Hormones and Behavior 58 (2010) 555–562

Contents lists available at ScienceDirect

Hormones and Behavior

journal homepage: www.elsevier.com/locate/yhbeh

Review

The neuroendocrine action potential
Winner of the 2008 Frank Beach Award in Behavioral Neuroendocrinology

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ARTICLE INFO

Article history:
Received 31 December 2009
Revised 15 June 2010
Accepted 17 June 2010
Available online 23 June 2010

Keywords:
Social behavior
Sexual selection
Seasonality
Reproduction
Hormones
Refractory period
Immediate early gene
Ejaculation
Photostimulated
Genomics

ABSTRACT

Animals are remarkably well equipped to respond to changes in their environment across different time scales and levels of biological organization. Here, I introduce a novel perspective that incorporates the three main processes the nervous system uses to integrate and process information: electrophysiological, genomic, and neuroendocrine action potentials. After discussing several examples of neuroendocrine action potentials, I lay out the commonalities of these temporally organized responses and how they might be interrelated with electrophysiological activity and genomic responses. This framework provides a novel outlook on longstanding questions in behavioral neuroendocrinology and suggests exciting new avenues for further research that will integrate across disciplines and levels of biological organization.

Contents

Introduction

Animals respond to changes in the social and physical environment with changes in the neural substrates underlying particular behavioral and physiological processes (Hofmann, 2003; Robinson et al., 2008). The remarkable plasticity associated with environmental and behavioral changes occurs at multiple time scales and at all levels of biological organization. Understanding the neural actions that govern these phenomena is a major goal in modern biology. Using several examples from the literature as well as my own work, I conceptualize the three main events the nervous system uses to integrate and process information: activity of excitable neuronal membranes, changes in gene expression, and neuroendocrine responses. This approach uncovers gaps in our understanding of neural and behavioral plasticity and suggests numerous exciting avenues for further research towards a more complete understanding

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doi:10.1016/j.yhbeh.2010.06.012

of the relationship between brain, behavior and environment. Although beyond the scope of this current discussion, it should be noted that the immune system can also play a pivotal role in regulating brain function, e.g., by cytokines (Zalcman & Siegel, 2006; Mélik-Parsadaniantz & Rostène, 2008), and affect the events being discussed here.

Ontology of neural action potentials

After information has been conveyed by the sensory systems, three principal mechanisms allow the nervous system to respond to and integrate this information from the environment: electrophysiological activity, gene expression changes, and neuroendocrine responses. These processes can all be subsumed under the term action potential because they follow a common pattern (albeit at vastly different time scales) comprised of a resting state, a rapid response, and a refractory period (Fig. 1). Additionally, these modes of integration are not mutually exclusive, as one likely depends on another.

On an immediate proximate level, different behavioral outcomes result from a change in ionic currents across the neuronal membrane, which constitutes a fundamental property of nervous systems (Barnett & Larkman, June 2007). Neurons commonly encode such changes in the form of electrophysiological action potentials (or "spikes"), which allow them to integrate inputs from a multitude of sources in real-time (with millisecond resolution) and to communicate with each other in a digital code. The electrophysiological action potential (eAP), whose underlying electrical and chemical processes have been uncovered in classic experiments by Hodgkin, Huxley, and many others (Hodgkin & Huxley 1952; Barnett & Larkman, June 2007). The eAP, which is generally generated near the center of the cell (the axon hillock), represents the basic currency of the nervous system.

