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Review article

The "highs and lows" of the human brain on dopaminergics: Evidence from neuropharmacology

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ABSTRACT

Rewards are appetitive events that elicit approach. Ground-breaking findings from neurophysiological experiments in animals, alongside neuropharmacology and neuroimaging research in human samples have identified dopamine as the main neurochemical messenger of global reward processing in the brain. However, dopamine's contribution to the different components of reward processing remains to be precisely defined. To facilitate the informed design and interpretation of reward studies in humans, we have systematically reviewed all existing human pharmacological studies investigating how drug manipulation of the dopamine system affects reward-related behaviour and its neural correlates. Pharmacological experiments in humans face methodological challenges in terms of the: 1) specificity and safety of the available drugs for administration in humans, 2) uncertainties about pre- or post-synaptic modes of action, and 3) possible interactions with inter-individual neuropsychological or genotypic variables. In order to circumvent some of these limitations, future research should rely on the combination of different levels of observation, in integrative pharmaco-genetics-neurobehavioral approaches, to more completely characterize dopamine's role in both general and modality-specific processing of reward.

1. Introduction

Rewards are appetitive events or objects that make subjects "come back for more", in contrast with punishments (which lead to avoidance behaviours) (Bissonette et al., 2014). Rewards are critical for survival and well-being, as they: 1) induce subjective feelings of pleasure (hedonia) and positive emotional states related to the notion of being recompensed for having done something useful (Berridge and Kringelbach, 2015); 2) serve as goals, eliciting approach behaviour (Gottlieb et al., 2014); and 3) have positive reinforcing effects, increasing the frequency and intensity of behaviour leading to such events or objects (learning) (Hikida et al., 2016).

Cumulative ground-breaking neurophysiological experiments in animals (Schultz, 2015), alongside neuropharmacological (Rutledge et al., 2015), genetic (Baker et al., 2016) and neuroimaging studies (Gonen et al., 2016) in humans, strongly position mesolimbic and neostriatal dopamine signalling as the 'common neural currency' for reward (for an critical overview of dopamine system neurobiology and brain reward pathways, see Box 1). In support, reward deficits have been consistently reported as symptoms in several dopamine-related neuropsychiatric disorders (such as parkinsonism (Foerde et al., 2016), schizophrenia (Deserno et al., 2016) or drug addiction (Jollans et al., 2016)) and as adverse effects of dopaminergic treatments, such as pathological gambling in Parkinson's patients under dopamine-enhancing treatment (Moore et al., 2014). Nevertheless, debate still continues over what specific component of reward (Berridge et al., 2009) is mediated by dopamine signalling (Berridge, 2007; Collins and Frank, 2016). Is it: 1) the activation of *sensorimotor* systems related to effort, arousal and response vigor (Rangel and Hare, 2010); 2) the affective *hedonic* codification of pleasure and 'liking' (Pool et al., 2016); 3) the *incentive salience* of reward 'wanting' or motivation (Robinson et al., 2014); and/or 4) the reward *learning* mechanism of associative stamping-in, teaching signals and prediction errors (Schultz, 2015)? The disentanglement of these components has been greatly helped by elegant computational modelling (theoretical and evidence-based) of the mesocorticolimbic circuitry. Nevertheless, with the exception of recent sparse works on the incentive salience component (Anselme, 2015), most of these have focused on the learning component (Keiflin and Janak, 2015). Thus, what *exactly* does dopamine do in reward? This cutting-edge remaining question of neuroscience requires the parsing out of dopamine's role in each specific component of reward processing (for a discussion of this, see Box 2).

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Box 1
Dopaminergic neurons and brain reward pathways: an overview.

In the adult brain, nearly all dopamine neurons reside in the ventral part of the mesencephalon which includes the substantia nigra pars compacta (SNc), the ventral tegmental area(VTA), and the retrorubral field(RRF) (Taber et al., 2012). In addition, a population of dopamine neurons is also present in the arcuate nucleus of the tuberal region of the hypothalamus and projects to the pituitary median eminence (the tuberoinfundibular pathway) to regulate the secretion of prolactin from the anterior pituitary gland. The currently best described dopamine neurons belong to the nigrostriatal circuit, which originates in the SNc and projects into the caudate nucleus and the putamen, playing an essential role in voluntary movement control by modulating the corticostriatal transmission in medium spiny neurons (MSNs) expressing dopamine D1 (D1R) (direct pathway) and/or D2 (D1R) receptors (indirect pathway), which leads to movement activation or suppression, respectively (Prensa et al., 2016). More medial to this, are the mesolimbic and mesocortical dopamine circuits (collectivelly, the mesocorticolimbic system (Hollerman et al., 2000)), arising from dopamine neurons originating in the VTA (Yokochi, 2007); these are involved numerous processes, including motivation and reward- and aversion- related cognition (mesolimbic pathway) (Gardner, 2011), as well as executive processes including attentional control (Floresco and Magyar, 2006), inhibitory control (Floresco and Magyar, 2006), working memory (Ott and Nieder, 2016), and cognitive flexibility (Floresco, 2013) (mesocortical pathway). The mesolimbic neurons project mainly to the nucleus accumbens (NAc), and the olfactory tubercle, but also the septum, amygdala, and hippocampus. The mesocortical neurons innervate almost the entire cortical mantle, with higher density in prefrontal, cingulate, motor and perirhinal cortices (Woodward et al., 2009; Zald et al., 2010). Although no segregation between the direct/indirect pathways based on D1R/D2R expression in the NAc has been described, D1 MSNs are assumed to mediate reward and reinforcement, and D2 MSNs, punishment and aversion (Cox et al., 2015; Soares-Cunha et al., 2016a). However, increasing evidence strongly suggests that the canonical view of this D1R signalling as pro-reward and D2R signalling as pro-aversive is too simplistic and should be revised (Soares-Cunha et al., 2016a). In fact, a very recent report furthered this discussion by demonstrating that activation and inhibition of only NAc D2 receptors increased and decreased motivation in rodents, respectively (Soares-Cunha et al., 2016b). Further studies fully exploring this dichotomy would certainly provide interesting insights about the precise neural mechanisms behind general and modality-specific processing of reward.

