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Modulatory actions of steroid hormones and neuropeptides on electrical activity in brain

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Abstract

Electrophysiological studies over the past decades have shown that many compounds in addition to 'classical' neurotransmitters affect electrical activity in the brain. These compounds include neuropeptides synthesized in brain as well as compounds which are released from peripheral sources and subsequently enter the brain compartment, such as corticosteroid hormones from the adrenal gland. In the present review, this principle is illustrated by describing the effects of two substances, i.e. vasopressin and corticosterone. Neuropeptides and corticosteroid hormones add at least two essential aspects to information processing in the brain. First, they both act conditional, i.e. they modulate the actions of 'classical' neurotransmitters, rather than changing basal neuronal activity by themselves. Second, the time-frame in which modulation of electrical properties takes place differs from that generally seen with 'classical' neurotransmitters. Neuropeptides modulate electrical activity over a period of minutes, while effects of corticosteroid hormones usually become apparent after at least an hour but then last for hours. In this way, neuropeptides and steroid hormones expand the repertoire of responses through which the brain reacts to environmental challenges.

Keywords: Corticosterone; Vasopressin; Firing pattern; Ion channel; Neurotransmitter

1. Introduction

Information transfer between cells in the central nervous system is to a large extent mediated by fast acting chemical messengers, neurotransmitters. These compounds are synthesized within the brain, rapidly released upon low frequency activation of the synaptic terminals and change the conductance of target cells within seconds after the activation of either the ionotropic or the metabotropic receptors (Cooper et al., 1996). The conductance changes are generally short lasting, due to in particular the local reuptake of the neurotransmitters. The fast and short-lasting effects of the neurotransmitters on the electrical properties of the target cells make these compounds very suitable for mediating information that should be rapidly transferred, such as sensory input to the brain.

In the 1960s, however, it became gradually clear that information flow in the brain may be affected by compounds acting in a different way than the neurotransmitters known at that time such as acetylcholine. David de Wied was among the first to state that compounds, up to then only known for their peripheral hormonal actions, could change the behavioral performance of animals, implying that these compounds are distributed in the brain and alter the information transfer between cells (De Wied, 1965). This pertained for instance to peptides involved in the hypothalamo-pituitary-axis such as adrenocorticotropin hormone and vasopressin. In later years, this concept was extensively substantiated by showing that many peptides are distributed within the brain and have modulatory effects on the electrical properties of brain cells (De Wied, 1990). The term neuropeptides was coined for this group of small proteins (De Wied et al., 1974). Neuropeptides are released upon extensive fiber stimulation and act through G-protein coupled receptors. Their actions are terminated by diffusion or conversion of the peptide; the presynaptic availability of the neuropeptides depends on transcriptional activity of the encoding gene in the nucleus and transport from the nucleus to the terminals, which is a slow process (Cooper et al., 1996). Electrophysiological studies over the past decades have shown that due to this mechanism of action of the neuropeptides, these compounds add a new element to the transfer of information sustained by 'classi-

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cal' neurotransmitters: Neuropeptides (1) affect information transfer at certain activity states of the circuit, (2) generally modulate the action of neurotransmitters and (3) exert their actions with a relatively slow onset (seconds to min) for a considerable period of time (range of min). In this review, such relatively slow modulatory effects of neuropeptides on electrical signaling in the brain will be briefly discussed and illustrated for one particular neuropeptide, vasopressin.

In the 1960s, it further became evident that apart from neurotransmitters and neuropeptides, other compounds that were up to then only known for their peripheral hormonal function could also affect information processing in the brain. This involved hormones that (in contrast to neuropeptides) are exclusively synthesized in the peripheral glands, transported via the circulation but due to their lipophylic character can nevertheless enter the brain compartment. A prime example is the adrenal hormone corticosterone, which like adrenocorticotropin hormone and vasopressin, is a key player in the hypothalamo-pituitary-adrenal axis. In 1968, Bruce McEwen showed that corticosterone binds with high affinity to receptors in the brain, particularly in the hippocampus (McEwen et al., 1968). Some years later, Pfaff et al. (1971) demonstrated that glucocorticoids attenuate hippocampal cell firing with a substantial delay in time (>30 min). These corticosteroid hormones act through intracellular receptors that upon activation regulate transcriptional activity of target genes (Beato and Sanchez-Pacheco, 1996). Over the past decade, it has become evident that corticosteroids have profound modulatory effects on the electrical properties of brain cells; effects that usually take 1–2 h to develop and then last for many hours (Joëls, 1997). Long-lasting corticosteroid actions on the electrical activity in the brain will be discussed below.

The picture that emerges now is that fast information transfer in the brain is sustained by 'classical' neurotransmitters that act within milliseconds to seconds. These signals are modulated by slower acting monoamines and neuropeptides (range of minutes). At an even longer timescale (h), hormones such as corticosterone can transcriptionally regulate the compounds that are essential for electrical signaling. In this way, key compounds of one biological system, such as the hypothalamo-pituitary-adrenal axis, can modulate brain function over a very wide range of time, taking care of immediate as well as delayed responses of the system. In the following, typical examples of such diverse actions exerted by neuropeptides and corticosteroid hormones will be discussed.