Populations of neurons can integrate external inputs not only via short-term changes in spike frequency. Synaptic inputs, via the activation of 2nd messenger cascades, can also lead to rapid (within minutes to hours) changes in gene expression, which in turn can result in the structural remodeling of synapses and other cellular structures (for a detailed and current review, see Loebrich & Nedivi, 2009). The genes that show a change in expression with the shortest latency (within minutes) are termed immediate early genes (IEGs, e.g., *c-fos*, *egr-1* and *c-jun*; Loebrich & Nedivi, 2009). IEGs encode transcription factors that are thought to coordinate the cellular responses to a variety of environmental stimuli, which eventually result in long-term plastic changes of neuronal function. However, the expression of many other genes that are more or less constitutively involved in the synaptic machinery used to fine-tune ongoing neuronal function can be altered by neuronal activity as well (Loebrich & Nedivi, 2009). In the context of functional neuroanatomy, mapping the induction of IEG expression after a neurochemical or behavioral stimulus has become a useful tool for inferring the neural circuitry that governs behavioral responses. However, IEGs are only the leading edge of a much more fundamental remodeling of neuronal function and thus deserve to be placed within the larger context of information processing and integration in the brain. In a thoughtful paper, Clayton (2000) introduced the term genomic action potential (gAP) to describe such responses, based on the realization that highly orchestrated cascades of gene activation (or repression) are involved, analogous to the voltage-regulated opening and closing of ion channels during an eAP. Similar to the eAP, gAPs originate at the center of a neuron (the transcriptional apparatus in the nucleus as well as the translational machinery in the surrounding cytoplasm) and then spread to dendrites and/or axon terminals in the form of proteins and mRNAs. It is not entirely clear to which extent the gAP also exhibits a refractory period, although *fos* can repress its own expression at least in some situations (for a detailed review, see Morgan & Curran, 1991). This negative auto-feedback appears to be mediated by Fos protein acting on its own promoter, in conjunction with cAMP responsive element-binding (CREB) proteins (Loebrich & Nedivi, 2009), and may in fact be required for the decline in immediate-early gene expression that is observed within a few hours of induction (Morgan & Curran, 1991). Because most of this work was done in cell culture, we know little about these processes in the nervous system in response to a behavioral stimulus. However, Mello et al. (1995) found that a novel stimulus administered 2.5 h after the initial one elicited a new gAP, although earlier time points have not yet been tested systematically.

Finally, a third fundamental mechanism underlying the integration of environmental and internal cues in the brain involves the neuroendocrine system. Events in the environment or inside the animal can activate a plethora of pathways involving biogenic amines, neuropeptides, and steroid hormones that alter the state of neural circuits and organ systems throughout the organism (for reviews on some representative systems see: Hofmann, 2003; Young & Wang, 2004; Crews, 2005; Wilczynski et al., 2005; Goodson & Kabelik, 2009; Ball & Balthazart, 2010). Such responses, which can be remarkably fast, generally follow a pattern reminiscent of the eAP, albeit with a much slower time course (minutes to hours or days). At least in some cases there is also a period immediately following the neuroendocrine activation when further stimulation has no effect (refractory period). I introduce here the term neuroendocrine action potential (nAP) to describe such events.

In the following, I will discuss some examples that could be used to highlight the utility of the nAP concept for understanding how

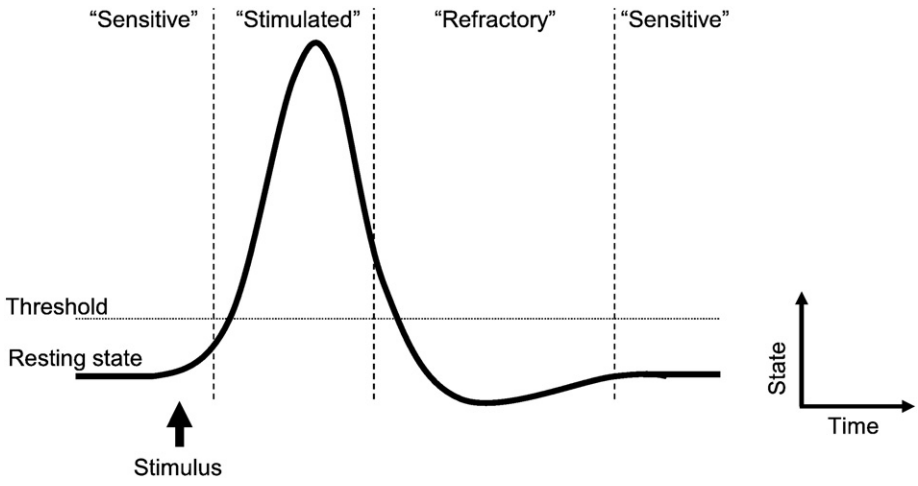

Fig. 1. Schematic description of the neural action potential.

animals can adjust their physiology and behavior to changes in the environment in an integrated and coordinated manner.

