Korshunov KS, Blakemore LJ, Trombley PQ\*. “Dopamine: A Modulator of Circadian Rhythms in the Central Nervous System.”

Supplementary Material: **Table 1. Dopamine’s influence on the neuronal circadian rhythms of the five brain areas.**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Brain area** | **Retina** | **Olfactory Bulb** | **Striatum** | **Midbrain (includes VTA and SNc)** | **Hypothalamus (arcuate nucleus)** |
| DA neurons | Amacrine and/or interplexiform cells (species specific) (see Witkovsky 2004; Popova 2014). | PGCs or SACs (Baker 1986; Ennis et al. 200l; Kosaka and Kosaka 2009, 2016). | GABAergic striatal interneurons (Ibanez-Sandoval et al. 2010). | Mesolimbic, nigrostriatal, and mesocortical projecting neurons (see Russo and Nestler 2013; Nelson and Kreitzer 2014). | TIDA neurons and THDA neurons (see Freeman et al. 2000). |
| DA receptors | D1, D2, D4, and D5 receptors (see Witkovsky 2004; Beaulieu and Gainetdinov 2011; Popova 2014). | D1 (Nickell 1991; Liu et al. 2013) and D2 (Nickell et al. 1991; Hsia et al. 1999; Berkowicz and Trombley 2000; Ennis et al. 2001; Davila et al. 2003) receptors. | D1, D2, D3, and D5 receptors (see Beaulieu and Gainetdinov 2011). | D1 D2, and D5 receptors in the SN, D2 receptors in the VTA, D3 receptors in both areas (see Beaulieu and Gainetdinov 2011). | D1 and D2 receptors in arcuate nucleus (see Romero-Fernandez 2014). |
| Daily expression of TH and DA | DA content is high during daytime and low during nighttime (circadian and light dependent)(see Popova 2014). | Rodent DA content is high during the daytime and low during the nighttime (Corthell et al. 2013). | NAcc TH levels are rhythmically expressed and are highest during dark phase (Webb et al. 2009). DA, DOPAC, and HVA show daily rhythms of expression in the striatum (Castañeda et al. 2004). | SNc and VTA TH levels are rhythmically expressed and show peak expression at subjective day (Webb et al. 2009; Chung et al. 2014). MAOA, an enzyme that suppresses DA activity, and *Maoa* are rhythmically expressed in the VTA (Hampp et al. 2008). | DA turnover from TIDA neurons is highest in the morning, while PRL is highest during sleep (see Freeman et al. 2000). |
| Effects on neuronal circadian rhythms | D4 receptors may mediate circadian aspects of contrast sensitivity (Jackson et al. 2011, 2012; Hwang et al. 2013) and D1 receptors may mediate visual acuity (Jackson et al. 2012). D4 receptors and ipRGCs (needed for circadian photoentrainment) are involved in light adaption (see Witkovsky 2004; Prigge et al. 2016). | Diurnal variations in DA release (Corthell et al. 2013) may imply circadian activity of OB dopaminergic neurons (see Mendoza and Challet 2014), which may cause diurnal variation in olfactory sensitivity. | Rhythmic expression of NAcc TH likely contributes to the diurnal variation of sex reward (Webb et al. 2009). | Midbrain DA may be involved in maintenance of daily motor rhythms (Fifel and Cooper 2014). Also, rhythmic expression of VTA TH potentially contributes to the diurnal variation of drug (amphetamine) reward (Webb et al. 2009). | DA provides daytime inhibition of PRL release, resulting in cycling (see Freeman et al. 2000). |
| DA interactions with circadian (“clock”) genes and proteins | D4 receptors mediate the expression of the *Npas2* gene (Hwang et al. 2013). D1 receptors influence PER2 expression (Ruan et al. 2008). D2 receptors mediate the rhythmic expression of melanopsin mRNA by ipRGCs, (Sakamoto et al. 2005). | OB exhibits intrinsic circadian rhythms in clock gene (PER) activity in vitro (but unknown if linked to DA) (Granados-Fuentes et al. 2004). | Dorsal striatum’s PER2 expression depends on D2 receptor activation (Hood et al. 2010). D1, and/or D2, and D3 receptors regulate expression of *Per1*, *Clock*, *Bmal1*, and *NPAS2* in striatal cultured neurons (Imbessi et al. 2009). Rhythmic expression of PER1 and BMAL1 protein levels in the NAcc (Webb et al. 2009). | CLOCK (McClung et al. 2005; Sidor et al. 2015) and REV-ERBα (Chung et al. 2014) inhibit TH expression in the VTA. | PER1 and 2, expressed in TIDA neurons, are necessary for DA release (Sellix et al. 2006). |
| Relationship between DA and PD | IPL, where DA neurons are found, is decreased in PD (Hajee et al. 2009; Adam et al. 2013; Spund et al. 2013). Reduced retinal DA levels in PD may impair foveal vision (Bodis- Wollner 2009), contrast sensitivity (Bulens et al. 1989) and light adaption (see Archibald et al. 2009). | DA and TH neurons *increased* in the OBs of patients with PD (Huisman et al. 2004; Mundinano et al. 2011). This may contribute to hyposmia. Increased OB DA may impair odor detection (Doty and Risser 1989) and discrimination (Tillerson et al. 2006) in PD. | Reduced striatal DA transporters may contribute to RBD (Eisensehr et al. 2003) and disturbed striatal DA transmission may contribute to RLS (Turjanski et al. 1999), both common in PD. Nigrostriatal degeneration in PD may blunt clock gene expression and contribute to circadian disruptions (Videnovic and Golombek 2013; Verwey et al. 2016). | Degeneration of dopaminergic neurons in SN causes classic motor symptoms of PD (Carlsson 1972). Loss of midbrain DA impaired locomotor activity in MitoPark mouse model of PD (Fifel and Cooper 2014). Loss of SNc DA neurons impaired REM sleep in an MPTP rat model of PD (Lima et al. 2007). | Significant decrease in hypothalamic DA neurons in postmortem PD brains (Conte-Devolx et al. 1985) and a decrease in DA levels of hypothalamic extracts from PD patients (Pique et al. 1985). Patients with PD have altered levels of PRL (Murri et al. 1980; Bellomo et al. 1991; Winkler et al. 2002). |

\*Corresponding author email: trombley@neuro.fsu.edu

**Abbreviations:** DA: dopamine; DOPAC: 3,4-Dihydroxyphenylacetic acid; GABA: γ-amino butyric acid; HVA: homovanillic acid; IPL: inner plexiform layer; ipRGCs: melanopsin-expressing intrinsically photosensitive retinal ganglion cells; MAOA: monoamine oxidase A; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NAcc: nucleus accumbens; OB: olfactory bulb; PD: Parkinson’s Disease; PGCs: periglomerular cells; PRL: prolactin; RBD: rapid-eye movement sleep behavior disorder; REM: rapid-eye movement; RLS: restless leg syndrome; SACs: short axon cells; SNc: substantia nigra pars compacta; TH: tyrosine hydroxylase; THDA neurons: tuberhypophyseal dopamine neurons; TIDA neurons: tuberoinfundibular dopamine neurons; VTA: ventral tegmental area.

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