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Dopaminergic System in Birdsong Learning and Maintenance

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Abstract

Dopamine function in birdsong has been studied extensively in recent years. Several song and auditory nuclei are innervated by midbrain dopaminergic fibers and contain neurons with various dopamine receptors. During sexually motivated singing, activity of midbrain dopaminergic neurons in the ventral tegmental area and dopamine release in the striatal Area X, involved in song learning and maintenance, are higher. In this review we provide an overview of the dopaminergic system and neurotransmission in songbirds and the outline of possible involvement of dopamine in control of song learning, production, and maintenance. Based on both behavioral and computational biology data, we describe several models of song learning and the proposed role of dopamine in them. Special attention is given to possible role of dopamine in incentive salience (wanting) and reward prediction error signaling during song learning and maintenance, as well as the role of dopamine-mediated synaptic plasticity in reward processing. Finally, the role of dopamine in determination of personality traits in relation to birdsong is discussed.

Keywords

vocal communication; reward; reinforcement; incentive salience; reward prediction error; dopamine modulated plasticity; personality

According to traditional views, nigrostriatal dopamine (DA) neurons located in the substantia nigra pars compacta (SNc) that project to the dorsal striatum play a role in the expression of motor acts, while mesolimbic DA neurons that originate in the directly adjacent ventral tegmental area (VTA) and project mainly to the nucleus accumbens and other ventral striatal regions play a role in reinforcement or incentive motivational processes. However, DA neurons within the SNc do not exclusively respond to phasic bodily movements, nor do DA neurons within the VTA respond exclusively to reward stimuli (Horvitz, 2000). These and other findings have led to a substantial restructuring of the traditional DA hypothesis, such that the classic emphasis on hedonia and primary reward is giving basis to diverse lines of research that focus on various aspects of instrumental learning, reward prediction, incentive motivation, and behavioral activation (Salamone et al., 2007).

The role of the dopaminergic system seems to be conserved across amniote vertebrates (for review see Smeets et al., 2000). In particular, a large body of evidence indicates that the principal function of DA is very similar in mammals and birds, and in both, the dopaminergic system is critically involved in numerous cognitive and behavioral functions, including appetitive and aversive behaviors, motor control, learning and memory, as well as working

memory and attention (Durstewitz et al., 1999). In the past two decades there is an increasing amount of data suggesting the role of DA in song learning and production in songbirds. In this review we first provide an anatomical basis of dopaminergic neurotransmission, and then describe function of DA in learning models including song learning as well as in song maintenance.

1 Anatomical relationship of singing-related nuclei and the dopaminergic system

In vocal learning birds, song learning and production is controlled by a system of specialized brain song nuclei described in the introduction of this issue. Briefly, the nuclei are organized in two pathways, the posterior motor pathway and the anterior one, called also the pallial-basal ganglia-thalamic-pallial loop or the anterior forebrain pathway, necessary for song learning and maintenance (Brainard and Doupe, 2000; Nottebohm et al., 1976). The posterior pathway sequentially connects HVC (used as a proper name) to robust nucleus of arcopallium (RA) to dorsal medial nucleus of the midbrain (DM), and both RA and DM project to motor neurons of the tracheosyringeal part of XII nucleus (nXIIts) and to nucleus retroambiguus (RAm) innervating vocal and respiratory muscles; the anterior pathway connects in its lateral part the lateral magnocellular nucleus of the anterior nidopallium (LMAN) to lateral Area X of the striatum (LArea X) to dorsal lateral nucleus of the dorsomedial thalamus (DLM) back to LMAN (Bottjer et al., 1989; Johnson et al., 1995; Nottebohm et al., 1982; Nottebohm et al., 1976; Striedter and Vu, 1998; Vates and Nottebohm, 1995; Vates et al., 1997; Wild, 1993). The posterior and anterior pathways are interconnected through the connection from HVC to Area X, from medial MAN to HVC, and from LMAN to RA.

The main areas where the dopaminergic innervations originate in the songbird brain are the midbrain cell groups VTA, SNc, and/or the periaqueductal gray (PAG; see Fig. 1 in Ball and Balthazart, this issue; Appeltants et al., 2000; Appeltants et al., 2002; Castelino et al., 2007; Gale et al., 2008; Hara et al., 2007; Lewis et al., 1981; Person et al., 2008) that are homologous to the mammalian VTA, SNc, and PAG, respectively (Gale and Perkel, 2006; Reiner et al., 2004b). These areas in zebra finch contain perikarya strongly labeled for tyrosine hydroxylase (TH), an enzyme necessary for catecholamine synthesis (Bottjer, 1993; Soha et al., 1996), but not for dopamine β -hydroxylase, that is an enzyme necessary for norepinephrine and epinephrine synthesis (Mello et al., 1998), suggesting that they are dopaminergic. However, neurons within VTA and SNc that project to the vocal areas HVC and RA include both dopaminergic and non-dopaminergic neurons (Appeltants et al., 2000; Appeltants et al., 2002). The dopaminergic neurons in songbird and mammalian VTA and SNc are characterized by their broad action potentials, calcium- and apamin-sensitive membrane potential oscillations (apamin blocks Ca^{2+} -activated K^{+} channels), and inhibition via D2 autoreceptors; the non-dopaminergic neurons show fast spontaneous firing and inhibition via μ -opioid receptors in zebra finches, properties similar to the GABA-ergic neurons in mammalian VTA and SNc, but show other properties different from the mammalian GABA-ergic neurons, such as the strong h-current that contributes to spontaneous firing (Gale and Perkel, 2006).