Seasonal plasticity in the reproductive system

In many vertebrates, reproductive physiology is regulated by day length throughout the seasons (teleosts: Guraya et al, 1976; Shimizu, 2003; amphibians: Polzonetti-Magni et al., 1984; reptiles: Crews & Licht, 1974; birds: Dawson et al., 2001; mammals: Robinson & Karsch, 1984; Prendergast, 2005). Even humans have been suggested to be seasonally photoperiodic, although the evidence is inconclusive (Bronson, 2004). Although the specific events can vary across taxa, the typical pattern is as follows: After a period of short days (i.e., winter), the hypothalamic-pituitary-gonadal (HPG) axis of many seasonally breeding vertebrates is photosensitive to increases in day length (as experienced during spring). Release of gonadotropin-releasing hormone (GnRH) from the preoptic area (POA, a crucial neuroendocrine control center) is stimulated by increases in day length (photostimulation), which leads to a fairly rapid activation of reproductive physiology and behavior. In songbirds, these annual changes are accompanied by corresponding changes in the song system and singing activity (Dawson et al, 2001). Later in the season, the reproductive system becomes photorefractory. In many songbirds, this means that gonadal growth can no longer be stimulated by continued exposure to long days (as in many songbirds). GnRH and the rest of the HPG axis become down-regulated in photorefractory animals and the gonads regress as a consequence. After experiencing a period of short days (i.e., winter), the animals become again photosensitive. Importantly, hypothalamic GnRH is already up-regulated–in an anticipatory manner–at the end of winter in photosensitive birds, although its release is inhibited until stimulated by increasing day length (Foster et al., 1987).

While the importance of increasing day length in triggering the reproductive nAP is well understood (although several other factors can modulate the basic pattern, see below), the mechanisms underlying the induction of photorefractoriness seem to be more complex (for review see Dawson & Sharp, 2007). In many temperate zone bird species, for example, a decline in photoperiod is not required, as (absolute) photorefractoriness in these species commences with continued exposure to long days. At the physiological level, the onset of photorefractoriness, and the subsequent down-regulation of reproductive physiology, appears to be modulated by prolactin (PRL; mammals: Lincoln, 1989; birds: Dawson et al., 2001). In birds at least, prolactin release is stimulated by vasoactive intestinal peptide (VIP; Christensen & Vleck, 2008). This increase in PRL at the end of the mating period is particularly intriguing, since high levels of this hormone may also drive parental behavior (Angelier & Chastel, 2009). Due to its role in many other physiological processes, including parental care and molt (Sockman et al., 2006; Angelier & Chastel, 2009), the increase in PRL (and associated decrease in testes size and circulating androgen levels) at the end of the mating period could facilitate the transition to offspring rearing and, later, preparation for fall and winter. Finally, thyroid hormones have also been strongly implicated in the control of photoperiodic seasonality, as they appear to inhibit GnRH release (Thrun et al., 1997; Prendergast, 2005; Yoshimura, 2006).

What is the upstream control mechanism that governs all these factors? The monoamine melatonin exhibits a nocturnal release pattern that constitutes a direct read-out of the circadian system. The amount of melatonin that is released depends on the length of the dark period (Bittman & Karsch, 1984; Prendergast, 2005), which makes this neurochemical ideally suited to act as an indicator of seasonal time. For mammals at least, there is indeed evidence that melatonin controls either directly or indirectly the release of PRL, thyroid hormones, and GnRH in a seasonal manner, although clear evidence is still lacking in birds (Tsutsui et al. 2009).

One of the obvious advantages of the nAP is that it is "anticipatory", i.e., it prepares the organism for a future opportunity: A neuroendocrine "potential" (or resting tone) is built up in the form of GnRH whose release is inhibited until the appropriate stimulus (such as an increase in day length) is applied, which then results in the rapid activation of the reproductive and other physiological systems. The processing of such a stimulus likely involves both eAPs and gAPs in the relevant brain regions (e.g., the circannual pacemaker and downstream hypothalamic regions), which in turn result in the activation of neuroendocrine pathways (see discussion below). As a consequence, the time course of nAPs is slow compared with the other APs (Table 1). This does not mean, however, that a neuroendocrine response can only be measured after a long-term exposure (for an impressive example, see Nicholls et al., 1983). When the stimulated state ends and the refractory period begins is not easy to discern. In some songbird species, a reduction in day length can result in *relative* refractoriness of the reproductive system (i.e., the system can still be activated again by even longer days or other cues, such as those of a social, climatic or nutritional nature; Dawson & Sharp, 2007). Other species appear to enter into an *absolute* refractoriness fairly soon after breeding has concluded, and in these cases the reproductive systems cannot be activated without the animal having gone through a period of short days (Dawson, 2007). The processes that govern gonadal regression at the end of the breeding system show some striking similarities with the events that take place after copulation, which have been best studied in rodents and, to some extent, in humans.