2. Neuropeptide actions on electrical activity

One of the first neuropeptides that was investigated for its effects on behavioral performance is vasopressin. Vasopressin is a nonapeptide synthesized in the magnocellular and parvocellular neurons of the hypothalamus (Buijs et al., 1980). Vasopressin from these cells is transported in various ways to the anterior and posterior pituitary and is involved in the peripheral actions of the hormone. Vasopressin, however, is also synthesized in other brain regions, such as the suprachiastmatic nucleus and the bed nucleus of the stria terminalis. Synthesizing neurons from these areas send axonal projections to extrahypothalamic sites, such as the lateral septum and hippocampus. When it became clear that vasopressin is transported to these extrahypothalamic regions, Ivan Urban and David de Wied set out to study the effect of vasopressin on electrical activity in the lateral septum and hippocampus.

In a first set of experiments, it was found that in the absence of vasopressin — i.e. in Brattleboro rats or control rats treated with a vasopressin antiserum mean and peak frequencies of hippocampal theta rhythm were shifted to lower values; this could be restored by the intracerebroventricular administration of the desglycinamide-vasopressin (Urban and De Wied, 1978). Microinjection of vasopressin into the septum, which is associated with the initiation and pacing of hippocampal theta rhythm, increased the peak theta frequency above the level normally observed (Urban, 1981). In all cases, vasopressin influenced but did not initiate theta-rhythm. These experiments suggested that vasopressin indirectly enhances septal and hippocampal neuronal activity.

In subsequent extracellular single unit recordings, this idea was further substantiated. Hippocampal fibers originating from CA1 and CA3 neurons send an excitatory projection to the lateral septum cells, which is mediated by glutamate acting on AMPA receptors (McLennan and Miller, 1974; Joëls and Urban, 1984a). With the microiontophoretic application of vasopressin to the lateral septum cells in anaesthetized rats, it was shown that only a minority of the septum cells respond to vasopressin with an increase of the basal firing rate. However, many cells showed an increased response to the stimulation of hippocampal afferents in the presence of vasopressin (Joëls and Urban, 1982, 1984b; see Fig. 1). This modulatory effect developed over the course of minutes, but persisted for many minutes after the application of vasopressin was terminated. A similar modulatory enhancement of amino acid-mediated neurotransmission by vasopressin was later also demonstrated in the hippocampus (Urban and Killian, 1990). These extracellular studies led to the idea that vasopressin does not change basal electrical properties but is nevertheless able to increase responsiveness to excitatory input.

The mechanism underlying this indirect effect of vasopressin was addressed in later intracellular studies in vitro. These studies indeed showed that resting membrane potential of lateral septum cells is in most cases not affected by vasopressin within a physiological dose-range (Van den Hooff and Urban, 1990). However, responses to stimulation of glutamatergic afferents were enhanced by vaso-