The main telencephalic brain subdivision that receives dopaminergic input from the VTA and SNc in birds and mammals is striatum including nucleus accumbens (Durstewitz et al., 1999; Joel and Weiner, 2000; Reiner et al., 2004b). The nucleus accumbens in birds is a relatively small brain region in ventrobasal forebrain between medial striatum, ventral pallidum, and lateral ventricle (Balint and Csillag, 2007; Reiner et al., 2004b) and its connection with song system is not known. On the other hand, the striatal song nucleus Area X in songbirds receives even more dense dopaminergic innervation relative to the surrounding striatum and to the rest of the telencephalon (Bottjer, 1993; Bottjer et al., 1989; Lewis et al., 1981; Soha et al., 1996) and Area X appears to be innervated by distinct population of dopaminergic neurons in VTA

and SNc than the surrounding striatum (Person et al., 2008). DA released by the dopaminergic terminals modulates excitability of medium spiny neurons in Area X, suggesting that DA influences information processing by altering the input–output functions of medium spiny neurons (Ding and Perkel, 2004; Ding et al., 2003; Ding and Perkel, 2002), the major neuron type in Area X (Reiner et al., 2004a), that is part of the anterior pathway of the song system described above. On the other hand, the axons from Area X to DLM have collaterals terminating in ventral pallidum which in turn projects to cells in VTA and SNc that project back to Area X (Gale et al., 2008). This loop enables then the Area X to influence its dopaminergic input.

Dopaminergic innervation of the pallial areas of the forebrain, including pallial song nuclei, is in comparison with striatum less dense, and the density of TH⁺ fibers is higher in HVC than in RA and higher in both of these motor pathway nuclei than in the surrounding brain regions (Bottjer, 1993; Bottjer et al., 1989; Lewis et al., 1981; Soha et al., 1996). The song nucleus HVC receives dopaminergic projections primarily from PAG with a minor contribution of VTA, while the surrounding telencephalon appears to receive projections from the SN and its rostral extension (Appeltants et al., 2000). The song nucleus RA receives dopaminergic inputs of similar origin as HVC, mostly from PAG and VTA dopaminergic cell groups, and the arcopallium dorsal and lateral to RA receives TH⁺ fibers from PAG, VTA, and SN (Appeltants et al., 2002). It is not clear, however, whether these song nuclei and possible Area X receive the dopaminergic input from the same neurons and thus whether some information can be transmitted to all of these nuclei simultaneously.

2 Dopamine Concentration and its Changes in Song Nuclei

The DA containing brain areas can be identified by the presence of TH, as mentioned above, and/or by the presence of DA itself and its metabolites 3,4-dihydroxyphenylacetic acid (DOPAC) and homovanilic acid (HVA). Harding et al. (1998) blocked DA synthesis and using high performance liquid chromatography (HPLC) measured DA levels from brain punches in male zebra finches. They found that DA levels were low in vocal and auditory nuclei such as nucleus interface of the nidopallium, HVC, RA, DM, LMAN, nucleus mesencephalicus lateralis, pars dorsalis (MLd), and Field L and high only in Area X (Table 1). The levels were generally higher during the development and strongly declined in adults (Harding et al., 1998), similarly to DA receptors (Kubikova et al., in press). Moreover, there was a pronounced peak in levels of DA and its metabolites in Area X at the age of 55 days (Harding et al., 1998), and peaks of DA receptor densities in Area X relative to the surrounding striatum between days 25 and 45 as well as between 75 days and adults (Kubikova et al., in press). Future experiments might show whether this coincidence with the starting point of singing (~day 35) and intense practice in zebra finch plays a role of DA in motivation to sing and/or in sensorimotor learning.

In order to measure the DA released from terminals in experimental animals, two prominent methods of *in vivo* neurochemical monitoring have been employed, microdialysis and voltammetry. Both methods enable to measure extracellular DA concentrations in discrete brain areas during ongoing behavior in awake, freely moving animals.

The principle of cerebral microdialysis is the perfusion of a microdialysis probe, fine catheter surrounded by a semi-permeable membrane, introduced stereotactically into the discrete brain area. The compounds from the extracellular space penetrate into dialysate based on the passive diffusion along concentration gradient, they are collected and analyzed (Di Chiara et al., 1996; Martin-Fardon et al., 1997). Due to technical limitations, such as the speed of perfusion, volume of dialysate and concentration of neurochemicals in it, DA release studies with microdialysis concern time scales of minutes. However, phasic changes of DA activity follow a time course in the order of tens and hundreds of milliseconds, and the birdsong related events

are within the range of seconds. Therefore *in vivo* microdialysis enables one to measure more tonic than phasic changes in DA levels during singing (Hernández and Shizgal, 2009; Robinson et al., 2009; Schultz, 2007). Sasaki et al. (2006) employed this technique to monitor the release of DA in Area X during singing in zebra finches. Using 10 min sampling intervals they found higher levels of DA in Area X during singing than silence and during directed than undirected singing (the directed singing is oriented towards another individual, usually a female, and is accompanied by courtship while undirected singing is not oriented to any particular individual). However, the social context difference seems to be not solely due to differential release of DA but also due to regulation of DA reuptake transporter, as blocking the reuptake transporter increased the DA levels and the social context differences disappeared. The differential release is supported by a finding which showed that the cells with lower baseline firing rates (presumably the dopaminergic neurons) in VTA/SNc are more active during directed singing than during silence or undirected singing (Hara et al., 2007; Yanagihara and Hessler, 2006). Hara et al. (2007) also reported that VTA/SNc is more active during directed singing, but the singing-driven immediate early gene expression was higher in GABAergic and not dopaminergic neurons. It is not clear how such a pattern is achieved. However, it is possible that other input (brain area) could affect activity of both of these cell types and the dopaminergic neurons respond stronger to this input than to the GABAergic inhibition. Further, the dopaminergic and GABAergic neurons can express different physiological properties in response to their stimulation as it has been shown in VTA in mammals (Bonci and Malenka, 1999). Other alternative explanation is that immediate early gene expression and neural activity do not always coincide.

Another *in vivo* method for measuring DA, voltammetry, enables seconds to subseconds time resolution, depending on the technique employed. This electrochemical method is based on measuring the currents due to oxidation and reduction of compounds, including DA, on the surface of a carbon fiber microelectrode inserted into the brain. Although it has been employed both *in vivo* and *in vitro* in numerous studies in mammals (Robinson et al., 2003; Schultz, 2007; Zhang and Sulzer, 2003), it only has been reported to date with *in vitro* slice preparation in songbirds (Gale and Perkel, 2005). Using voltammetric method enabling to detect subsecond changes in extracellular DA concentration they proved electrically stimulated (action potential-dependent) release of DA in Area X brain slices. Nevertheless, actual *in vivo* monitoring of DA release in Area X or other relevant areas during ongoing singing using fast cyclic voltammetry stays for future experiments.