Refractory period after sexual behavior in male mammals

In the presence of an appropriate sexual stimulus (such as a receptive female), males will attempt to engage in sexual behavior. Associated with this change is a surge in circulating testosterone (Bronson & Desjardins, 1982; Batty, 1978) and–driven by eAPs in the mesolimbic reward system–an increase in dopamine released into the POA (Hull et al., 1997). Immediately after ejaculation, males enter a refractory period (also termed post-ejaculatory interval, PEI, in

Table 1

Type of AP	Electrochemical	Genomic	Neuroendocrine
Time scale	Fast (ms)	Medium (min–h)	Slow (min–month)
Resting ("sensitive") state	Maintenance of ion gradients via leak channels and Na^+/K^+-pumps	Expression of many genes involved in basic neuronal function	Neural and/or pituitary tissues contain large amounts of neuropeptides/ hormones whose release is inhibited
Stimulus	Synaptic potential	Neural activity	Photic or non-photic (e.g., social) cues
Activation	Opening of voltage-gated ion channels	IEG induction	Neurochemicals (e.g., melatonin), hormones
State change	Depolarization	IEG transcription/translation	Release of stimulatory neuropeptides/other hormones
Inactivation	Closing of voltage-gated ion channels	Mechanism unknown	Photic cues (e.g., continued long days); behavioral cues (e.g., ejaculation)
Refractoriness	Depolarization impossible/difficult	Negative auto-feedback?	Prolactin (other hormones?) inhibit further release of stimulatory neuropeptides
Restoring resting state	Ion channels transitioning back into resting state	Unknown	Photic cues (short days); other cues?

rodents), which can last for minutes to hours depending on the species and circumstances (see below). While the adaptive value (if any) of this phenomenon is not well understood, it can serve as an accessible experimental system to uncover the factors that cause a neuroendocrine system to become inhibited after stimulation. It is thus surprising how little is known about this process. In the human male, sexual behavior (specifically, ejaculation) triggers the release of PRL, which in turn prevents the penis from becoming erect again for some time (Krüger et al., 2002). Interestingly, administration of a PRL receptor antagonist can abolish this refractory time in human males (Krüger et al., 2002).

In both men and women, plasma PRL concentrations increase significantly after orgasm (for review see Krüger et al., 2002), which appears to play a role in the control of acute sexual arousal following orgasm. However, the post-orgasmic increase of PRL is likely only one of a series of complex signals, including neuropeptides, monoamines and neurotransmitters that constitute a negative feedback onto the CNS (Argiolas, 1999; Pfaus, 1999; Meston & Frohlich, 2000). A decrease in dopamine signaling, in particular, has been implicated, which may be mediated by PRL (Mas et al., 1995). In rats, lesions in parts of the mesolimbic dopaminergic system (such as the ventral tegmental area or the nucleus accumbens) increase the refractory post-ejaculatory interval (reviewed by Hull et al., 2006). However, it is not yet clear whether PEI in rodents is directly mediated by PRL as it is in humans (Kalra et al., 1983; Doherty et al., 1985).

Can we formulate hypotheses regarding the adaptive value of the sexual nAP within a comparative context? There is remarkable individual variation in the duration of the post-mating refractory time in humans (Krüger et al., 2002), as there is across species in rodents (reviewed by Hull & Dominguez, 2007). In rats, PEI may last for 6 to 10 min before resuming mating, and in mice this period lasts longer and is highly variable (17–60 min), depending on the strain examined. Exposure to a novel female can significantly decrease this time interval (Mosig & Dewsbury, 1976). In general, in male mice and rats refractory time appears to be required for developing a preference for a female (for review, see Pfaus, 1999). In contrast, male Syrian hamsters resume mating within 35 s to 90 s after ejaculation (Hull & Dominguez, 2007). To which extent this variation in PEI across species is associated with correlated differences in PRL release, and whether it has any adaptive value is unclear. However, it is known that sperm competition, or more generally, sexual selection, can drive variation in copulation frequency (for a review in mammals see Dixson & Anderson, 2004). Could PEI thus be related to the mating system of a species? In the polygamous hamster, both males and females are highly territorial and come together only for short mating bouts early during the breeding season (Demas et al., 2005). Because a male may not encounter another receptive female again during this time period, it may well be advantageous to accomplish as many ejaculations as possible during the short time a female is available, thus increasing the chances for successful fertilization. In contrast, rats live in fairly complex social communities, where females may synchronize their estrous cycles and mating often takes place in groups (for a detailed review, see Chapter 6 in Nelson, 2005). It may thus be advantageous for a male to display a PEI just long enough to monopolize the female for the minimum period required to increase his chances of successful fertilization, yet short enough to take advantage of other available females. Male mice may have an incentive to remain with a female longer, as dominant individuals tend to monopolize access.