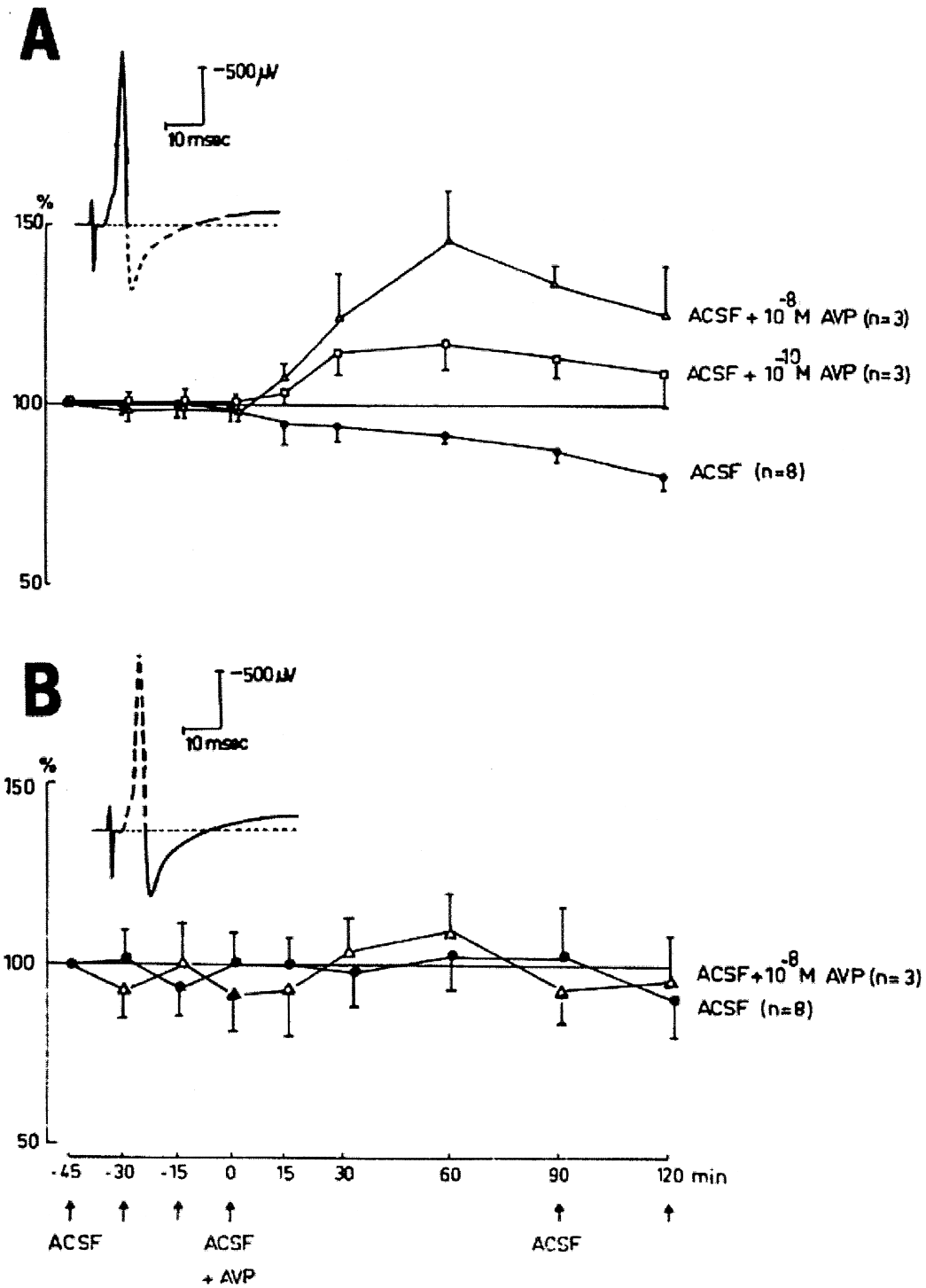

Fig. 1. Mean amplitude (+SEM) of the negative (A) and positive (B) waves of averaged field potentials (example: insets) recorded in the lateral septum after stimulation of hippocampal afferents, during topical application of various concentrations of arginine^8-vasopressin or the control artificial cerebrospinal fluid (ACSF). In each experiment, the field potential amplitude was expressed as a percentage of the amplitude obtained for the first field potential of the experiment. Arrows at the *x*-axis indicate the moment of topical application of control ACSF or vasopressin dissolved in ACSF. From Joëls and Urban (1984b).

pressin application. This effect was not mediated by vasopressin V_1 receptors.

These studies uncovered an important principle of neuropeptide actions on the electrical activity in the brain. In many instances, neuropeptides will not affect electrical activity when cells are at resting conditions. However, when cells are activated by synaptic input mediated by fast acting neurotransmitters, neuropeptides can alter the re-

sponsiveness to this input for a considerable period of time. The time-window at which peptides are active may be dictated by the mechanism of action, involving G-protein and second messenger activation, and/or by the slow degrading processes which cause neuropeptides to linger for considerable periods of time in the vicinity of their receptors. The functional implication of such lasting modulatory effects may be particularly evident for the phenomena that critically depend on the activity of circuits, such as long-term potentiation. In this respect, it is of great interest that the maintenance of long-term potentiation in the lateral septum was found to depend on the activation of vasopressin V_1 receptors (Van den Hooff et al., 1989). This supports a role of neuropeptides in activity-dependent phenomena associated with learning and memory (De Wied, 1965, 1971).

3. Corticosteroid hormone actions on electrical activity

Corticosteroid hormones are among the best studied examples of peripheral hormones exerting actions on electrical activity in brain. Corticosterone, the adrenal glucocorticoid hormone in rodents, is secreted in a circadian pattern: high levels of the hormone are found just prior to the active period of the organism, i.e. for rats in the late afternoon; the trough of the circadian release takes place just before the onset of the inactive period (De Kloet, 1991; De Kloet et al., 1998). On top of this circadian variation, elevations in circulating corticosteroid levels are caused by exposure of the organism to stress.

Corticosterone easily passes the blood–brain barrier, due to its lipophylic nature. Within the brain, the hormone binds to two receptor types, each with a specific binding profile and distribution (De Kloet, 1991). Mineralocorticoid receptors have a high affinity for corticosterone (K_d ~ 0.5 nM). The mineralocorticoid receptors are mostly expressed in limbic structures, such as the lateral septum and hippocampus, and in the motor nuclei in the brain stem. Glucocorticoid receptors have a 10-fold lower affinity for the mixed natural agonist corticosterone and display a widespread distribution. Principal cells in the hippocampal CA1 region and dentate gyrus abundantly co-express mineralocorticoid and glucocorticoid receptors. Due to the difference in affinity, circulating levels of the hormone will determine to what extent receptors will be activated. At rest, at the nadir of the circadian cycle, hippocampal cells will show predominant activation of mineralocorticoid receptors. At the circadian peak or after stress, glucocorticoid receptors will become activated in addition to mineralocorticoid receptors. Over the past decade, we have employed electrophysiological methods to investigate the consequences of differential mineralocorticoid and glucocorticoid receptor activation for electrical activity of hippocampal cells.