3 Dopamine receptors

DA acts through its binding to specific membrane receptors that are members of seven transmembrane domains G protein-coupled receptor family. Dopamine receptors belong to two families, D1-like and D2-like, each comprising of several receptor types (for review see Callier et al., 2003; Le Crom et al., 2003; Missale et al., 1998; Vallone et al., 2000). Within the D1-like family, mammals have two receptors, D1A (called also D1; Dearry et al., 1990; Sunahara et al., 1990; Zhou et al., 1990) and D1B (D5; Grandy et al., 1991; Sunahara et al., 1991). Birds have three receptors belonging to the D1-like family, D1A, D1B (Kubikova et al., in press; Sun and Reiner, 2000), and a special avian D1D receptor (Demchyshyn et al., 1995; Kubikova et al., in press). In addition, fish and amphibians have a fourth receptor, called D1C (Cardinaud et al., 1997; Hirano et al., 1998; Macrae and Brenner, 1995; Sugamori et al., 1994). Within the D2-like family, mammals, fish, and birds have the same three receptors, D2, D3, and D4 (Boehmler et al., 2007; Boehmler et al., 2004; Bunzow et al., 1988; Fidler et al., 2007; Kubikova et al., in press; Schnell et al., 1999; Sokoloff et al., 1990; Van Tol et al., 1991).

There are major differences between the two dopamine receptor families. The D1-like receptors, after DA binding, activate adenylate cyclase and induce cAMP accumulation

(Kebabian and Calne, 1979), inhibit Na⁺/K⁺ pump and sodium channels (Aizman et al., 2000), and desensitize rapidly (Callier et al., 2003). The D2-like receptors show the opposite effects. In both mammals and birds the D1-like receptors increase neuronal firing, while activation of D2-like receptors decreases it (Ding and Perkel, 2002), and D1-like receptors have lower affinity for DA than the D2-like receptors (Acerbo et al., 2005; Košťál et al., 1999; Kubikova et al., 2009; Richfield et al., 1987; van Hierden et al., 2005). Further, there are differences among the individual receptor types within each family. One of the most apparent differences among the D1-like receptors is their affinity to DA, decreasing in the order D1D>D1B> D1A in birds (Demchyshyn et al., 1995). The pharmacological profile for the D2, D3, and D4 receptors in birds is not known, however, their general binding properties are similar to those in mammals (Kubikova et al., 2009).

Perhaps the most important factor for dopaminergic signaling is the distribution of dopamine receptors. There are both D1-like and D2-like receptors in Area X of male songbirds, as shown by pharmacological (Ding et al., 2003) as well as ligand binding studies where D1-like receptors have higher density in Area X than in the surrounding striatum in male but not female European starling (Casto and Ball, 1994). A disadvantage of pharmacological and ligand binding studies is that they cannot identify all individual receptors as the specific ligands binding to each receptor are not available. However, all six of the songbird dopamine receptors have been cloned recently, D1A, D1B, D1D, D2, D3, and D4 (Fidler et al., 2007; Kubikova et al., in press), and their distribution in both adult and developing male zebra finch brain has been determined (Kubikova et al., in press). The combined distribution of the mRNAs belonging to each family (Fig. 1, except D1D because there is no available specific antibody or ligand binding to D1D) is similar to the distribution of dopamine receptor binding sites shown in D1-like and D2-like ligand binding studies for birds (Ball et al., 1995; Casto and Ball, 1994; Demchyshyn et al., 1995; Dietl and Palacios, 1988; Košťál et al., 1999; Kubikova et al., 2009; Richfield et al., 1987; Schnabel and Braun, 1996; Schnabel et al., 1997; Stewart et al., 1996) as well as in mammals (Missale et al., 1998; Vallone et al., 2000).

Similar to the DA concentration and dopaminergic innervations density data, the highest levels of all dopamine receptors among the song nuclei are in Area X, containing D1A, D1B and D2 receptors; all three receptors are expressed at higher levels in Area X relative to the surrounding striatum (Fig. 1; Table 1). In HVC and RA, different distributions were found; D2 receptors were in sparsely isolated cells, and D1B and D3 receptors levels were high (Kubikova et al., in press). Interestingly, D3 receptors are almost exclusively located only in these motor vocal pathway nuclei and the mesopallium suggesting their potential specialized role for vocal output (Fig. 1). On the other hand the special avian receptor type D1D might influence the vocal output only from the auditory areas as it is present in the whole pallium including auditory areas but not in any of the song nuclei. The D4 receptors are expressed at very low levels in the whole songbird brain including the song nuclei.

Although the dopamine receptors are present in most of the areas where the TH is found (Bottjer, 1993; Sakaguchi and Saito, 1989; Soha et al., 1996) there are some discrepancies, reflecting the fact that TH immunostaining detects not only DA but also norepinephrine. The main difference related to song nuclei is that TH is high in LMAN but very low to non-detectable levels of dopamine receptors have been found there suggesting more the role of adrenergic and not dopaminergic system in LMAN function in adults.

There is an ongoing discussion on co-localization of D1-like and D2-like receptors (with opposing functions) in the literature (for review see Callier et al., 2003). Early in situ hybridization studies reported segregation of D1A and D2 receptors to different populations of medium spiny neurons (Gerfen et al., 1990; Le Moine and Bloch, 1995) and this was confirmed in single cell RT-PCR studies in normal rats (Surmeier et al., 1996) as well as in

D1 and D2 bacterial artificial chromosome transgenics (Gertler et al., 2008; Matamalas et al., 2009). Further, the populations of neurons containing D1-like and D2-like receptors differ in their electrophysiological properties (Cepeda et al., 2008; Schen et al., 2008; Gertler et al., 2008). Other studies show co-expression of D1A and D2 receptors in mammalian striatum to various degrees (Aizman et al., 2000; Ariano et al., 1997; Lee et al., 2004b). Although Ding and Perkel (2002) suggest in the study of physiological properties of Area X neurons after pharmacological manipulation in zebra finch that there is a considerable co-localization of D1-like and D2-like receptors in avian striatal spiny neurons and that there is also a segregation to some extent, it was shown in mammalian striatum that dopaminergic agents can modulate both classes of medium spiny neurons also through cholinergic interneurons (Wang et al., 2006).. More direct evidence for co-localization of mRNA for D1A and D2 receptors in birds comes from a double labeling study where it was calculated that about half of the neurons in Area X expressed both receptors in an adult male zebra finch (Kubikova et al., in press). Such co-localization provides a basis for more complex neuronal responses where perhaps the affinity, subcellular localization and density will play an important role. The effect of DA seems to be biased toward a reduction in excitability, as shown by electrophysiological recordings from the pharmacologically manipulated Area X in brain slices (Ding and Perkel, 2002), suggesting that the D2-like DA receptors are functionally dominant in the medium spiny neurons.