A natural test of this hypothesis can be gleaned from studies in the genetically monogamous pine vole, *Microtus pinetorum*, a close relative of the better known prairie vole, *M. ochrogaster*, which is socially monogamous (i.e., exhibits extra-pair copulations; Fink et al., 2006). In pine voles, PEI after the first ejaculation is on average 16 min, and its duration increases considerably in successive mating events with the same female (Dewsbury, 1976). These long refractory times may well facilitate pair-bond formation in this and other monogamous species. A comparative analysis of PEI across the genus *Microtus* would be worthwhile, as some species are (either genetically or socially) monogamous and others are polygamous (Fink et al., 2006). According to the reasoning above one would predict that monogamous species show long PEIs, whereas polygamous species exhibit shorter refractory period (maybe dependent on the availability of receptive females).

In birds, the role sexual selection (particularly sperm competition) plays in driving variation in timing and frequency of copulatory behavior has been discussed in great depth (e.g., Birkhead et al., 1987). It is thus surprising how little research has been directed towards post-ejaculatory inhibition of sexual behavior in birds. In emus, *Dromaius novaehollandiae*, at least, sexual motivation is decreased for three or more hours after copulation (Malecki et al., 1997). Whether there is an associated increase in circulating PRL is not known, even though on a longer temporal scale PRL is strongly associated with photorefractoriness in birds and seasonal mammals (see above).

A putative nAP during social defeat in cichlid fish

Do nAPs also occur in other social, though not directly reproductive contexts? In the following, I put forward a scenario within the framework of social defeat, which is more speculative than the first two, as it cannot rely on decades of work for solid evidence for nAP-like processes. However, this example hopefully highlights the possibility that nAPs might be widespread and deserving of more detailed attention.

The diversity of their life-history strategies makes teleost fishes ideal for the study of the mechanisms underlying behavioral and neuroendocrine plasticity. The Lake Tanganyikan cichlid fish, *Astatotilapia* (formerly *Haplochromis*) *burtoni*, has become a well-known model system for the study of socially regulated physiology and behavior (Fernald, 2002; Hofmann, 2003). Males of this species are either reproductively mature and socially dominant (D), or reproductively suppressed and subordinate (S). Because their native habitat is close to the equator, these fish do not show any seasonal pattern in their reproductive and social behavior. However, in response to cues from the social environment, D and S males often change plastically into the other phenotype, and they can do so repeatedly throughout life. Because many neuroendocrine (and other) systems are regulated as a consequence of this social change (Fox et al., 1997; Hofmann et al., 1999; Hofmann & Fernald, 2000; White et al., 2002; Greenwood et al., 2008; Renn et al., 2004, 2008), this system provides a unique opportunity to investigate neuroendocrine signaling from an organismal perspective.

Of importance for the current treatment of nAPs is the fact that social dominance status in males is accompanied by reduced somatic growth rate as well as increased somatostatin neuron size and increased somatostatin mRNA levels in the preoptic area (Hofmann et al., 1999; Hofmann & Fernald, 2000; Trainor & Hofmann, 2006). Although somatostatin is commonly studied within the context of growth, this finding nevertheless suggested that somatostatin might also regulate aggressive behavior in the context of social dominance. Despite the up-regulation of the POA somatostatin system in D males, exogenous somatostatin antagonists increase aggressive behavior in a dose-dependent manner and administration of the potent somatostatin agonist octreotide decreases aggression in these fish (Trainor & Hofmann, 2006, 2007). To explain this surprising result, the authors suggested that preoptic somatostatin release is inhibited in dominant males. This hypothesis has not yet been tested experimentally, although the finding that hypothalamic expression of the somatostatin receptor 3 subtype (sstR3) and the somatostatin prepropeptide are positively correlated is suggestive, possibly implying an autocrine feedback inhibition of release (Trainor & Hofmann, 2006). Also, it is unlikely that the behavioral effects of somatostatin are mediated

by androgens, since the somatostatin agonist octreotide does not reduce plasma androgen levels (Trainor & Hofmann, 2006), which is consistent with the finding that *A. burtoni* males maintain their reproductive physiology (as determined by preoptic GnRH expression) for two or more weeks after social descent (White et al., 2002; Hofmann, 2006).

