3. Contribution of female subjects to human fMRI data. A male bias is common in various disciplines of biomedical research including neuroscience (Beery and Zucker, 2011). As expected, male subjects were included in most of the reviewed fMRI experiments with few exceptions (Tabbert et al., 2010; Fleischer et al., 2019). However, there is also a number of studies investigating female subjects as separate groups (Stark et al., 2006b; Merz et al., 2010; Abercrombie et al., 2011; Merz et al., 2012, 2013; Kinner et al., 2016; Ma et al., 2017; Kinner et al., 2018) or jointly with males (Lovallo et al., 2010; Schwabe et al., 2012; Symonds et al., 2012; Brown et al., 2013; Sudheimer et al., 2013; Nakataki et al., 2017). A number of experiments showed that brain responses to cortisol are affected by sex (Stark et al., 2006b; Merz et al., 2010; Abercrombie et al., 2011; Kinner et al., 2016; Ma et al., 2017; Kinner et al., 2018) and hormones as indicated by differences observed in women taking oral contraceptives (Merz et al., 2012). Importantly, a comparison between cortisol and placebo showed even opposite responses in some areas (amygdala, prefrontal cortex, hippocampus, cingulate gyrus and other) of male and female brains at the time when participants were engaged in a task involving aversive stimuli (Stark et al., 2006b; Merz et al., 2010; Kinner et al., 2016; Ma et al., 2017; Kinner et al., 2018). These data indicate that we should be careful with generalization of animal data that are obtained mostly in males.

9.2.1.4. Basal/resting activity. Resting activity consumes most of the energy produced in the brain and has vital functions such as monitoring the internal and external environment, preparation for actions and offline processing of information (Miall and Robertson, 2006; Raichle,

2010). Nonetheless, very few MRI studies provided information about the effect of cortisol on the resting brain activity in humans (Lovallo et al., 2010; Strelzyk et al., 2012; Symonds et al., 2012) and rats (Ferris and Stolberg, 2010). Furthermore, these studies were restricted to the initial 5 min (Ferris and Stolberg, 2010), 19 min (Symonds et al., 2012), 27 min (Strelzyk et al., 2012) and 45 min (Lovallo et al., 2010) after drug administration. Therefore, available data are restricted to short-term effects relying exclusively or mostly on non-genomic mechanism.

The rat study detected a significantly increased activity in four brain areas already within the first minute and even more robust increases in most of the brain within five minutes after the treatment with corticosterone (Ferris and Stolberg, 2010). Maximum changes in BOLD signal were within the range of 10–14% including hippocampus and cortex, which displayed about 8% increase after 1 min and 12–14 % after 5 min. Such fast and widespread changes were not detected in any other fMRI experiment testing acute effects of cortisol in humans. Importantly, the rat experiment (Ferris and Stolberg, 2010) is different from other studies because the procedure included adrenalectomy combined with corticosterone replacement therapy (see also Section 2.3), application of transient anesthesia preceding the brain imaging, immobilization of animals, administration of corticosterone that differs from cortisol in terms of blood-brain permeability (Section 3.1) and utilization of hydroxypropyl-cyclodextrin to dissolve corticosterone. Despite a unique character of the rat fMRI study, the immediate effect of corticosterone that was visible already after 1 min is puzzling, considering the delayed penetration of the blood-brain by corticosterone (Section 3.2.1). A possibility that was not discussed previously is that this central effect of glucocorticoids detected during first few min could result from rapid peripheral effects altering sensory signaling transmitted to the brain. It is known that GCs affect the peripheral nervous system (Hua and Chen, 1989; Shaqura et al., 2016) and such effect can be especially important in this case because of application of body restrainers and head holders with the animal's canines secured over a bite bar and ears positioned with adjustable screws (Ferris and Stolberg, 2010). Despite the usage of topical lidocaine in most sensitive areas of ears and bridge of the nose, application of such procedure means massive tactile stimulation that is not present in human studies.

An increased hippocampal activity but with different time-course was found in humans after a high dose of cortisol (100 mg) which triggered a gradual rise in BOLD signal during 19 min after the treatment (Symonds et al., 2012). However, the rise in BOLD signal was much slower than in the aforementioned rat study because it changed about 2–2.5% after 5 min and maximally about 5% after 19 min (Symonds et al., 2012). Therefore, this time course is comparable with data showing delayed entrance of GCs into the brain (Section 3.2.1). In another study, a ten times lower dose of cortisol induced a transient increase in hippocampal BOLD signal after 5–10 min (medium effect) that was followed by return to the baseline (10–20 min) and a subsequent large decrease that achieved a maximum value after 30–35 min (Lovallo et al., 2010). A similar decrease was found in amygdala but not in thalamus, insula and posterior parahippocampal gyrus, which were selected as additional ROIs (Lovallo et al., 2010). The discrepancies in the time course of hippocampal changes between these two human studies (Lovallo et al., 2010; Symonds et al., 2012) can be easily explained by the difference in applied doses since both the peak concentration of brain GCs and the return to the baseline occurs faster after administration of lower doses of the hormone (Bouchez et al., 2012). Although Lovallo et al (2010) found no changes in the thalamus after administration of 10 mg of cortisol, another study found that even a lower dose (4 mg) decreased the thalamic activity during the first 7–17 min together with some decreases and increases in frontal, occipital and parietal lobes that were analyzed separately (Strelzyk et al., 2012).