Similar to what was found for the neuropeptide vasopressin, corticosterone generally did not affect passive membrane properties of hippocampal cells under resting conditions of the cell (Joëls and De Kloet, 1989; Kerr et al., 1989; Beck et al., 1994). Only when the membrane potential of the cell is shifted away from the resting situation do the corticosteroid effects become apparent. The research focussed on two specific types of membrane characteristics that are important for the function of cells in networks: (1) intrinsic properties such as voltage-gated ionchannels; (2) ionotropic and metabotropic receptors for neurotransmitters and neuropeptides projecting onto hippocampal cells (see Fig. 2). The main findings are summarized in the following paragraphs.

3.1. Corticosteroid effects on voltage-gated ionchannels

The effect of corticosteroid hormones on Na^+, K^+ and Ca^{2+} channels was investigated in vitro, using whole cell patch clamp recording. In our studies, we used corticosteroid concentrations that are within the physiological range. Moreover, we focussed on slow and persistent effects of corticosteroids, by investigating electrical properties 1–4 h after a brief application of the hormone.

It was found that particularly Ca^{2+} currents are markedly affected by corticosteroid receptor activation. Low levels of corticosterone, resulting in predominant mineralocorticoid receptor activation, are associated with a small amplitude of voltage-gated Ca^{2+} channels (Karst et al., 1994). Additional activation of glucocorticoid receptors increase the amplitude of the Ca^{2+} currents (Kerr et al., 1992; Karst et al., 1994; Hesen et al., 1996). Interestingly, in the absence of corticosteroid hormones (i.e. in tissue

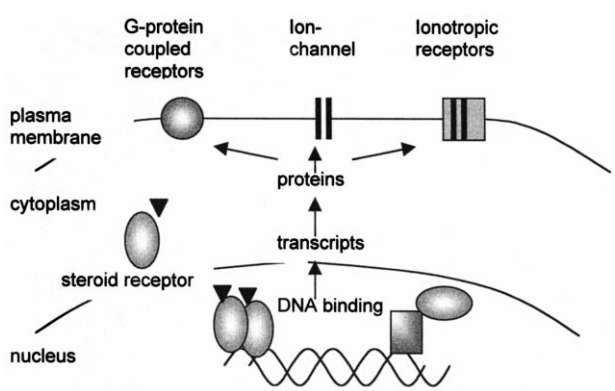

Fig. 2. Corticosteroid hormones (triangle) enter a neuron and bind to intracellular corticosteroid receptors, which at that time are associated with heat shock proteins. Upon binding, the receptor dissociates from the protein complex, homodimerizes and translocates to the nuclear compartment. Homodimers bind to glucocorticoid responsive elements in the DNA and regulate transcriptional activity of genes. As a consequence, transcript levels for particular genes are altered. The proteins encoded by steroid responsive genes may directly or indirectly alter the function of intrinsic membrane properties (e.g. voltage gated ion channels), or ionotropic and G-protein coupled neurotransmitter receptors.

from adrenalectomized rats) the Ca^{2+} current amplitude is also large, pointing to a U-shaped steroid dose-dependency for Ca^{2+} current amplitude (Karst et al., 1994). Ca^{2+}-dependent phenomena of hippocampal cells, such as the accommodation of firing (caused by activation of a Ca^{2+}-dependent K^+ channel), display a similar dose-dependency (Joëls and De Kloet, 1989, 1990; Kerr et al., 1989).

More recently, the molecular mechanism underlying the slow modulatory effects of corticosterone on Ca^{2+} currents was investigated. Several observations indicate that these modulatory effects take place via transcriptional regulation. First, the pharmacological profile of the steroid effects fits with the known profile of the nuclear receptors for corticosterone (Kerr et al., 1992; Karst et al., 1994). Second, the effects are slow in onset and very persistent which is compatible with gene-mediated actions (Joëls and De Kloet, 1990). Third, corticosteroid effects on Ca^{2+} currents or related phenomena do not develop in the presence of a protein synthesis inhibitor (Karst and Joëls, 1991; Kerr et al., 1992). Finally, no glucocorticoid receptor-mediated increases in Ca^{2+} current amplitude were observed in mice with a point mutation in the glucocorticoid receptor-gene, preventing homodimerization and DNA-binding of the glucocorticoid receptor (Karst et al., 2000). Although in particular the latter experiment shows that glucocorticoid receptor homodimer binding to recognition sites in the DNA is necessary for glucocorticoid effects on Ca^{2+} current amplitude, it is presently unknown which genes are involved in such effects. Data so far available show that these genes may include those that encode for Ca^{2+} channel subunits (Nair et al., 1998). However, it cannot be excluded that other target genes, e.g. encoding for phosphatases or kinases which indirectly alter the function of Ca^{2+} channels, are involved.