Together, these findings lead to a model, in which somatostatin may function to contain energetically costly processes such as somatic growth and aggressive behavior in socially defeated males. Specifically, somatostatin is thought to act as a shunt, which upon release shuts down aggressive behavior and somatic growth in defeated fish, obviating the need for the HPG axis to become down-regulated right away. Such a system may reflect a certain degree of "optimism" on the part of the defeated individual that it will soon again be able to return to social dominance, as defeated males maintain their reproductive physiology for two or more weeks after defeat (White et al., 2002). Studies in both field and laboratory that examined the amount of time animals spend in either social state have found that changes in social status likely occurs every three to four weeks on average (Hofmann et al., 1999).

Social defeat triggers gAPs in the brain (reviewed by Martinez et al., 2002) along with many other neurochemical and epigenetic changes (Krishnan & Nestler, 2008). While it is not known at this point whether similar processes take place in *A. burtoni* immediately after defeat, it does seem likely. Burmeister et al. (2005) showed IEG induction in the POA of males presented with an opportunity to ascend to social dominance, suggesting (not surprisingly) that these animals are clearly able to generate a gAP.

Within the framework of the nAP, assuming the somatostatin pathway in the cichlid is regulated in a manner analogous to the HPG axis in seasonally breeding vertebrates, it will be interesting to determine whether–after the likely stimulation of somatostatin release by social defeat–this system also enters into a refractory period. Is there a time window during which repeated social subordination (which is exactly what losers experience) will not result in any additional surges of somatostatin, and where ultimately production of this neuropeptide in the POA is indeed decreased? Somatostatin-immunoreactive neurons in the POA are still relatively large one week after social defeat, yet contract significantly after four weeks of social subordination (Hofmann & Fernald, 2000). It is thus plausible that a refractory period (if any) in this system will (i) commence after about one week in subordinate status (even though release of the neuropeptide from the POA might be inhibited much sooner after losing social dominance); (ii) prevent another stimulation of this system for some time even if the animal manages to regain social dominance quickly and lose it again shortly thereafter. If correct, one would predict that males provided with an opportunity to ascend in social status within several days after a defeat only to be (experimentally) defeated again a few days later will not show an increase in somatostatin release, which in turn might result in these males displaying aggressive behaviors even though it is socially disadvantageous. Finally, given its likely roles in regulating refractory periods in the context of reproduction in birds and mammals, it will be interesting to find out whether PRL mediates any of the processes associated with social defeat in *A. burtoni* (or any other species).

Differences and commonalities across the three kinds of action potentials

A critical reader may ask whether the proposed analogy of the three types of APs discussed here is really more than superficial. The three different kinds of action potential evidently differ greatly in the time scales in which they occur. eAPs are commonly very fast (ms), although some neurons can produce slower spikes that may last for several seconds. The induction of IEGs in the gAP can occur within minutes, and mRNA levels may return to resting levels within one to several hours (Loebrich & Nedivi, 2009), yet protein levels of IEGs usually do not peak until 1 to 2 h after a stimulus and can take several more hours to decay again to pre-stimulus levels (Clayton, 2000; Loebrich & Nedivi, 2009).

Despite this obvious difference in temporal dynamics, there are several basic features that all three APs have in common (Fig. 1; see also Table 1 for a summary). In all three kinds of APs, there is a resting tone (e.g., resting membrane potential maintained by leak ion channels and Na^+/K^+-ATPase; baseline IEG expression and expression of many genes involved in basic neuronal function; anticipatory accumulation in the POA of GnRH in photosensitive songbirds or somatostatin in socially dominant cichlids) that can be interpreted as preparatory in that it allows the system to quickly mount a response to an appropriate stimulus. Further, in all three cases APs are only generated once the stimulus reaches a threshold (e.g., change in voltage that activates ion channels and the resulting ion flux; minimal duration of neuronal stimulation that triggers IEG induction; increase in day length and associated changes in melatonin release). Finally, certainly eAPs and nAPs, but likely also gAPs exhibit a refractory period (e.g., via ion channel inactivation; negative autoregulation of IEG promoters; increase in PRL after ejaculation).