Summing up, these studies showed a number of different brain areas that increased or decreased the activity in resting conditions after administration of GCs. The most consistent change was an increased hippocampal activity (Ferris and Stolberg, 2010; Lovallo et al., 2010;

Symonds et al., 2012) that can be followed by more pronounced inhibition (Lovallo et al., 2010). However, our understanding of GC-induced changes in the resting brain activity is still fragmentary due to a limited amount of published data, restriction of analysis to few brain areas and a short period of recording time. Additionally, existing studies are difficult to compare because of differences in applied experimental procedures including detection methods (BOLD/CASL), applied doses of cortisol, duration of measurements blocks that were used for averaging data and other aspect that were reviewed earlier in this section.

9.2.1.5. Memory. An interest in the role of GCs in memory started with the finding that radiolabeled corticosterone is accumulated in the hippocampus (for historical perspective please see McEwen et al., 2015 and Joels and de Kloet, 2017) and this topic evolved together with the better understanding of mechanisms underlying memory formation. This issue is, however, complicated because there are multiple memory systems that frequently operate in parallel but serve different functions and depend on different neural circuits (Squire, 2004; Cowan, 2008; Norris, 2017). Furthermore, memory is decomposed into acquisition, consolidation and retrieval and the last process can be tested while using different approaches, for example free recall, recognition and cued recall that are not fully comparable (Dobbins et al., 1998; Nobel and Shiffrin, 2001; Yonelinas et al., 2010). Therefore, the problem of GC-induced alterations in memory and associated changes in the brain activity is a complex issue.

9.2.1.5.1. Working memory. Very few fMRI studies tested the effect of GCs on working memory. It has been found that both high (100 mg) and low (10 mg) dose of cortisol had no effect on working memory 30 min after the treatment (Henckens et al., 2011; Symonds et al., 2012) while after 4 h there was a slight improvement that approached the level of significance (Henckens et al., 2011). Despite the lack of significant cognitive effects, the high dose increased the activity in hippocampus, prefrontal cortex and precentral gyrus after 30 min (Symonds et al., 2012) while the low dose had only a delayed (4 h) effect characterized by an increased activity in dorsolateral prefrontal cortex at the time when subjects performed the working memory task (Henckens et al., 2011). Therefore, although GCs affected the brain activity, significance of these effects for working memory is not clear.

9.2.1.5.2. Long-term declarative memory. More brain imaging studies tested the effect of GCs on long-term declarative memory including the process of memory encoding (van Stegeren et al., 2010; Abercrombie et al., 2011; Henckens et al., 2012a), consolidation (van Marle et al., 2013) and retrieval (de Quervain et al., 2003; Oei et al., 2007; Fleischer et al., 2019). One study also tested an effect of cortisol administered for 2.5 days on memory retrieval (Brown et al., 2013). Cortisol administered 30–180 min before memory encoding had a variable effect on subsequent recollection. On the one hand, there was no effect on performance in free and cued recall tests (van Stegeren et al., 2010; Abercrombie et al., 2011; Henckens et al., 2012a) while cortisol improved recognition memory (van Stegeren et al., 2010). Cortisol also differentially affected performance of depressed subjects in a sex specific way because they impaired encoding of positive words (but not neutral and negative) in females but improved in depressed men (Abercrombie et al., 2011). Finally, cortisol administered after viewing pictures improved consolidation of emotional memory during subsequent sleep (van Marle et al., 2013). Changes in the brain activity during memory encoding were time-dependent and in some but not all experiments were related to subsequent performance in recall tests (van Stegeren et al., 2010; Abercrombie et al., 2011; Henckens et al., 2012a). Cortisol had no effect on the brain activity in case when encoding was performed 30 min after the treatment (Henckens et al., 2012a) but affected the brain after longer intervals ranging from 45–60 min (van Stegeren et al., 2010; Abercrombie et al., 2011) to 180 min (Henckens et al., 2012a). Cortisol administered 45 min before encoding increased activation in hippocampus and frontal cortex (van Stegeren et al., 2010) while at longer

latencies they had an opposite effect (Henckens et al., 2012a). Cortisol also affected the brain activity in depressed subjects in a sex-specific way (Abercrombie et al., 2011).

