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## REVIEW

# SENSORY REGULATION OF DOPAMINERGIC CELL ACTIVITY: PHENOMENOLOGY, CIRCUITRY AND FUNCTION

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**Abstract**—Dopaminergic neurons in a range of species are responsive to sensory stimuli. In the anesthetized preparation, responses to non-noxious and noxious sensory stimuli are usually tonic in nature, although long-duration changes in activity have been reported in the awake preparation as well. However, in the awake preparation, short-latency, phasic changes in activity are most common. These phasic responses can occur to unconditioned aversive and non-aversive stimuli, as well as to the stimuli which predict them. In both the anesthetized and awake preparations, not all dopaminergic neurons are responsive to sensory stimuli, however responsive neurons tend to respond to more than a single stimulus modality. Evidence suggests that short-latency sensory information is provided to dopaminergic neurons by relatively primitive sub-cortical structures – including the midbrain superior colliculus for vision and the mesopontine parabrachial nucleus for pain and possibly gustation. Although short-latency visual information is provided to dopaminergic neurons by the relatively primitive colliculus, dopaminergic neurons can discriminate between complex visual stimuli, an apparent paradox which can be resolved by the recently discovered route of information flow through to dopaminergic neurons from the cerebral cortex, via a relay in the colliculus. Given that projections from the cortex to the colliculus are extensive, such a relay potentially allows the activity of dopaminergic neurons to report the results of complex stimulus processing from widespread areas of the cortex. Furthermore, dopaminergic neurons could acquire their ability to reflect stimulus value by virtue of reward-related modification of sensory processing in the cortex. At the forebrain level, sensory-related changes in the tonic activity of dopaminergic neurons may regulate the impact of the cortex on forebrain structures such as the nucleus accumbens. In contrast, the short latency of the phasic responses to sensory stimuli in dopaminergic neurons, coupled with the activation of these neurons by non-rewarding stimuli, suggests that phasic responses of

dopaminergic neurons may provide a signal to the forebrain which indicates that a salient event has occurred (and possibly an estimate of how salient that event is). A stimulus-related salience signal could be used by downstream systems to reinforce behavioral choices.

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**Key words:** sensory stimuli, tonic, phasic, salience, reward.

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## INTRODUCTION

In 1979, Chiodo et al. reported that tail pressure, cervical probing and light flashes produced responses in dopaminergic (DA) neurons in the substantia nigra pars compacta (SNc) of anesthetized Sprague Dawley rats. Since then, the finding that DA neurons respond to sensory stimuli has been extended to other stimulus types, to the awake preparation and to other species. Although perhaps a little premature to summarize, non-noxious sensory stimuli in awake animals tend to elicit short-latency, short-duration ‘phasic’ responses in DA neurons whereas noxious stimuli in awake and anesthetized animals (and non-noxious stimuli in anesthetized animals) tend to elicit protracted ‘tonic’ responses which temporally track or even outlast the inducing stimulus. Tonic and phasic modulation of dopamine levels in the forebrain have been argued to subservise different functions (Grace, 1991; Floresco et al., 2003; Goto and Grace, 2005; Goto et al., 2007; Redgrave et al., 2008; Howe et al., 2013) and consequently the influence of sensory stimuli on these

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Q2 **Abbreviations:** DA, dopaminergic; GABA, gamma aminobutyric acid; PBN, parabrachial nucleus; PPTg, pedunculopontine tegmental nucleus; RMTg, rostromedial tegmental nucleus; SC, superior colliculus; SNc, substantia nigra pars compacta; TH, tyrosine hydroxylase; VTA, ventral tegmental area.

two modes of activity in DA neurons will be considered separately below. However, it is important at the outset to acknowledge a caveat with respect to the studies we are about to discuss – namely that the neurochemical identity of the neurons under consideration has usually not been firmly established. Hence, for ‘DA neuron’ below it is probably safest to read ‘putative DA neuron’ (unless identification has taken place) because of this uncertainty.