While Ca^{2+} channel function is apparently very sensitive to corticosteroid receptor activation, the functioning of other voltage-gated ionchannels was found to be far less regulated by corticosteroid hormones. The properties of most K^+ channels tested were not altered by selective steroid receptor activation, except for the inwardly rectifying K^+ channel which is active at very negative membrane potentials (Karst et al., 1993). Similarly, the fast tetrodotoxin-sensitive Na^+ conductance was only marginally affected by corticosteroid hormones (Werkman and Joëls, 1997). These slight changes in channel conductances may nevertheless, to some extent, alter the shape of the action potential, as was indeed observed under current clamp conditions (Beck et al., 1994).

In summary, corticosteroid receptor activation selectively alters particular voltage sensitive ionconductances in hippocampal cells, most notably Ca^{2+} conductances. These effects or slow in onset, long lasting and involve transcriptional regulation of presently unknown genes. Low levels of corticosterone result in limited Ca^{2+} influx into hippocampal cells, which favors viability of cells and stability of the network. High levels of corticosterone, such as seen after exposure to stress, are associated with considerable influx of Ca^{2+}. When cells are subjected to this condition for a limited period of time, the increased Ca^{2+} influx may serve e.g. to enhance accommodation of firing; increased cell firing accommodation will reverse temporary raised firing activity. However, when cells are exposed to glucocorticoid receptor activation for a prolonged period of time, particularly in combination with depolarizing stimuli (such as occur during ischemia or seizures), Ca^{2+} influx may rise beyond control, imposing a situation of enhanced risk for delayed cell death.

3.2. Corticosteroid effects on ligand-gated ionchannels

The study of corticosteroid effects on ligand-gated ionchannels has so far been quite limited. Specific interactions between corticosteroids on the one hand and AMPA, *N*-methyl-D-aspartate or $GABA_A$ receptors on the other hand have not been addressed. However, several studies have examined whether corticosteroid receptor activation affects synaptic transmission mediated by glutamate or GABA.

In general, modulatory actions of corticosterone or cortisol on synaptic transmission mediated by glutamate- or GABA receptors were seen with very high concentrations of the hormone (exceeding 1 μM) and with a relatively short (less than 30 min) time-lag (Vidal et al., 1986; Rey et al., 1987, 1989; Zeise et al., 1992). In some reports, though, the effects were observed with lower corticosteroid concentrations (Reiheld et al., 1984; Rey et al., 1987, 1989; Joëls and De Kloet, 1993), depending, for example, on the extracellular Ca^{2+} concentration (Talmi et al., 1992). It is presently unclear whether these modulatory effects of corticosteroid hormones on glutamate and GABA-mediated transmission involve nuclear receptors acting through changes in gene transcription.

When effective, glucocorticoids were shown to suppress amino acid-mediated transmission. These effects were not only relatively fast in onset (<20 min delay) but also reversible within 10–20 min (Reiheld et al., 1984; Vidal et al., 1986; Rey et al., 1987, 1989; Zeise et al., 1992; Joëls and De Kloet, 1993). Predominant activation of mineralocorticoid receptors is associated with stable transfer of glutamate as well as GABA-receptor-mediated synaptic responses (Reiheld et al., 1984; Joëls and De Kloet, 1993; Birnstiel et al., 1995). In the absence of corticosterone (i.e. in untreated adrenalectomized animals), amino acid receptor-mediated responses were comparable to the responses in sham-operated control animals (Kerr et al., 1989), although stability of the responses upon repeated stimulation was attenuated (Joëls and De Kloet, 1993). In one study only, synaptic responses were found to be markedly reduced after adrenalectomy (Doi et al., 1991). Interactions of corticosterone with other ligand-gated ionchannels, such as the nicotinic or serotonin-3 receptors, have not been specifically examined.

In summary, the present studies indicate that ligand-gated ionchannels do not seem to be a major target for transcriptional regulation by corticosteroid hormones in the brain, although extensive studies have not yet been performed. Steroid modulation of responses by ligand-gated ionchannels that were found may be due to external factors such as Ca^{2+} concentration or metabolic state of the cells that are regulated by the hormones (Virgin et al., 1991; Sapolsky, 1992). In contrast to cortisol or corticosterone, steroid hormones that possess a 5α-reduced A-ring — such as metabolites of progesterone — are known to affect ligand-gated ionchannel function in a rapid and reversible manner (Baulieu et al., 1999; Compagnone and Mellon, 2000). These actions, however, do not involve nuclear receptors but membrane recognition sites to which these steroid metabolites bind with a relatively low affinity.

3.3. Corticosteroid effects on G-protein coupled receptors

Most of the receptors for monoamines and all of the presently known receptors for neuropeptides belong to the class of G-protein coupled receptors. Corticosteroid modulation of signals via several receptors belonging to this class was tested with intracellular recording techniques. Signals mediated via two receptors appeared to be very sensitive, i.e. the 5-HT_{1A} and the muscarinic acetylcholine receptors.