In case of memory retrieval, prednisolone (de Quervain et al., 2003) and cortisol (Oei et al., 2007) administered one hour before memory testing had no effect on performance in recognition task but impaired cued recall (de Quervain et al., 2003). The effects on the brain activity at the time of memory retrieval were variable, considering affected brain areas but in all cases they were restricted to significant decreases. A lower activity was found for example in hippocampus (Oei et al., 2007) and prefrontal cortex (Fleischer et al., 2019) after administration of cortisol and in parahippocampal gyrus after administration of prednisolone (de Quervain et al., 2003). Decreased activity was also found in hippocampus at the time of memory retrieval in case when cortisol was administered for 2.5 days before testing (Brown et al., 2013). Changes in the brain activity were found even in cases when cortisol did not significantly affect performance of tested subjects (Oei et al., 2007; Brown et al., 2013).

Although experiments testing an effect of GCs on declarative memory yielded variable results, it should be noted that there are numerous methodological differences such as learned material (images vs words), awareness of participants about the purpose of watched stimuli (intentional vs unintentional encoding), measurement latency and testing methods (recognition or free and cued recollection tasks) that could contribute to differences in obtained results. Nonetheless, it is striking that with similar doses and latencies, cortisol differentially affected the brain activity depending on the performed task. For example, cortisol increased the activity in working memory task (Henckens et al., 2011) while decreased it at the time of encoding the long-term declarative memory (Henckens et al., 2012a). This shows that GCs are not inducing exclusively inhibitory or excitatory responses. Instead, the effect depends on the performed task.

9.2.1.5.3. Nondeclarative memory. Only one study tested the effect of GCs on the brain activity at the time of instrumental learning but it produced negative results when cortisol was administered without concomitant stimulation of adrenergic receptors with yohimbine (Schwabe et al., 2012). However, combination of both drugs decreased the activity in prefrontal cortex and made instrumental behavior insensitive to changes in the value of the goal. This effect means a shift from goal-directed to habitual responses that involve striatal circuits. Later experiments in stressed subjects implicated in this process mineralocorticoid receptors (Schwabe et al., 2013; Wirz et al., 2017). Such switch favoring striatal pathways may render other areas, such as hippocampus, more vulnerable to stress (Wirz et al., 2017).

Relatively well documented is the effect of cortisol on fear conditioning that is also classified as nondeclarative memory (Squire, 2004). It has been found that cortisol affects fear conditioning in a sex-specific way (Stark et al., 2006b; Merz et al., 2010, 2012) and that the direction of changes depends additionally on contingency awareness (explicit vs implicit learning). Cortisol also affects extinction of conditioned fear responses but the effect depended on the timing between conditioning, extinction and the treatment. Cortisol administered immediately after fear conditioning and 45 min before fear extinction increased skin responses indicating impaired fear extinction (Merz et al., 2014). However, cortisol administered at similar interval before fear extinction but one day after conditioning had an opposite effect (Merz et al., 2018). This shows that a consolidation phase between acquisition and extinction is important for effects induced by GCs (Merz et al., 2018). Finally, cortisol also affected the return of extinguished fear but again the effect depended on the timing between fear extinction, reinstatement and the treatment (Kinner et al., 2018; Merz et al., 2018). The crucial role of timing found in brain imaging experiments is consistent with other studies that tested a relationship between stress hormones and memory (de Quervain et al., 2017).

Effects of cortisol on brain responses to fear conditioning were complex and sex-specific as already described in Section 9.2.1.3. The

variability in detected brain responses was likely to result at least partly from differences in experimental protocols which were associated with aforementioned behavioral responses. In general, cortisol both increased and decreased the activity in numerous brain areas involved in memory, emotions, pain responses and behavioral control such as hippocampus, amygdala, cingulate cortex, insula and prefrontal cortex (Stark et al., 2006b; Merz et al., 2010; Tabbert et al., 2010; Merz et al., 2012). A similar set of brain areas was also involved in fear extinction (Tabbert et al., 2010; Merz et al., 2014, 2018) and the return of fear responses (Kinner et al., 2018; Merz et al., 2018). Collectively, these data show a complex effect of GCs on fear conditioning and indicate involvement of neuronal circuits controlling a wide range of processes such as pain responses, emotions, memory and behavioral control.