4 Song Learning Models

To understand the role of DA in song learning, we briefly review behavioral and computational biologists' hypotheses on mechanisms of learning. There are three models of song learning based on evidence from behavior (Marler, 1997). 1) The *instructive learning model*, called also "sensorimotor model" of vocal learning, is based on an assumption that prior to auditory experience of song, oscine brains are uninformed about the structure of their species song, i.e. the bird is not capable of producing the target vocalizations before hearing the tutor song and auditorily-guided developmental processes. 2) In contrast to the common assumption that prior to auditory experience of song oscine brains are relatively uninformed about the structure of their species song, the *selective learning model*, assumes that the naive songbird brain has an extensive foreknowledge about the natural song patterns of its species, a system of innate neural templates that facilitate the recognition and rapid memorization of conspecific song patterns. Instead of modeling the process of song acquisition as if it were based on instruction, an alternative is to invoke a process of selection, operating on preexisting circuitry. 3) The third model, *action-based learning*, combines memorization by both instruction and selection. The bird first memorizes songs by instruction, then it starts to produce imitations and overproduces repertoire. The repertoire is then winnowed by selection during social interactions at the time of stabilization of the motor patterns and the song repertoire crystallizes (Marler, 1997; Marler and Peters, 1977; Nelson, 1992; Nelson and Marler, 1994).

Computational learning theorists discriminate 1) *supervised learning*, which is the kind of learning from examples provided by a knowledgeable external supervisor, and 2) *reinforcement learning* that is learning what to do to maximize a numerical reward signal. In the second case the learner is not told which actions to take, but instead must discover which actions yield the most reward by trying them (Sutton and Barto, 1998). In supervised learning the learner is given training examples while reinforcement learning comes into play when examples of desired behavior are not available but where it is possible to score examples of behavior according to some performance criterion (Barto and Dietterich, 2004). For better understanding we can use the example of Rosenstein and Barto (2004). Consider a young child learning to throw a ball. For this motor task, as well as many others, ongoing practice is inevitable. The child repeatedly throws a ball under varying conditions and with variation in the executed motor commands. The outcome of each movement, such as the visual confirmation of whether the ball reached a nearby parent, acts as an evaluation signal that

provides the child with feedback about the quality of performance, but with no specific information about what corrections should be made. The parent may interject error information in the form of verbal instruction or explicit demonstration of what went wrong with each preceding throw. The evaluation signal drives skill optimization, whereas the error signal provides a standard of correctness that helps ensure a certain level of performance (Rosenstein and Barto, 2004). In a model combining the two previous, termed 3) ***supervised reinforcement learning***, both kinds of feedback are available to a learning system at the same time (Rosenstein and Barto, 2004).

Although there is no direct correspondence between the behavioral and computational learning models, both behavioral and computational models have implications for the possible underlying brain mechanisms and involvement of the reinforcement processes. Reinforcement processes in the brain are usually linked to dopaminergic neurotransmission. Over the past decade, there is increasing evidence that reinforcement learning computational algorithms are substantiated in the brain by the phasic activity of dopamine neurons (Daw, 2003; Dayan and Niv, 2008; Schultz, 2000; Schultz et al., 1997), i.e. the computational role for DA has been identified (Montague et al., 2004).

5 Dopamine in Reinforcement and Reward

The use of the term ‘reinforcement’ in the literature is ambiguous. It has been used to denominate 1) the positive affective value of a reward stimulus, 2) an associative strengthening of learned stimulus-stimulus or stimulus-response links without any affective implications, or 3) an observed strengthening of prior responses (Berridge, 2007). The term ‘reward’ has also multiple meanings. In the noun form (a reward) it denominates an object or event that elicits approach and is worked for; its analogue is ‘a reinforcer’. In the verb form (to reward) the term is synonymous with ‘to reinforce’ (Wise, 2004).

The role of DA in reinforcement, whichever definition we will use, is broadly accepted. However, there are several hypotheses on its role in reward processing, such as the ***anhedonia hypothesis***, the ***incentive salience*** or ***reward prediction error hypothesis***.

The ***anhedonia hypothesis*** was the first. It was based on the observation that the blockade of dopamine receptors (by neuroleptic pimozide) reduced lever pressing for food in rats, or as it was interpreted, reduced the motivation of animals directed at acquiring rewards (Wise et al., 1978). Similar decrease of pecking performance after pimozide was observed also in pigeons (Tombaugh, 1981). The anhedonia hypothesis presumed that the DA synapse is the ‘pleasure center’ that mediates the subjective feeling of pleasure (hedonia) associated with rewarding stimuli (Wise, 1980, 2008).