Interestingly, the modulation by corticosteroids of responses via these receptors is very similar to what was observed with respect to the Ca^{2+} conductances. Thus, responses mediated via 5-HT_{1A} and muscarinic acetylcholine receptors were relatively small in amplitude under conditions of rest, i.e. with predominant mineralocorticoid receptor activation (Fig. 3; Joëls et al., 1991; Joëls and De Kloet, 1992; Hesen and Joëls, 1993; Beck et al., 1996). Subsequent activation of glucocorticoid receptors resulted in enhanced responses via the 5-HT_{1A} and muscarinic acetylcholine receptors. Large responses to serotonin were also seen after exposure to an acute stressor (Hesen and Joëls, 1996a). By contrast, muscarinic acetylcholine receptor-mediated responses were suppressed after exposure of the organism to stress, indicating that stress affected cholinergic responses not only via glucocorticoid receptor activation but also via additional stress-dependent processes (Hesen and Joëls, 1996b). Responses via the 5-HT_{1A} and muscarinic acetylcholine receptors were large in the absence of corticosteroids, showing that also with respect to modulation of these G-protein coupled receptor signaling pathways a U-shaped steroid dose-dependency was found. Responses mediated via β-adrenoceptors appeared to be somewhat differently modulated by corticosteroids. Thus, activation of glucocorticoid receptors resulted in a delayed suppression of membrane effects induced by β-adrenoceptor activation, compared to the situation where no steroid receptors were activated (Joëls and De Kloet, 1989).

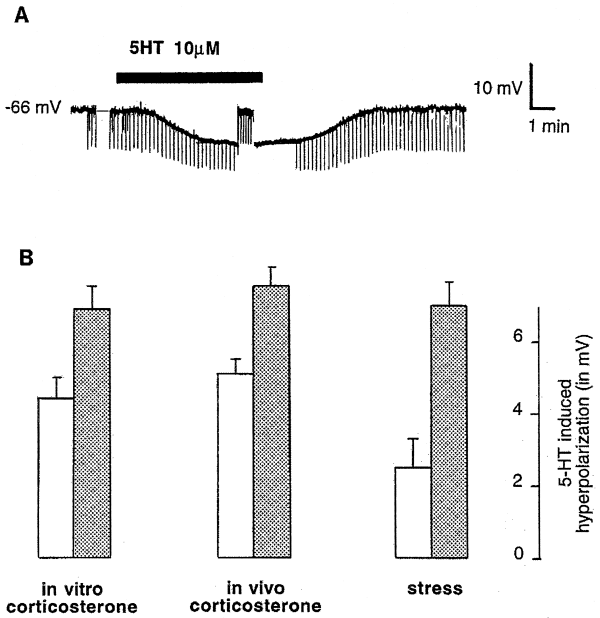

Fig. 3. (A) Serotonin (5-HT) hyperpolarizes the membrane of CA1 pyramidal neurons in the hippocampus. This is due to opening of K-channels, which results in a decrease of the membrane resistance during application of 5-HT. (B) The effect of 10 μM 5-HT on the membrane potential of hippocampal cells is relatively small with predominant mineralocorticoid receptor activation (open bars), compared to the situation where both receptor types are activated (stippled bars). This was demonstrated in studies where receptors where activated in vitro, in tissue from adrenalectomized rats (left), in studies where 5-HT responses were recorded from tissue of adrenalectomized animals that were treated in vivo with various doses of corticosterone (middle) and in tissue from adrenally intact rats that were stressed after pretreatment with a glucocorticoid receptor antagonist or vehicle (right). From Joëls (1997).

The mechanism underlying the modulation of 5-HT_{1A} receptor-mediated responses was studied in more detail. Many factors support a gene-mediated mechanism of action for the steroid hormones. Thus, synthetic compounds that specifically activate or block nuclear receptors modulated the 5-HT_{1A} receptor-mediated response (Joëls et al., 1991). The corticosteroid modulation developed with a delay of 1–2 h and persisted for at least 4 h, compatible with a slow gene-mediated signaling pathway (Joëls and De Kloet, 1992). The modulation of serotonin responses by corticosteroid hormones was not observed in the presence of protein synthesis inhibitors (Karst and Joëls, 1991). Moreover, in mice with a mutated glucocorticoid receptor precluding homodimerization and DNA binding of the activated glucocorticoid receptor, no enhancement in the response to 5-HT was observed when cells were exposed to a very high dose of corticosterone (Karst et al., 2000). It seems unlikely, though, that the 5-HT_{1A} receptor gene itself is a major target for activated glucocorticoid receptor homodimers. For instance, the promoter sequence of the 5-HT_{1A} receptor gene (as far as presently known) does not contain a consensus glucocorticoid response element. Also, responses to 5-HT are attenuated 1–2 h after mineralocor-

ticoid receptor occupation (Joëls and De Kloet, 1992), but transcripts for the 5-HT_{1A} receptor are decreased with a much longer delay (Meijer and De Kloet, 1994); this does not fit with the idea that changes in 5-HT_{1A} receptor mRNA level underlie the changes in 5-HT receptor function. These observations suggest that steroid receptors target a gene encoding a protein that alters the 5-HT_{1A} receptor function by posttranslational modification. The nature of this gene is presently unknown.