9.2.1.6. Exposition to neutral and emotional stimuli. Several studies tested an effect of GCs on brain responses to emotional stimuli. Experiments employing angry faces and aversive words suggest that cortisol facilitate responses to highly emotional stimuli in both sexes (Ma et al., 2017), interrupting at the same time the processing of information that is not related to emotions in men (Henckens et al., 2012b; Ma et al., 2017). Cortisol also decreased fear responses to spiders in patients with spider phobia but the effect was not generalized to fear ratings for other stimuli (Nakataki et al., 2017). Finally, cortisol increased arousal evoked by sad stimuli compared with happy and neutral stimuli but the effect was restricted to treatment repeated for four days (Sudheimer et al., 2013). Therefore, the subjective effects were rather mild because they were confined to specific stimuli triggering phobic reactions or to repeated treatments. Brain imaging revealed two general patterns of responses to GCs during exposure to emotional stimuli. On the one hand, some researchers reported decreases in the brain activity in various areas when subjects treated with cortisol watched fearful/happy faces (Henckens et al., 2010), sad faces (Sudheimer et al., 2013) and spiders (Nakataki et al., 2017). On the other hand, increases in the brain activity after treatment with cortisol (Henckens et al., 2012b; Bos et al., 2014) and prednisolone (Buades-Rotger et al., 2016) were reported during the task requiring participants to identify colors of aversive words (Henckens et al., 2012b) and in response to both negative socio-emotional stimuli (Buades-Rotger et al., 2016) and infant crying (Bos et al., 2014). Additionally, the responses were modified by past experiences (Bos et al., 2014) and sex of participants (Buades-Rotger et al., 2016; Ma et al., 2017).

Variability in responses to aversive and threatening situations may result from the perceived ability to control the situation. Such scenario was tested in an experiment that combined images of a rapidly approaching virtual predator with a female scream occurring at the end of the attack (Montoya et al., 2015). In trials with an escapable threat, subjects could terminate the attack by pressing a button. The experiment showed that cortisol decreased the brain activity during inescapable threat while opposite changes were observed during an escapable threat. This context-dependent changes help to explain variability between studies using various stimuli and protocols that can affect the perception of experimental environment. They are also important for the general understanding of effects induced by GCs that are not purely excitatory or inhibitory but rather context-dependent. This conclusion is also supported by a number of studies showing a variable effect of GC on the brain responses to emotionally charged stimuli (Henckens et al., 2010, 2012b; Sudheimer et al., 2013; Bos et al., 2014; Buades-Rotger et al., 2016).

9.2.2. Imaging of chronic effects in Cushing's disease

Acute treatments with cortisol had mild subjective and cognitive effects and many of these studies failed to reveal any significant behavioral effects (Section 9.2.1.2). In contrast, a prolonged elevation in the level of GCs has a much stronger effect on emotions and cognition as indicated both by side effects of GCs administered as anti-inflammatory

drugs and symptoms observed in patients with Cushing's disease. GCs administered at therapeutic doses induce a number of psychiatric side effects that occur usually after about 4 days (early onset) or 3 weeks (late onset) of treatment (Hall et al., 1979; Lewis and Smith, 1983; Sirois, 2003) and affect 1–62 % of patients depending on the dose and inclusion criteria (Program, 1972; Lewis and Smith, 1983; Naber et al., 1996; Wada et al., 2001; Bolanos et al., 2004). Most of this data concern synthetic GCs that exert complex effects on the brain because of combination of peripheral and central effects (Section 5, Fig. 1). Serious psychiatric symptoms are also very common in patients with Cushing's disease that are exposed to sustained long-term hypercortisolism lasting for months or even years (Starkman et al., 1981; Starkman, 2013; Pivonello et al., 2015).

Despite the fact that GCs are commonly used as anti-inflammatory drugs, fMRI testing of chronic effects was performed only in patients with Cushing's disease. This means an important gap in knowledge because patients with Cushing's disease differ from those receiving exogenous steroids in terms of duration of hypercortisolism (Starkman, 2013). fMRI experiments showed both an increased and decreased resting activity in various brain areas (Jiang et al., 2017) and mainly increased activity during memory and recognition tasks (Maheu et al., 2008; Langenecker et al., 2012). Significant changes in the resting brain activity were detected by the whole brain analysis with multiple comparisons (Jiang et al., 2017), suggesting more pronounced changes in Cushing's disease compared with the brain activity after acute treatments in humans that were detected mostly by direct comparisons in preselected regions of interest (Section 9.2.1.2). Patients with Cushing's disease had an increased resting activity in precuneus, cingulate and prefrontal cortex while decreases were found in thalamus, cerebellum, occipital cortex and postcentral gyrus (Jiang et al., 2017). In contrast, recognition of facial expressions was associated mainly with increased activity in several brain areas including frontal areas, cingulate cortex and left hippocampus while lower activity was found in right middle hippocampus compared with healthy control (Langenecker et al., 2012). The higher activity in hippocampus and amygdala was also found in Cushing's patients during an encoding phase of a memory task (Maheu et al., 2008). Preferential increases in the task-related brain activity in patients with Cushing's disease are consistent with changes in neuronal activity assessed with the c-fos expression in rats treated for 25 days with corticosterone and next subjected to fear conditioning (Skorzewski et al., 2006).

Summing up, chronic exposition to cortisol in Cushing's patients triggers variable effects in resting conditions and mainly increased task-related activity. Normalization of the cortisol level leads to partial restoration of altered spontaneous brain activity in remitted patients (Jiang et al., 2017) but some changes are present even in patients with long-term remission of the disease (Bas-Hoogendam et al., 2015; Ragnarsson et al., 2017) consistently with persistent structural changes found in brains of Cushing's patients (Andela et al., 2015). These data indicate that changes in the brain activity observed after long term exposure to cortisol depend both on ongoing signaling mediated by GRs and persistent structural changes.