Five distinct G protein-coupled dopamine receptor subtypes exist (Zawilska, 2003): Two D1-like (D1A-1D and D5) activating adenylyl cyclase; and three D2-like (D2, D3, and D4) inhibiting adenylyl cyclase and activating K+ channels. D1-like receptors are more common than D2 receptors in the prefrontal cortex (PFC), whereas the opposite is true in the caudate nucleus, putamen, and NAc of humans (Hall et al., 1994). It is important to keep in mind that alternative splicing of D2R mRNA means that the same gene encodes two distinct isoforms of the same receptor, D2S and D2L, that have distinct functions *in vivo*: while D2L acts mainly at postsynaptic sites, D2S is a presynaptic autoreceptor (Ford, 2014).

Neurophysiological studies have shown dopamine can be transmitted in two modes: 'tonic' and 'phasic', both of which are highly regulated by cortical glutamatergic inputs and by striatal cholinergic and GABAergic inputs (Grace, 1991). In the 'tonic' mode, dopamine neurons maintain a steady baseline level of dopamine in downstream neurons, thought to target mostly D2-like receptors (as they seem to have higher affinity to dopamine) (Richfield et al., 1989). In phasic mode, dopamine neurons sharply increase or decrease their firing rates for 100–500 milliseconds, causing large changes in dopamine concentrations in downstream neurons lasting for several seconds (Zhang et al., 2009) and are thought to target mostly D1-like receptors (which have lower affinity to dopamine) (Grieder et al., 2012). However, recent studies show that high-affinity D2Rs are also activated by phasic dopamine bursts, which raises new possibilities to the actual contribution of the D2-MSNs pathway in the control of several behaviours (Marcott et al., 2014). Once released, dopamine diffuses in the extracellular fluid where it is then slowly cleared by reuptake (dopamine transporter −DAT- and D2 auto-receptor-driven cascade) and catabolism (mainly by Catechol-O-methyl-transferase − COMT and Monoamine Oxidase − MAO) (Ford, 2014; Kaakkola and Wurtman, 1992; Napolitano et al., 1995). Importantly, we note that much of our knowledge about the neurophysiology of dopamine comes from studies of the VTA-to-striatum pathways (Flagel et al., 2011). Considerably less is known about the function of phasic DA release in other regions, such as the prefrontal cortex (PFC). Indeed, we should not loose sight of important differences between striatal and frontal function. Significant regional differences are observed not only on dopamine's receptors distribution but also on signaling pathways: for example, compared with the striatum, the medial prefrontal cortex (mPFC) receives fewer DA projections (Descarries et al., 1987), expresses fewer DA reuptake transporters (Sesack et al., 1998), and exhibits an overall lower level of DA (Bassareo and Di Chiara, 1997). These differences are expected to lead directly to differential effects of dopaminergic drugs in these regions (Hernaus and Mehta, 2016).

We hereby systematically summarize and discuss all existing studies investigating how pharmacological manipulation of central dopamine signalling affects human reward-related behaviour and its neural correlates. We aim to facilitate an objective overview of such findings, by highlighting and analysing potential issues and limitations: 1) the considerable heterogeneity in measurement (e.g. in behavioural tasks used), 2) the heterogeneity in type and pharmacokinetics of the drugs employed and 3) their interaction with baseline genetic/cognitive inter-individual variables. The reviewed findings will be discussed in light of existing knowledge of the pharmacological and inter-individual determinants of neurobehavioral responses and conciliated with the current mechanistic frameworks of dopaminergic coding of reward in the brain. We hope our review can serve to: 1) speed up important nosological advances in reward neuroscience, 2) help researchers in the design of future studies; and 3) inspire the rationally informed design of neuropharmacological strategies to treat reward dysfunction in common neuropsychiatric disorders.

2. Methods

2.1. Search strategies

We followed the *PRISMA guidelines for systematic reviews* (Welch et al., 2012) to identify relevant studies for inclusion (Fig. 1). Initially, a first search round in *Medline* was used to identify the dopaminergic drugs that have been used in human experimental studies with drug manipulation, measuring reward appraisal and related behaviour, using the query: *"Dopamine* AND (*agonist* OR *antagonist* OR *precursor* OR *transporter* OR *metabolism)* AND *Reward*". A second search round was performed using the name of the drugs retrieved from the first search