Opposed to this idea is the ***incentive salience hypothesis***. According to it DA systems are not needed to mediate the pleasure of reinforcers, but instead, DA is needed for attributing incentive salience (motivational value) to the neural representations of reward-related stimuli. Processing of reward is dissociated into two separate components, appetitive ‘wanting’ and consummatory ‘liking’. They are mediated by different neural systems, ‘wanting’ by DA and ‘liking’ by opioid peptides (Berridge, 2007; Berridge and Robinson, 1998). This hypothesis has been used for an interpretation of the role of DA and opioids in song production by Ritters and coauthors (Heimovics and Ritters, 2008; Ritters, 2009). On one hand, the density of TH fibers in VTA, medial preoptic nucleus (POM), and Area X of male European starling was linked to the amount of songs produced within a highly sexually motivated context associated with the wanting of a female (Heimovics and Ritters, 2008), similarly as the D1-like receptor densities in POM and PAG (Heimovics et al., 2009). On the other hand, opioid neuropeptide met-enkephalin immunoreactivity in the POM was linked to song produced within a context that has no obvious form of immediate external reinforcement, i.e. a non-breeding context (Heimovics and Ritters,

2005). In support of this hypothesis are also the results using pharmacological manipulation. While the dopamine reuptake inhibitor GBR-12909 increased the amount and duration of songs and the D1-like dopamine receptor antagonist SCH-23390 decreased the song, in contrast the opioid agonist fentanyl decreased the song, and the antagonist naloxone increased it (Riters et al., 2005; Schroeder and Riters, 2006). The authors interpreted their results in terms of the context-dependent roles of DA and opioids in the regulation of song and differential involvement of 'wanting' versus 'liking' associated with song behavior (Heimovics and Riters, 2008; Riters, 2009).

According to the *reward prediction error hypothesis*, not necessarily incompatible with the previous one (McClure et al., 2003), mesocortical dopamine projections carry a signal of error between predicted and actual reward, a sort of signal presumed by computational reinforcement learning models. Over the past decade, experimental work by Wolfram Schultz and colleagues has shown that dopaminergic neurons of mammalian VTA and SNc show phasic changes in spike activity that correlate with the history of reward delivery. These neurons fire in response to the difference between the actual reward received and predictions of the time and magnitude of reward. The more predictable the reward is, the less strongly the neuron fires when it appears. If a predicted reward fails to be delivered, these neurons respond with depressed activity (Schultz, 2006; Schultz et al., 1997). The dopamine response coding an error in the prediction of reward resembles in all major aspects the reinforcement signal presumed in reinforcement learning models based on temporal difference (TD) algorithms introduced by Sutton (1988). Whereas conventional prediction-learning methods are driven by the error between predicted and actual outcomes, TD methods are driven by the error or difference between temporally successive predictions. To make the distinction between these two approaches more clear, let us use the Sutton's example with predicting the weather (Sutton, 1998). Let us imagine an attempts to predict on each day of the week whether it will rain on the following Saturday. The conventional approach is to compare each prediction to the actual outcome whether or not it does rain on Saturday. A TD approach, on the other hand, is to compare each day's prediction with that made on the following day. If a 50% chance of rain is predicted on Monday, and a 75% chance on Tuesday, then a TD method increases predictions for days similar to Monday, whereas a conventional method might either increase or decrease them depending on Saturday's actual outcome.

Reward prediction error hypothesis has its critics. Redgrave and collaborators (Redgrave et al., 1999) argued that the latency of dopamine responses is too short to be consistent with the hypothesis that dopamine is a reward prediction signal. However, although these competing explanations differ with respect to the specific claims, they agree that dopamine function is located between the identification of a potential future reward and the generation of action to pursue it (McClure et al., 2003; Montague et al., 2004).

The reward prediction error hypothesis is in line with the computational model of avian song learning proposed by Doya and Sejnowski (1995, 1999). Its main assumption is that the pallial-basal ganglia-thalamic-pallial loop (anterior pathway) works as a reinforcement learning system that is similar to the adaptive critic architecture proposed by Barto et al. (1983) and that Area X receiving dopaminergic projection from the VTA provides evaluation or error signal.

There are several other models of birdsong learning assuming involvement of reinforcement learning rules. Fiete et al. (2007) proposed a model of songbird learning that focuses on avian brain areas HVC and RA, involved in song production, and nucleus LMAN, important for generating song variability. Plasticity at HVC → RA synapses is driven by hypothetical "rules" depending on three signals: activation of HVC → RA synapses, activation of LMAN → RA synapses, and reinforcement from an internal critic that compares the bird's own song with a memorized template of an adult tutor's song. An associational model of birdsong sensorimotor

learning by Troyer and Doupe (2000a, b) proposes that the AFP does not directly evaluate auditory feedback, but instead, receives an internally generated prediction of the feedback signal corresponding to each song “syllable”. This prediction, or “efference copy,” is learned in HVC by associating premotor activity in RA-projecting HVC neurons with the resulting auditory feedback registered within AFP-projecting HVC neurons. Syllable learning is guided by nonspecific reinforcement signals provided by the AFP that modulate the degree of ongoing associational plasticity throughout RA. Although both abovementioned models suppose involvement of the reinforcement signals originating from the AFP, they do not specify in detail their nature or the exact role of DA in this signaling. Farries and Fairhall (2007) in their general reinforcement learning model based on spike-timing-dependent synaptic plasticity (STDP) assume that changes in synaptic efficacies are modulated by DA, with increased DA promoting long-term potentiation (LTP) at corticostriatal synapses and decreased DA promoting long-term depression (LTD). However, implementation of this reward-modulated STDP model for song learning in oscine birds also does not provide more detailed idea on how DA is involved. Farries and Fairhall (2007) suggest that AFP plays the role of the “evaluation system”, evaluates the bird’s vocal performance and transmits information to motor pathway that enables learning. Projections from HVC to anterior forebrain pathway supplies auditory and premotor information needed to predict performance, while the activity in LMAN, controlled by basal ganglia circuitry, could influence the occurrence of dendritic spikes in RA neurons, and thereby control the magnitude and polarity of plasticity induced at HVC-RA and intrinsic RA-RA synapses.

To summarize, multiple hypotheses on the role of DA in reinforcement and reward have been formulated. Some of them have been also used for interpretation of birdsong learning and maintenance. Among the models of birdsong assuming involvement of the reinforcement learning processes the model of Doya and Sejnowski (1995, 1999) seems to provide most the most straight forward implications for the role of dopamine. In the next section we will analyze in more detail possible implications of the DA reward prediction error hypothesis for the mechanisms of birdsong learning and maintenance.