9.3. c-fos expression

c-Fos protein is a molecular marker of the neuronal activity that is applied postmortem in animal studies (see Section 7.2 for more details). It should be noted that the c-Fos expression is not always able to capture functional changes because the analysis of slices averages activations during a prolonged period of time spanning between the treatment and brain dissection. Actually, the c-Fos expression simply shows that some populations of neurons were activated during an investigated period of time but it is not providing quantitative information about the frequency and duration of evoked activity. This problem is illustrated by an experiment that tested an effect of acute corticosterone on the activity of the hypothalamic-pituitary-adrenal axis during prolonged

immobilization stress lasting for one hour (Ginsberg et al., 2003). This study showed considerable inhibition of the hypothalamic-pituitary-adrenal axis by GCs (corticosterone and RU28362) as indicated by an amount of released hormones and hypothalamic CRH transcription but not at the level of hypothalamic c-Fos expression measured three hours after treatment (Ginsberg et al., 2003). Despite these limitations, detection of c-Fos expression can provide valuable information about the brain activity. In case of GCs, available c-Fos data can be divided into immediate (Briski et al., 1997; Zhang et al., 2013) and delayed (Skorzewska et al., 2007b) responses to acute treatment and responses observed after repeated treatment (Skorzewska et al., 2006; Sasaki-Hamada et al., 2013).

Acute treatment with dexamethasone revealed activated neurons in a priori selected parts of brain such as lateral habenula (Zhang et al., 2013), hypothalamus and preoptic area (Briski et al., 1997) in resting conditions 1–2 hours after drug administration. The main shortcoming of these experiments is usage of dexamethasone that is characterized by restricted penetration of the blood-brain barrier compared with corticosterone and may exert a complex effect on the brain (Section 3.1 and 5, Fig. 1). Nonetheless, detected activations of hypothalamic neurons are consistent with animal electrophysiological experiments (Table 3 and 5). Interestingly, such an effect was not reported in human fMRI studies that failed to detect hypothalamic changes after treatment with cortisol (Supplementary file 2). One likely reason is that the fMRI signal averages the activity of all neurons present in a relatively large volume of tissue leading to low sensitivity toward changes in dispersed or small subpopulations of local neurons. Second, human studies commonly applied the analysis based on preselected brain areas such as hippocampus, amygdala and cerebral cortex but not hypothalamus showing bias in research interests of cognitive neuroscientists.

In addition to immediate c-Fos responses assessed in resting conditions after treatment with dexamethasone (Briski et al., 1997; Zhang et al., 2013) there is also one study that tested c-Fos expression 27 h after acute treatment with corticosterone in combination with fear conditioning (Skorzewska et al., 2007b). This study failed to detect a significant effect in resting conditions which is not surprising while considering the long delay. However, despite negative results in resting conditions, corticosterone decreased the expression of fear responses on the next day after treatment and increased the concomitant activity in paraventricular hypothalamic nucleus, medial amygdala and cingulate while a number of other areas including hippocampus were not affected (Skorzewska et al., 2007b). This shows that corticosterone administered before fear conditioning leads to long lasting changes affecting delayed responses to context associated with previous noxious stimulation.

An opposite behavioral and c-Fos responses in paraventricular hypothalamic nucleus were observed after a prolonged treatment with corticosterone lasting for 25 days (Skorzewska et al., 2006). Additionally, a long-term treatment increased the task-evoked activity in the hippocampal CA2 area, central and medial amygdala and motor cortex while decreased the activity in dentate gyrus (Skorzewska et al., 2006). Therefore, the long-term treatment with corticosterone had much more widespread effects on the brain activity than acute treatment. In contrast, mostly negative results (infralimbic cortex, amygdala, and hippocampus) were found in resting conditions after 10 days of treatment with dexamethasone (Sasaki-Hamada et al., 2013). In this case, increased c-Fos expression was found only in dorsomedial hypothalamic nucleus that is involved in the regulation of arterial pressure and heart rate during acute psychological stress (Sasaki-Hamada et al., 2013). Unfortunately, conclusions drawn from experiments using dexamethasone are restricted by the limited entrance into the brain in combination with other properties of this drug (Section 3.1, 4 and 5 Fig. 1). Collectively, available c-Fos studies indicate that GCs activate some populations of hypothalamic, habenular and preoptic neurons in basal conditions although the data are restricted to few predefined regions of interest and dexamethasone treatments. c-Fos experiments show also task-specific effects that are more pronounced after prolonged treatment

compared with single administration of corticosterone.