In the case of the eAP, once the voltage threshold is reached, the resulting depolarization will reach more or less the same amplitude independent of the amount of current, which produced it; i.e., an increase in current beyond the threshold will not create a larger eAP. The gAP appears to follow a similar all-or-none principle, as even short stimulus sessions can result in the full induction of IEGs (Clayton, 2000). For example, in the rat hippocampus a 30-s train of endogenous eAP activity is sufficient to induce *c-fos* expression (Shin et al., 1990; Worley et al., 1993). Within a behavioral context, Kruse et al. (2000) showed that a bout of birdsong as short as 20 s induces a full IEG response in the zebra finch brain. Does the nAP exhibit a similar property? There is some evidence that it can. In the Japanese quail, *Coturnix japonica*, a single long photoperiod is sufficient to trigger the release of gonadotropins (Nicholls et al., 1983; Perera et al., 1992).

Real-time changes in neural circuits of the basic properties of the eAP is usually achieved by modulation, e.g., by activation of a variety of ion channel types or a whole suite of neuromodulators, such as biogenic amines or neuropeptides (Katz, 1999). Of particular interest from a neuroendocrine perspective are also the fast-acting, non-genomic effects steroid hormones can have on neurophysiological events (see below). A variety of factors play a modulatory role in the gAP as well, such as behavioral context and neurotransmitters (for review see Clayton, 2000). It is also clear that both steroid hormones and neuropeptides can alter IEG responses to sensory/social stimulation in birds and mammals (e.g., Halem et al., 2001; Goodson & Evans, 2004). Similarly, experimental disruption of the modulatory input arising from the mesolimbic dopaminergic system alters gAP responses to auditory stimulation in a song nucleus of the zebra finch (Hara et al., 2007). The basic nAP in the seasonally regulated reproductive system of birds can also be modulated by a variety of stimuli as well as prior experience. Social, climatic (temperature, precipitation) and food/nutritional cues all can alter the timing and/or shape of the nAP (for review see Dawson, 2008). In starlings, for example, the absence of social cues and/or a nest box (i.e., a lack of reproductive opportunities) can advance the onset of photorefractoriness (Dawson & Goldsmith, 1982). Similarly, Dawson (2005) showed that an increase in ambient temperature advances the onset of photorefractoriness, whereas low temperature delays it, an effect also brought about by low food (Dawson, 1986). Prior experience can also have profound effects on the reproductive nAP. Sockman et al. (2004) showed in female starlings that prior breeding experience can "prime" the HPG axis to respond faster and more vigorously to the relevant photic cue. Experienced photosensitive females indeed exhibit a higher concentration of circulating

gonadotropins and more GnRH fibers in relation to the number of GnRH cells, which indicates an increased release of the hormone.

eAPs originate at the axon hillock (where the axon emerges from the neuronal soma) and are rapidly propagated in a centrifugal and unidirectional fashion along the axon. gAPs, by definition, originate from the nucleus as transcriptional changes of IEGs. Various gene products may then be transported–much slower than eAPs, yet still centrifugally–to the dendrites and/or axon terminals for the purpose of structural remodeling of synapses (Loebrich & Nedivi, 2009). However, it is conceivable that any gAP effects in the neuronal periphery may well feed back in a bidirectional manner onto the nucleus and influence ongoing transcriptional programs there. nAPs may not require any "central" action (i.e., originating from the cell body) during the response to an appropriate stimulus, as neurohormones can be released from synaptic and paracrine vesicle stores on demand. Such a response would, however, require nAPs to occur first, as well as gAPs in order to allow for a long-term remodeling of the neural circuitry that is found, e.g., in the seasonal regulation of the GnRH system across many vertebrates. In other words, there appears to be a strong functional relationship between the different kinds of APs.

Functional relationships between the different kinds of action potentials

IEG induction is often thought of as a consequence of neuronal activity (Loebrich & Nedivi, 2009). Similarly, neuroendocrine activation appears preceded by IEG induction. In the context of sexual behavior, this three-layered response is maybe best understood in rats, where mating induces IEG in various fore- and midbrain regions of males and females, including the POA (Robertson et al, 1991; Coolen et al, 1996). This gAP is likely mediated by dopaminergic activation coming from mid-brain VTA neurons (Baum et al., 1992; Lumley & Hull, 1999). As for the refractory period after ejaculation, neural activity in the medial amygdala appears to induce the PEI (Minerbo et al., 1994), possibly modulated by AVP (Smock et al., 1992).