Summarizing, responses to in particular 5-HT display a U-shaped steroid dose-dependency, similar to what was earlier observed for the Ca^{2+} conductances. The modulation of 5-HT responses was found to have implications for the information flow in the CA1 area. Since 5-HT_{1A} receptor activation hyperpolarizes CA1 cells, the transfer of excitatory input is attenuated in the presence of 5-HT. This was indeed observed (Karten et al., 1998). This attenuation was less apparent under conditions of predominant mineralocorticoid receptor activation, but very marked when glucocorticoid receptors were active in addition to mineralocorticoid receptors, e.g. after exposure to an acute stressor. It should be realised that the effect of stress exposure depends on the history of the animal: If animals were repeatedly exposed to very high doses of corticosterone, a gradual development of resistance to the normal glucocorticoid receptor-mediated cellular responses was observed (Karten et al., 1999b).

3.4. Implications of corticosteroid actions for network function

The picture that emerges is that corticosteroid hormones change particular properties of neurons, all with a U-shaped dose-dependency (Joëls, 1997). Under rest, i.e. with predominant mineralocorticoid receptor activation, amino acid receptor-mediated neurotransmission is stable and maintains basal activity in the hippocampal circuit. Modulatory inputs, such as the inhibitory input via serotonergic fibers, are attenuated. The steady transfer of excitatory input is not associated with extensive Ca^{2+} influx. All of these effects will promote stability and viability of the hippocampal cells involved. Mineralocorticoid receptor activation is indeed necessary to maintain stability, since many studies have shown that cell turnover in the dentate gyrus is largely accelerated when mineralocorticoid receptors are unoccupied (Sloviter et al., 1989; Gould and Tanapat, 1999).

Following exposure to a stressor, glucocorticoid receptors will become occupied in addition to mineralocorticoid receptors. The electrophysiological studies have shown that, with a delay of 1–2 h, this enhances Ca^{2+} influx. Consequently, activation of Ca^{2+}-dependent K^+ channels will become more prominent so that transfer of excitatory information during brief periods of depolarization will be attenuated. Modulatory inputs such as the inhibitory 5-HT_{1A} receptor-mediated input are no longer restrained which adds to the attenuation of excitatory input. At very high corticosteroid levels, there may even be a direct suppression of excitatory, glutamatergic input. As a consequence of all these actions, temporary glucocorticoid receptor activation will suppress the transfer of excitatory input through the hippocampus.

These corticosteroid effects by themselves will already alter the network function of hippocampal circuits, which has implications for processes that depend on hippocampal excitability as well as for hippocampal output to other brain regions. The latter is of particular interest for the transsynaptic inhibitory projection of the hippocampus to parvocellular neurons in the paraventricular nucleus which produce a corticotropin-releasing hormone (Herman and Cullinan, 1997). It is inferred from the above data that steady hippocampal output maintained under basal activity of the hypothalamo-pituitary-adrenal axis (via mineralocorticoid receptors) will exert a tonic inhibitory control over the activity of corticotropin-releasing hormone producing cells. Disinhibition may occur with higher corticosteroid levels, but it is assumed that under those conditions hippocampal input to corticotropin-releasing hormone producing cells is entirely overriden by the direct negative feedback actions of corticosteroids onto corticotropin-releasing hormone producing cells in the hypothalamus (De Kloet et al., 1998).

One particular example of hippocampal network function has been studied in more detail, with respect to corticosteroid sensitivity, i.e. long-term potentiation and long-term depression. Repeated high frequency stimulation of perforant path or Schaffer collateral fibers is known to induce a long-lasting enhancement of synaptic responses (long-term potentiation) in the dentate gyrus and CA1 areas of the hippocampus, respectively (Bliss and Collingridge, 1993). By contrast, prolonged stimulation at lower frequency can suppress synaptic strength (long-term depression; Bear and Abraham, 1996). Normally, long-term potentiation can be readily induced in freely moving animals, while it is quite hard to evoke long-term depression. It was shown that induction of long-term potentiation is greatly hampered in animals where glucocorticoid receptors are extensively activated in addition to mineralocorticoid receptors, both in vitro and in vivo (Shors et al., 1989; Diamond et al., 1992, 1994; Pavlides et al., 1993; Xu et al., 1997, 1998a,b; Kim and Yoon, 1998). At the same time, induction of long-term depression is promoted. Whether the steroid effects on long-term potentiation and long-term depression induction are an indirect consequence of the cellular effects described above or develop independently is not known. Since long-term potentiation and long-term depression are thought to be associated with formation and removal, respectively, of memory traces, this infers that exposure to stressful conditions interferes with memory function. In this respect, it is important to realise that the stressful conditions which were shown to hamper long-term potentiation and promote long-term de-

pression induction were usually presented out of the context of a learning paradigm. This may explain why these data are seemingly in conflict with behavioral studies where glucocorticoid receptor activation in the context of a learning situation was shown to be essential for consolidation of learned information (De Kloet et al., 1999).