9.4. Microdialysis

9.4.1. Acute effects on glutamate / GABA balance

Microdialysis allows tracking local changes in the extracellular level of neurotransmitters that are responsible for signal transmission between neurons. Two most important neurotransmitters for the brain activity is glutamate and GABA which are responsible for excitation and inhibition, respectively. Acute treatments with corticosterone increased the hippocampal level of glutamate (Venero and Borrell, 1999; Skorzewska et al., 2007a) with latency ranging from 10 to 15 min but not after 5 min (Venero and Borrell, 1999). The peak was achieved after 25–60 min and the level of glutamate returned to the baseline after 45–120 min depending on the dose ranging from 2.5–20 mg/kg (Venero and Borrell, 1999; Skorzewska et al., 2007a). This time course is consistent with the resting changes in hippocampal BOLD signal detected by human fMRI experiments but not with very rapid changes observed in the rat fMRI experiment (for more details see Section 9.2.1.4). An increased level of glutamate detected *in vivo* (Venero and Borrell, 1999; Skorzewska et al., 2007a) is also consistent with *in vitro* experiments performed on isolated nerve terminals that showed increased glutamate release after treatment with corticosterone, dexamethasone and methylprednisolone (Wang and Wang, 2009; Neiva et al., 2020). The experiment performed by Skorzewska et al. (2007a) also included a long recording period that extended beyond the time of initial normalization of the glutamate level. This experimental setup revealed a fluctuation of the glutamate level that repeatedly increased and returned to the baseline during 220 min of the recording period (Skorzewska et al., 2007a). This fluctuation can be one of the factors contributing to the variability of experimental data collected at single time points after treatment.

An increased level of glutamate was associated with a less pronounced increase in the level of GABA that achieved significance during some time points after acute treatment with corticosterone (Skorzewska et al., 2007a). Importantly, the glutamate / GABA ratio was not significantly altered which indicates that there was no marked change in the balance between excitatory and inhibitory processes in hippocampus (Skorzewska et al., 2007a). The mechanism of this effect is, however, not clear. Methylprednisolone, a synthetic GC, did not affect GABA release from isolated nerve terminals in contrast to glutamate release (Neiva et al., 2020). This indicates that the effect observed *in vivo* (Skorzewska et al., 2007a) requires a preserved structure of neuronal network that is destroyed during preparation of isolated nerve terminals (Neiva et al., 2020). Summing up, microdialysis data show that acute treatment with GCs increase excitatory neurotransmission but it is balanced by concomitant inhibitory effects. Therefore, the net effect is small consistently with fMRI experiments (Section 9.2.1.2).

9.4.2. Glutamate / GABA balance after repeated treatments

In animals chronically pretreated with corticosterone (25 days), both the baseline concentrations of glutamate and the Glu/GABA ratio were increased, indicating an enhancement of excitatory processes in the hippocampus (Skorzewska et al., 2007a). However, a challenge dose of corticosterone administered to rats chronically pretreated with corticosterone almost completely depleted hippocampal glutamate, and decreased the glutamate/GABA ratio (Skorzewska et al., 2007a). It has been suggested that this phenomenon results from enhancement of local feedback mechanisms, operating to eliminate excess of extracellular glutamate from the synaptic cleft to maintain the equilibrium between the excitatory and inhibitory processes (Skorzewska et al., 2007a). Collectively, these data indicate that prolonged treatment with corticosterone leads to increased hippocampal excitability but this effect is reversed by acute elevation of GCs. Importantly, these findings help to reconcile apparently contradictory results obtained not only during the brain imaging of Cushing's syndrome but also in acute treatment in

healthy population. Small groups of volunteers recruited in some social groups such as students may share the history of stress experienced over weeks prior to the imaging experiment affecting the apparently acute effects of cortisone.

9.4.3. Serotonin and noradrenaline

Two other tested neurotransmitters were serotonin and noradrenaline. Serotonin was increased in the hippocampus 2 h after treatment with corticosterone (10–40 mg/kg) but not earlier (Li et al., 2019). Acute treatment with corticosterone (3 mg/kg, i.p.) also induced a transient increase in the noradrenaline level in the amygdala 15 min after the inhibitory avoidance training while no effect was observed in resting conditions (McReynolds et al., 2010). The repeated treatment lasting for 1 week had an opposite effect in paraventricular nucleus and the differences were much higher during immobilization stress than during basal conditions showing a well-known inhibitory effect of GCs on the hypothalamic-pituitary-adrenal axis (Pacak et al., 1995). However, a longer treatment (2 weeks) administered in the form of implanted pellets had no effect on the basal release of noradrenaline in two other brain areas (prefrontal cortex and locus coeruleus) (Horrillo et al., 2016). Collectively, these data indicate that it is important to test the effect of GCs in different conditions (resting and task/stimulus evoked) because some effects may be less pronounced or even absent in basal conditions as evidenced by the effect on the release of noradrenaline. This observation is consistent with data from electrophysiological (Section 9.1.1) and c-Fos experiments (Skorzewska et al., 2007b).