### TONIC CHANGES IN DA CELL ACTIVITY IN RESPONSE TO NON-NOXIOUS AND NOXIOUS STIMULI

In the anesthetized rat, non-noxious sensory stimuli do not typically elicit responses in DA neurons that are clearly time locked to the onset or offset of individual discrete stimuli. Instead, accounts suggest that sensory stimuli lead to a general elevation or reduction in firing rate, i.e. a tonic change in activity. In the rat, continuous tail or foot pressure, continuous cervical probing, trains of light flashes, olfactory stimuli and trains of air puffs to the snout all produce long latency (~400 ms) activations and inhibitions in SNc DA neurons which last for the duration of the applied stimuli (Chiodo et al., 1979, 1980; likewise for tail and foot pressure, and cervical probing, in ventral tegmental area (VTA) DA neurons; Maeda and Mogenson, 1982). Not all cells respond, but responsive cells tend to respond more than a single stimulus modality, and individual cells can be activated and inhibited by different modalities. These tonic responses almost certainly reflect the temporally extended nature of the stimuli used by the authors (continuous, chemical, trains), and show that under certain conditions, the activity of DA neurons can track such prolonged stimuli. Indeed, in the anesthetized preparation, it seems that stimuli have to be temporally extended for DA neurons to respond to them at all. In our hands, short-duration, discrete light flash stimuli do not elicit responses in DA neurons in the anesthetized rat (Dommett et al., 2005) and discrete somatosensory (whisker) stimuli are similarly ineffective (Overton, Vautrelle and Redgrave, unpublished observations). An important issue of course is the relevance of sensory-related tonic changes in the activity of DA neurons in the anesthetized preparation to the regulation of DA neurons in the awake animal, where discrete non-noxious sensory stimuli can elicit phasic responses (see the next section). However, tonic responses to sensory stimuli have been described in the awake restrained rat – to continuous tail pressure, trains of light flashes, olfactory stimuli and sound stimuli (Kiyatkin, 1988; Kiyatkin and Zhukov, 1988; Roesch et al., 2007), and to long-duration light stimuli associated with chocolate milk reward (see Figure 2 of Miller et al., 1981), suggesting that tonic responses in DA neurons to non-noxious sensory stimuli are part of the ‘natural’ repertoire of responses in these cells.

So far we have been considering non-noxious stimuli, both conditioned and unconditioned. However, DA neurons also respond to noxious stimuli. In the

anesthetized rat, noxious stimuli tend to induce responses which last for (and can outlast) the period for which the stimulus is applied. Hot water applied to the tail produces responses in SNc DA neurons (Tsai et al., 1980) and noxious tail pinch produces responses in both SNc and VTA DA neurons (Mantz et al., 1989; Ungless et al., 2004). Tsai et al. (1980) initially reported that all DA neurons are inhibited, an observation which was confirmed by Ungless et al. (2004) for neurochemically identified DA neurons in the VTA, and which fits with the accounts of short-latency (<100 ms) inhibitory responses in SNc and VTA DA neurons to protracted stimulation of the sciatic nerve (Hommer and Bunney, 1980; Tsai et al., 1980; Kelland et al., 1993). However, some DA neurons are activated rather than inhibited by noxious tail pinch, foot pinch or foot shock (Mantz et al., 1989; Coizet et al., 2006), and the most recent picture that has emerged is that there may be two populations of DA neurons in the VTA of the rat – one which responds with activation and one which responds with inhibition to noxious stimuli (Brischoux et al., 2009). Although the responses to long-lasting noxious stimuli tend to track the duration of the applied stimulus, there is evidence that the response is stronger toward the early phase of the stimulation, at least in the VTA (see Figure 1 of Mantz et al., 1989; Figure 2 of Brischoux et al., 2009).

These general findings in the anesthetized rat also extend to the anesthetized monkey. In the anesthetized monkey, midbrain DA neurons are not responsive to a range of non-noxious sensory stimuli (such as rubbing of the skin, muscle taps and passive joint rotation; Schultz and Romo, 1987; Romo and Schultz, 1989). In contrast, noxious pinch is effective and the responses, which are more frequently inhibitions rather than activations, last for as long as the stimulus is applied (Schultz and Romo, 1987; Romo and Schultz, 1989). Presumably for ethical reasons, the majority of studies looking at the responses of DA neurons to noxious stimuli have been conducted under anesthesia. However, in the awake restrained rat, Kiyatkin (1988) and Kiyatkin and Zhukov (1988) report that a tail prick or intense electrical stimuli to the tail produce responses (inhibitions or activations) in VTA DA neurons which temporally track the applied stimuli. Likewise, long-duration tones associated by classical conditioning with electric shocks to the tail produce tonic inhibitory responses in neuro-chemically identified VTA DA neurons in the awake rat (see Figure 3 of Mileykovskiy and Morales, 2011), and tones associated with electric shocks to the pinnae produce tonic responses (this time most often activations) in VTA DA neurons in the awake rabbit (Guarraci and Kapp, 1999). Again, in both cases, these responses are greater at the beginning of the period of stimulation, but do persist throughout the stimulation, suggesting – in combination with the above – that tonic changes in activity are the standard, system-level response of DA neurons to both conditioned and unconditioned noxious stimuli. Phasic responses in DA neurons to noxious stimuli are of course possible. However, these responses – which tend to be short-latency (<100 ms) – only seem to occur when the

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