6 Reward Prediction Error, Song Learning and Maintenance

It is possible to interpret birdsong learning within the framework of the computational reinforcement learning theory based on the actor/critic architecture (Fig 2; Doya and Sejnowski, 1995, 1999). This architecture presumes that the actor chooses actions according to some policy of behavior, and the critic evaluates the present performance relative to the recent average performance. A perturbation is given to the motor commands, and if it results in better performance, the perturbed motor command is reinforced and stays permanent. Doya and Sejnowski identified the Actor with HVC, RA, and the motor neurons that control vocalization and the critic with Area X receiving dopaminergic projection from the VTA/SNc. Area X evaluates how well the produced syllable matches the template. LMAN perturbs the synaptic connections from HVC to RA. Similarly, Fiete et al. (2007) proposed a model with HVC and RA as an actor, and LMAN as “an experimenter” generating song variability. This is supported by the data where LMAN lesions in adult zebra finches prevent variability in the song (Kao et al., 2005), similar to inactivation of LMAN in juveniles (Olviczky et al., 2005). Induction of the variability by LMAN is probably not caused by dopaminergic system directly as there are no dopamine receptors nor dopaminergic projection to LMAN. However, the singing-driven ZENK in LMAN was shown to require LArea X (Kubikova et al., 2007a) that receives the strong dopaminergic input. Therefore it is possible that the dopaminergic system might modulate also the song variability.

Since some authors argue that the location of the critic within the birdsong learning system is still unknown, the search for the error signals and their location continues (Deregnacourt et

al., 2004; Fiete et al., 2007). What is the evidence for the hypothesis that the midbrain (VTA/SNc) dopaminergic projection to Area X can be identified with the adaptive critic, the source of reward prediction signal? In the following subsections we will look at the possible evidence for the model coming from the lesion studies, neural activity of VTA and AreaX neurons and DA-mediated synaptic plasticity in Area X.

Reinforcement learning models using TD algorithms have been successfully used for modeling birdsong acquisition (see Section 5). According to Schultz (1998) rewards not only increase the frequency and intensity of behavior leading to learning, but also maintain learned behavior by preventing extinction. Reduction and cessation of a predictive relationship and behavior following the omission of a reinforcer (negative prediction error) leads to extinction (Schultz and Dickinson, 2000). Responses of DA neurons to conditioned reward predicting cues also dynamically encode classical features of extinction: decrement in amplitude of previously learned excitatory responses and spontaneous recovery (Pan et al., 2008). Therefore we can suppose that activity of DA neurons contributes also to the birdsong maintenance.

6.1 Lesions of the VTA/SNc–Area X Pathway

Considerable support for the hypothesis that VTA/SNc – Area X pathway plays a role in evaluation of the singing behavior comes from lesion experiments. Although there are no data on the effects of the VTA/SNc lesions during song acquisition period, there are data on their effect in adulthood (Hara et al., 2007). Following unilateral lesion of VTA/SNc the singing rate of the directed singing in zebra finch males was significantly decreased, but not that of the undirected singing suggesting that VTA/SNc might play different role in the song maintenance depending on social context.

The process of matching the vocal output with the tutor song template might be disrupted in the experiments with early Area X lesions (during song acquisition period) in zebra finches where as a consequence the songs consisted of series of unusually long and variable notes and the song stability normally seen in intact birds was never achieved in the lesioned birds (Scharff and Nottebohm, 1991). Although originally there were reported no notable effects on song after lesions of Area X in adult zebra finches (Sohrabji et al., 1990), more detailed analyses including large-scale song bout organization revealed motor deficit – stuttering (Kubikova et al., 2007b). Similarly, in adult Bengalese finch, a bird with more variable song repertoire, a lesion in Area X caused many syllable repetitions (Kobayashi et al., 2001).

The consequences of Area X lesions during song acquisition are consistent with the failures expected for a reinforcement learning system (Doya and Sejnowski, 1995, 1999), i.e. with the fact that LMAN that perturbs the synaptic connections from HVC to RA loses evaluative guidance of Area X. The effects of VTA and Area X lesions in adulthood imply a possible role of this pathway also for the song maintenance.

6.2 Neural Activity of VTA/SNc and Area X Neurons

The idea that phasic DA encodes reward prediction error originated from the single neuron recordings of the monkey VTA (Schultz et al., 1997). To our knowledge there are no data on VTA dopaminergic projection neurons firing patterns during song acquisition that would be of great interest within the framework of the reward prediction error signaling and its role in learning processes. Therefore we can only hypothesize whether their activity encodes reward prediction error based on comparison of the bird's song to the tutor's song template.

However, there are data on firing of VTA neurons related to singing in adulthood that can have relevance to the song maintenance. Whereas some signals recorded from neurons in the male zebra finch VTA showed phasic peak of activity prior to song onset, others tended to decrease

prior to singing and there was a sharp peak after song initiation. The firing rate of VTA neurons was also affected by social context - directed vs. undirected (Yanagihara and Hessler, 2006). Although in this study it was not possible to differentiate whether the recorded signal was from dopamine projecting neurons or GABAergic interneurons, nevertheless, even if part of recordings was from the GABAergic interneurons, it can be assumed that modulation of their activity should directly affect the firing pattern of nearby dopaminergic projection neurons.

Whereas phasic responses of mammalian midbrain dopamine neurons reflect errors in the prediction of rewards and thus may constitute teaching signals for learning, striatal neurons are activated in response to reward expectation (Schultz, 2000; Schultz et al., 1998). In contrast to VTA/SNc neurons striatal neurons respond to the delivery of rewards, but do not exhibit the specific reward prediction error activity. The Area X of young male zebra finches early in the process of song learning contains song-responsive neurons, but these juvenile neurons lack the song and order selectivity present in adult birds (Doupe, 1997). While the neurons in Area X are initially broadly song-responsive during development of male zebra finches, in adult birds it contains neurons that are strongly selective for both spectral and temporal properties of song. They respond more robustly to playbacks of the bird's own song than to songs of conspecific individuals, and they respond less well to the bird's own song if it is played in reverse (recorded in anesthetized animals; Doupe, 1997; Doupe and Konishi, 1991). Further, the firing rate of the Area X neurons differs markedly between directed and undirected singing. Neurons in Area X of adult birds increase their firing rate immediately before the onset of song as well as during singing. The presence of modulation before song output suggests that singing-related Area X activity originates, at least in part, in motor control nuclei (recorded in awake animals; Hessler and Doupe, 1999a; Hessler and Doupe, 1999b).