10. Integration of experimental data

10.1. Production of energy

The most crucial issue for interpretation of metabolic data is the total amount of available energy in the brain as indicated by the level of ATP (Section 8.7). Modest doses of GCs applied for up to several days do not decrease the total amount of brain ATP and in some cases they even increase it (Section 8.7.1). Additionally, GCs slow ATP loss during a short-term brain ischemia resembling a situation that can be found during strangling (Section 8.7.2). In contrast, a decreased level of ATP was observed after application of very high doses of corticosterone or after prolonged treatments (Hoyer and Lannert, 2008; Zhao et al., 2008). This shows that elevated levels of GCs are not impairing production of energy with an exception of prolonged treatments and high doses that induce a toxic effect consistently with the concept of allostatic load and overload (McEwen, 2020). Production of energy is maintained despite an initial decrease in mitochondrial oxidative metabolism occurring during the first 2 h after treatment (Morin et al., 2000; Katyare et al., 2003; Fujita et al., 2009) probably because of increased glycolysis in astrocytes (Allaman et al., 2004; Juszczak and Stankiewicz, 2018; Skupio et al., 2019). Although the short-term decrease in mitochondrial oxidative metabolism may seem maladaptive, it can be easily understood, considering a metabolic response to an increased neuronal activity observed for example during intense sensory stimulation or mental effort. Such activation is associated with highly increased nonoxidative glycolytic metabolism despite an excessive supply of oxygen due to a locally increased blood flow (Dienel, 2012; Dienel and Cruz, 2016). Therefore, the biphasic effect of GCs on oxygen consumption (Section 8.6) may constitute an adaptation for initial increase in glycolytic metabolism associated with a task-related brain activation followed by delayed compensation for a metabolic debt.

10.2. Energetic substrates

During the first two hours there are no changes in the brain glucose uptake at least in resting conditions while increases are frequently found *in vivo* after longer treatments that lead to insulinemia (Section 8.3.2, Table 1). GCs also increase the blood level of several metabolites such as

lactate, pyruvate, mannose and hydroxybutyrate (ketone bodies) (Thurston et al., 1980; Thompson et al., 2000; Bordag et al., 2015) that can be used by the brain as an alternative source of energy (Section 8.5). Increased availability of ketone bodies means that brain energetics can benefit from increased metabolism of lipids (Section 8.1, Fig. 3) although it has a negligible ability to directly oxidize fatty acids (Dhopeshwarkar and Mead, 1969; Yang et al., 1987). Therefore, GCs not only increase an amount of available blood glucose but also lead to diversification of available sources of energy that can be used to fuel brain at the time of increased energy expenditures associated with stress response (Picard et al., 2018). These changes in the level of various energetic substrates can be classified as allocative brain-pull mechanisms enabling the brain to actively demand energy from the body (Peters, 2011). Finally, GCs increase both synthesis and utilization of glycogen (Watanabe and Passonneau, 1973) enabling flexible storage and utilization of surplus glucose depending on the local neuronal activity. Such flexibility is important because brain responses to stress are variable. In fact, depending on the type of stressful experience, brain metabolism may either increase or decrease (Bryan, 1990; Warnock and Steckler, 2011). The differences in energy utilization also lead to important consequences in situations not requiring energy-consuming activities because a prolonged elevation of glucose and lipids together with insulin resistance constitutes metabolic stress for the organism (Gandhi et al., 2010; Picard et al., 2018; Rowan et al., 2018).

10.3. Brain activity

10.3.1. Acute effects of GCs

Brain metabolism and activity are intimately connected with each other because most of the brain energy is consumed by neuronal signaling (Yu et al., 2018) which in turn regulates local blood flow and transport of glucose across the blood-brain barrier (Kim and Ogawa, 2012; Koepsell, 2020), glycolysis (Dienel, 2012; Dienel and Cruz, 2016) and utilization of glycogen (Dienel and Rothman, 2019) (Fig. 4). Acute effects of GCs on the net brain activity are modest as indicated by the proportion of excited and inhibited neurons (Table 3 and 5), ratio of released excitatory and inhibitory neurotransmitters (Skorzewska et al., 2007a) and magnitude of effects detected by fMRI (Section 9.2.1.2). Instead of inducing purely excitatory or inhibitory effects, GCs rather alter dynamics of the neuronal activity leading to context-specific changes that are expected to support responses to environmental threats.

Available data also indicate that changes in the activity of single neurons after treatment with GCs do not always lead to gross changes in the activity of studied brain area because of concomitant excitatory and inhibitory effects in local subpopulations of cells (Section 9.1.2). This indicates that some functional effects may occur even without gross changes in the local brain activity. Restricted acute effects of GCs on brain metabolism and activity are consistent with absent or mild subjective effects reported by humans after acute administration of the hormone (Section 9.2.1.2).