While short-term activation of glucocorticoid receptors will attenuate the hippocampal excitability, both at the cellular and at the network level, more prolonged glucocorticoid receptor activation may compromise hippocampal cell viability (McEwen, 1999), particularly when hippocampal cells are extensively depolarized such as occurs in association with ischemia or seizure activity. Under conditions of depolarization, the voltage-gated Ca^{2+} channels will be activated. Since the conductance through these channels is enhanced after glucocorticoid receptor activation, cells may become exposed to relatively high levels of Ca^{2+}, a condition known to present a risk factor for delayed cell death. In accordance, it was shown that exposure of rats to high corticosteroid levels in the early phase of epileptogenesis accelerates the onset of seizure activity and induces long-lasting enhancement of voltage-dependent Ca^{2+} influx, even after the corticosteroid levels have been normalized again (Karst et al., 1999). It is to be expected that restraining corticosterone levels so that mostly mineralocorticoid receptors but few glucocorticoid receptors are activated should exert protective actions. This is indeed supported by data obtained with an animal model for ischemia: restraining corticosterone levels prior to but even following ischemic insults reduces histological damage and loss of function in the CA1 area (Sapolsky and Pulsinelli, 1985; Krugers et al., 1999, 2000).

How network function is affected by long-term exposure to high levels of corticosteroids is not very well investigated. Morphological data indicate that CA3 pyramidal cells show signs of atrophy in their distal dendrites when exposed for three weeks to very high corticosterone doses (Woolley et al., 1990). However, this was found to have only marginal consequences for network function in the area to which CA3 cells project, i.e. the CA1 region (Karten et al., 1999a). It is possible that hippocampal cells slowly develop a resistance to the effects of glucocorticoid receptor activation when continuously exposed to high corticosteroid levels, as was indeed demonstrated with respect to the response of CA1 cells to serotonin (Karten et al., 1999b). Clearly, these conditions of chronic corticosteroid over-exposure, which occur in association with many disorders, need to be investigated more extensively in the future.

4. Concluding remarks

Electrophysiological research over the past decades has clearly shown that many compounds in addition to the ‘classical’ neurotransmitters alter the electrical activity of cells in the central nervous system. These compounds include neuropeptides which are synthesized in the brain. However, compounds that are synthesized outside of the brain but nevertheless can enter the brain compartment — such as corticosteroid hormones from the adrenal gland — do have strong effects on brain function also. In this review, this was illustrated by describing the effects of two substances, i.e. vasopressin and corticosterone.

The data presented show how neuropeptides and peripheral hormones each add specific aspects to signal transduction in the brain. First and foremost, they both act conditional, i.e. they modulate the actions of ‘classical’ neurotransmitters, rather than changing basal neuronal activity by themselves. This may seem to place these compounds in a subordinate position relative to ‘classical’ neurotransmitters, but given the pleiotropic effects of particular steroid hormones, the consequences for network function may nevertheless be substantial. For instance, both vasopressin and corticosterone play an essential role in the phenomenon of long-term potentiation and as such could largely contribute to the neuronal substrate underlying memory formation. Also, the role of these modulatory compounds may become particularly evident under pathological conditions, adding to the risk for instability and delayed cell death, as was shown for corticosteroid hormones with respect to ischemic damage.

A second feature in which neuropeptides and steroid hormones add new aspects to brain signal transduction is the time-frame in which the modulation of electrical properties takes place. While most ‘classical’ neurotransmitters act within seconds, neuropeptide actions are slow in onset and can last for many minutes, as was shown e.g. for vasopressin. Corticosteroid hormones affect neuronal activity even over a range of hours. Activation of one particular biological system, for instance, the system involved in a stress response, results in the release of compounds that can alter brain function over a very wide range of time. Catecholamines will almost instantaneously alter neuronal activity, inducing an immediate state of arousal. At a somewhat slower timescale neuropeptides such as adrenocorticotropin hormone, corticotropin-releasing hormone and vasopressin will modulate brain function, which (among other things) results in altered processing of learned information. Finally, after several hours corticosteroid hormones will affect neuronal activity, promoting behavioral adaptation and termination of the stress response.

Vasopressin and corticosterone both act at the interphase of the brain and body. Vasopressin is synthesized in the brain and from there transported to other brain regions as well as the circulation. Corticosterone is synthesized in a peripheral gland, transported via the circulation to peripheral organs but also reaching the brain compartment. This principle, in which one substance plays a role in both the neuronal and endocrine system, was revolutionary at the time that it was proposed by David de Wied and others in the 1960s. Meanwhile, we have gained much more

insight into the processes that are affected by these compounds and into their cellular/molecular mechanism of action. By now, it is textbook knowledge that communication between body and brain is essential for many biological functions and we can hardly imagine that once this view was challenged: a true hallmark for breakthroughs in science.

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