6.3 Dopamine-Mediated Synaptic Plasticity in Area X

Dopaminergic neurons projecting from midbrain to striatum fire in a reward-dependent manner (Schultz et al., 1998). This activity of dopamine neurons overlaps with activity of glutamatergic neurons projecting into striatum from motor and sensory cortex. The interactions between glutamate and DA within the striatum produce long-term changes of synaptic efficacy, long term depression (LTD) and long-term potentiation (LTP) (Calabresi et al., 2007; Calabresi et al., 1997). According to some authors D1 and D2 DA receptors appear to modulate long-term changes in glutamatergic synaptic plasticity in medium spiny neurons in different ways. D1 receptor signaling promotes LTP, whereas D2 receptor signaling promotes LTD (Shen et al., 2008; Surmeier et al., 2007). On the other hand, both D1 and D2 receptor antagonists block LTD and co-administration of D1 and D2 agonists in the dopamine depleted striatum restores the induction of LTD suggesting that D1 and D2 receptors act synergistically to enable formation of LTD (Calabresi et al., 1992). According to this view, the D1 and D2 receptors have opposing roles on the induction of LTP; while D1 and D5 (D1B) antagonists block LTP, D2 antagonist enhances it (Calabresi et al., 2007). In both cases, because of the segregation of D1 and D2 receptors, cholinergic interneurons and NOS-positive interneurons seem to play an important integrative role within the intrinsic neuronal network in which they act. It has been hypothesized that the induction of LTD in neurons containing only D1 receptors could be sustained by the D2 receptor-dependent reduction of muscarinic M1 receptor tone, whereas in neurons containing only D2 receptors the activation of D1 receptors could be required to facilitate nitric oxide release from nitric oxide synthase-positive interneurons (Calabresi et al., 2007).

In songbirds it was shown that DA modulates the strength of excitatory synaptic inputs to Area X spiny neurons. In zebra finch brain slices, pairing high-frequency presynaptic stimulation with postsynaptic depolarization induces LTP of the glutamatergic inputs to medium spiny neurons of Area X (Ding and Perkel, 2004). The LTP induction requires activation of D1-like

dopamine receptors (LTP induction failed in the presence of a D1-like DA receptor antagonist) and glutamate *N*-methyl *D*-aspartate (NMDA) receptors but not D2-like receptors (there was no significant effect of the presence of D2-like DA receptor antagonist on LTP induction). The induction of LTP was observed in adult and juvenile birds but not in birds younger than 40 days. This indicates that synaptic plasticity on inputs from HVC and LMAN to Area X could be the candidate mechanism for reinforcement-based vocal learning in juveniles and song maintenance in adult birds (Ding and Perkel, 2004).

The biochemical cascades involved in dopamine modulated synaptic plasticity, based on mammalian data, is shown in Fig. 3. Several components of this cascade are affected during song acquisition and/or production. First, the large majority of zebra finch Area X cells that express DARPP-32 also express CaMKII (Hein et al., 2007). Dramatic increase in levels of phosphorylated CaMKII in Area X of young zebra finch males is promoted by familiar adult tutoring (Singh et al., 2005). This could reflect DA-modulated plasticity (LTP) involved in encoding reward value of tutor song, that is accessed later to guide motor learning. Second, CREB is abundant in Area X of both zebra finch and European starling (Auger et al., 2002; Sakaguchi et al., 1999). Although song playback-induced phosphorylation of CREB in Area X of adult zebra finches was not observed (Sakaguchi et al., 1999), its presence during the sensorimotor learning period needs to be confirmed. Third, both *c-fos* and ZENK are often used in the birdsong literature as markers of electrophysiological activity of neurons. In mammals it has been shown that ZENK is essential for stabilizing synaptic plasticity, expression of long-term memory (Jones et al., 2001), and memory reconsolidation (Lee et al., 2004a). In zebra finches ZENK expression is higher in lateral Area X (LAreaX) after the more variable undirected than directed song (Jarvis et al., 1998; Kubikova et al., 2007a) and after the more variable song of chipping sparrows at dawn when the level of ZENK expression in Area X is positively correlated with variability in song rate (Liu and Nottebohm, 2005). ZENK is up-regulated by D1 receptors and inhibited by D2 receptors in mammals (Gerfen et al., 1995). ZENK expressed after both undirected and directed singing is localized more in D1A than D2 receptor containing neurons (Kubikova et al., in press) suggesting its activation by dopamine via D1A receptors. ZENK can be expressed in mammals also by activation of glutamate NMDA receptors (Snyder-Keller et al., 2002). After deleting the dopaminergic input from VTA/SNc the zebra finch LArea X still expresses ZENK, although in reduced levels (Hara et al., 2007) which suggests that in songbirds too ZENK can be induced by the glutamatergic input from HVC and/or LMAN, although other neurotransmitters such as acetylcholine can also play a role in the induction (von der Kammer et al., 1998). However, the question of the exact molecular mechanisms of LTP, memory formation, and song maintenance in songbirds is complex and still many questions are unanswered.

7 Dopamine, Personality and Singing Behavior

Individuals differ non-randomly in how they deal with stressors, novelties, manage their social relations or control their aggressive behavior. Temperament, personalities, copying styles and other related phenomena, i.e. stable inter-individual differences in behavior and physiology, were documented in a wide range of animal species from invertebrates to mammals (Groothuis and Carere, 2005; Sih et al., 2004). The dopamine D4 receptor (*DRD4*) gene is one of the candidate genes studied in relation to personality traits, mainly novelty seeking. Association of its polymorphism with personality traits has been implicated in mammals and humans (Bailey et al., 2007; Hejjas et al., 2007; Momozawa et al., 2005; Munafo et al., 2008) as well as in songbirds (Fidler et al., 2007), where significant association of single nucleotide polymorphism in *DRD4* with early exploratory behavior was shown in great tits.