It should be emphasized, however, that there are many feedback mechanisms in place that integrate neurophysiological events with the changes in gene transcription and/or hormone action that occur as a consequence of gAPs and nAPs. For example, recent research on the non-genomic effects of estradiol has shown how this steroid can change neuronal activity within seconds and alter membrane excitability as well as gene expression through the activation of second messenger systems. Specifically, in rodents, fluctuations in estradiol at puberty and over the ovarian cycle change signaling onto GnRH neurons by the inhibitory neurotransmitter GABA and a suite of excitatory and inhibitory neuromodulators (Smith & Woolley, 2004; Moenter et al. 2009; Roepke et al., 2009). These exciting discoveries no doubt will spur more research into how steroid hormones in particular integrate the three kinds of action potential.

Neuronal activity is clearly required for triggering subsequent gAPs and nAPs. Across vertebrates, the excitatory neurotransmitter glutamate controls the pulsatile release of hypothalamic GnRH through the activation of NMDA-subtype glutamate receptors, and treatment with exogenous NMDA causes increased secretion of gonadotropins (Brann, 1995). In the context of reproductive seasonality, Dawson (2005) found that starlings treated with NMDA exhibited the greatest gonadotropins increase when photosensitive compared with a slight increase when photostimulated; fully photorefractory birds showed no response. Associated with the activation of the GnRH system by NMDA is the induction of the IEG c-fos in the POA (though apparently not in GnRH neurons) and infundibular region of basolateral hypothalamus (Deviche et al., 2008), which parallels the gAP generated by photostimulation in quail (Meddle & Follett, 1997) and white-throated sparrow, *Zonotrichia albicollis* (where IEG induction was also observed in GnRH neurons; Saab et al., 2010).

The ring dove, *Streptopelia risoria*, provides an ideal model system to study how the different kinds of APs are functionally integrated, and the AP-based view introduced here suggests numerous new experiments. As is the case in many birds, vocalizations play a pivotal role in the reproductive function of this species. Classical studies by Lehrman and colleagues (Lehrman, 1965) established the social control of reproduction in female ring doves. In fact, it is the female's own vocalization (the nest coo produced during courtship) that is required for ovarian maturation (Cheng, 1992). In an elegant study, Cheng et al. (1998) established a direct link between the neuronal processing of vocal input and the subsequent release of gonadotropins. Specifically, they recorded electrophysiological activity from neurons in the preoptic and anterior hypothalamus that selectively responded to species-specific coo vocalizations while simultaneously measuring gonadotropin levels in blood from the pituitary veins. Plasma gonadotropin levels were significantly elevated in birds hearing species-typical courtship coos compared with birds exposed to white noise or no vocal stimulation, suggesting that eAP activity in female-coo-specific feature detecting neurons triggers the nAP that results in the release of GnRH. Terpstra et al. (2005) showed that the nest coo also induces IEG expression in various forebrain nuclei. However, these authors did not examine the preoptic area. Taken together, this system beautifully illustrates the strengths of an integrative approach towards understanding the relationship between behavior and brain, as it offers exciting avenues for future research aimed at elucidating the functional relationships between eAPs, gAPs and nAPs regulated by social context in the service of reproduction.

Conclusion

In this essay, I have introduced a novel perspective that integrates the three main events the nervous system uses to process information in response to changes in the environment: electrophysiological activity, gene expression, and neuroendocrine responses. All three mechanisms are used in neural contexts that are both experience-dependent and experience-expectant (Greenough et al., 1987; Clayton, 2000) in the way they implement and anticipate plastic change in brain, behavior and physiology. However, remarkably little is known about how these processes have co-evolved and how individual variation emerges from their characteristics. The framework proposed here provides a novel outlook on these and other longstanding questions, suggesting exciting new avenues for further research in behavioral neuroendocrinology that will integrate across disciplines and levels of biological organization.

Acknowledgments

I thank David Clayton, David Crews, Juan Dominguez, Andrea Gore, Kim Hoke, and members of my laboratory for helpful discussions, and Peter Dijkstra, Annette Dörnhofer and Lauren Munchrath for detailed comments on earlier versions of the manuscript. I am particularly indebted to David Crews, Russell Fernald, Franz Huber, Edward Kravitz, Andrew Murray, Naomi Pierce, Gene Robinson and Michael Ryan for their guidance and support over the years. HAH is supported by NSF grants IOS 0843712 and IOS 0751311, the Alfred P. Sloan Foundation, a Dwight W. and Blanche Faye Reeder Centennial Fellowship in Systematic and Evolutionary Biology, and an Institute for Cellular and Molecular Biology Fellowship.

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