Methodological approaches enabling the assessment of a net effect of GCs on the brain activity such as fMRI and microdialysis with concomitant measurement of excitatory and inhibitory neurotransmitters help to put various mechanisms implicated previously in actions induced by GCs in a broader context. Such mechanisms include changes in neurotransmitter clearance (Zschocke et al., 2005; Autry et al., 2006; Popoli et al., 2011), altered excitability depending on expression and trafficking of glutamatergic receptors (Liu et al., 2010; Popoli et al., 2011; Yuen et al., 2011; Nasca et al., 2015) and increased probability of neurotransmitter release that can be either MR-dependent (Karst et al., 2005) or GR-dependent (Wang and Wang, 2009). Furthermore, GC-induced changes in neurotransmission also involve retrograde endocannabinoid release (Di et al., 2003, 2005) and both increased (Di et al., 2005) and decreased GABA release (Hill et al., 2011). These mechanisms studied in isolation are not informing us, however, about

the net effect of altered excitatory and inhibitory neurotransmission at the level of entire brain. However, reviewed fMRI and microanalysis studies show that these various mechanisms are in fact roughly balanced after acute treatments with GCs leading to restricted changes both in terms of size of affected brain areas and magnitude of the excitatory and inhibitory effects.

10.3.2. Chronic effects of GCs

In contrast to acute effects, prolonged elevation in the level of GCs has a much stronger effect on brain metabolism, activity and function as indicated by animal studies (Skorzecka et al., 2006; Skorzecka et al., 2007a) and patients with Cushing's disease (Section 9.2.2). Chronic effects are associated with region-specific changes in resting blood flow (Jiang et al., 2017) and glucose utilization including both increases and decreases (Brunetti et al., 1998; Liu et al., 2018) and mainly an increased task-related activity (Skorzecka et al., 2006; Maheu et al., 2008; Langenecker et al., 2012). The altered brain activity observed after a long-term exposure to high levels of GCs results to some extent from structural changes as indicated by only partial restoration of altered brain activity in remitted patients (Bas-Hoogendam et al., 2015; Jiang et al., 2017; Ragnarsson et al., 2017).

11. Major gaps and future directions

There are many gaps in available data that were discussed in detail in previous Sections (2.2, 8.8, 9.1.4, 9.2.1.1) and methodological shortcomings (2.3, 5, 7, 9.3) frequently preventing us from drawing firm conclusions. A general weakness of available data is that both animal and human studies were focused mainly on brain responses during the first two hours after acute treatments while longer latencies (Section 6) and repeated treatments are underrepresented in the scientific literature (Section 8.8, 9.1.4, 9.2.1.1). Furthermore, animal *in vivo* studies were usually performed in resting conditions and frequently applied GCs characterized by a restricted ability to cross the blood-brain barrier (Section 5, Fig. 1). Therefore, a bulk of animal studies is difficult for interpretation and has no behavioral relevance. This is an important gap because a number of different methodological approaches such as fMRI (Section 9.2), microdialysis (Pacak et al., 1995; McReynolds et al., 2010) and postmortem c-Fos immunohistochemistry (Skorzecka et al., 2007b) show that the effect of GCs on the brain activity depends on exposure to sensory stimuli and their emotional valence, task engagement and conditions affecting escapability of aversive stimulation. Additionally, we are not able to assess the replicability of many findings because of restricted number of studies. A final major gap results from the fact that most of available studies focused exclusively on the effects of an increased level of GCs without the consideration of interaction with other stress molecules (Section 2.2). This issue is important because few available studies suggest that actions induced by GCs vary considerably depending on the presence or absence of noradrenergic stimulation and timing of this interaction (Allaman et al., 2004; van Stegeren et al., 2010; Schwabe et al., 2012; Karst and Joels, 2016). Therefore, despite the fact that GCs are studied extensively for many decades, there are still considerable gaps in our knowledge. One of the most promising research opportunities is offered by the development of new methods enabling detection of neurotransmitters with biosensors (Leopold et al., 2019) and analysis of large populations of neurons in behaving animals (Aronov and Tank, 2014; Weisenburger and Vaziri, 2018; Piatkevich et al., 2019). The second major opportunity is offered by recent advancements in magnetic resonance spectroscopy and other related imaging methods enabling measurement of brain metabolism (Hyder and Rothman, 2017; Rothman et al., 2019). Application of these methods will advance our understanding of effects induced by GCs in brain. Furthermore, linking functional effects of glucocorticoids with specific subpopulations of MRs and GRs differing in binding affinity, cellular localization and interacting partners involved in genomic and non-genomic effects will help to better understand their role in adaptive and

maladaptive responses. Especially interesting in this context are still poorly understood interactions between GRs and mitochondrial genome (Du et al., 2009; Weger et al., 2020). It can be expected that this topic will attract more attention in the future, considering the role of mitochondria in cellular metabolism that affect the function of the entire organism (Picard et al., 2014, 2018).

Declaration of Competing Interest

None.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:<https://doi.org/10.1016/j.neubiorev.2021.03.007>.

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