Singing behaviour is also affected by personality, as shown recently by Garamszegi et al. (2008) in collared flycatchers, where risk-taking as a personality trait affects the choice of posts

when singing. Although relation between personality traits and birdsong is far from being understood, a possible relation between personality traits related to dopaminergic neurotransmission and song learning or song quality is a field deserving further attention.

8 Summary and Conclusions

Young songbirds memorize a tutor song that they later use as a template to shape their own song by auditory feedback (Konishi, 1965, 2004). One of the fundamental questions that birdsong researchers try to answer is the question of neural sites and mechanisms related to song learning and maintenance. Since the discovery of brain pathways controlling bird song (Nottebohm et al., 1976) anatomical and physiological studies made further progress in specifying the role of distinct nuclei and neuronal connections in song control. Importance of DA for behavior, cognition, motivation, reward, and learning stimulated interest in neurochemistry and chemical neuroanatomy of dopaminergic system in relation to song system already in 80s and 90s (Bottjer, 1993; Casto and Ball, 1994; Lewis et al., 1981; Sakaguchi and Saito, 1989). This process still continues, as illustrated by recent work such as mapping the expression of five DA receptor subtypes in zebra finch (Kubikova et al., in press) or estimating D1-like DA receptor density in relation to social context in European starling (Heimovics et al., 2009).

In comparison to mammals the use of the *in vivo* methods for measuring concentrations of extracellular DA and its metabolites during ongoing behavior is in birds underdeveloped. There is only one study using *in vivo* microdialysis in relation to singing behavior (Sasaki et al., 2006) and *in vivo* voltammetry has been applied in brain slices only (Gale and Perkel, 2006; Gale and Perkel, 2005). Broader use of *in vivo* methods can bring further progress in our understanding of dynamics of extracellular DA in relation to behavior.

Ideas about the functions of the central dopamine system have evolved considerably over the last decade. The new concepts, such as incentive salience (Berridge, 2007; Berridge and Robinson, 1998) or reward prediction error hypothesis (Schultz, 2007; Schultz and Dickinson, 2000; Schultz et al., 1998) bring new testable hypotheses also to the birdsong research. Role of DA in wanting in relation to birdsong, possible role of VTA/SNc – Area X dopaminergic projection as a critic within the actor/critic architecture of the song reinforcement learning system, the role of DA in error coding, dopamine-induced plasticity in Area X, or the role of DA and its receptor subtypes in activity-dependent synaptic plasticity are just few examples of the challenges in this area. The influence of DA on personality traits determination and relation of these traits to song learning and song quality is another practically unexplored area.

To conclude, behavioral neuroscience of birdsong is a fast growing area of research, which offers also the unique opportunity to study the role of DA in reward, learning or generally in control of behavior.

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Fig. 1.

Expression of dopamine receptors in adult zebra finch male brain. Calibration bar shows pseudocolour coding of the mRNA signal strength on autoradiograms of sagittal sections. In the first row are representative autoradiograms of the D1-like dopamine receptor family, in the second row the D2-like dopamine receptor family. Drawing delineates some of the brain regions on the sections with the focus on song nuclei. Abbreviations: A – arcopallium, DM – dorsal medial nucleus of the midbrain, DNH – dorsal nucleus of the hyperpallium, GP – globus pallidus, H – hyperpallium, HVC – nucleus HVC (a letter based name), IH – interstitial layer of the hyperpallium, LArea X – lateral part of AreaX of striatum, LMAN – lateral magnocellular nucleus of anterior nidopallium, L2 – Field L2, MLd – dorsal part of the lateral mesencephalic nucleus, MV – ventral mesopallium, RA – robust nucleus of the arcopallium, SVZ – subventricular zone, TeO – optic tectum

Fig 2. Birdsong reinforcement learning scheme. Red arrows show glutamatergic input; blue arrows show GABA-ergic input; green arrows show dopaminergic input; black arrows show other connections with unspecified input. D1A, D1B, D2, and D3 are dopamine receptors present and/or present at higher levels in the song nucleus than in the immediate surrounding area (bold). Based on Doya and Sejnowski (1995, 1999) and Fiete et al. (2007).

Fig. 3.

A possible scheme of the cascades involved in dopamine modulated synaptic plasticity in the AreaX, based on mammalian data. DA acting through the D1-like receptors elevates the level of cAMP and stimulates protein kinase A (PKA) (Stoof and Kebabian, 1981) which in turn activates phosphorylation of dopamine and cAMP-regulated phosphoprotein (DARPP-32). DA acting through the D2-like receptors inhibits PKA (Centonze et al., 2001) and reduces DARPP-32 phosphorylation (Gould and Manji, 2005). DARPP-32 plays a central role in dopaminergic and glutamatergic signaling, and is integrating the activity of these two pathways. In elevated calcium levels the dephosphorylated DARPP-32 leads to dephosphorylation of glutamate receptors while the activated calcium calmodulin-dependent protein kinase II (CaMKII) increases the phosphorylation of glutamate receptors (Worgotter and Porr, 2005). The calcium influx through NMDA receptors leads to rapid phosphorylation of MAPK/ERK and to activation of cAMP response element binding protein (CREB) (West et al., 2002; Zhou et al., 2009). CREB can be activated also by PKA through MAPK/ERK (Gerits et al., 2008). CREB and the ternary complex factor Elk-1 can increase the transcription of many genes, including c-fos and ZENK (Davis et al., 2000).

Table 1

Densities of tyrosine hydroxylase (TH) fibers, concentrations of dopamine (DA), and densities of dopamine receptors (DR) in some vocal nuclei of an adult male zebra finch. The DR in bold stands for higher dopamine receptor density in the song nucleus relative to the surrounding area.

	TH	DA (pg/μg protein)	DR
HVC	low-moderate	low (16)	D1A, D1B , D2 , D3
RA	low-moderate	low (23)	D1A, D1B , D2 , D3
LMAN	low-moderate	low (18)	D2
Area X	high	high (68)	D1A , D1B , D2
	(Bottjer, 1993; Sakaguchi and Saito, 1989; Soha et al., 1996)	(Harding et al., 1998)	(Kubikova et al., in press; Sasaki et al., 2003)