Journal of Neurochemistry

JOURNAL OF NEUROCHEMISTRY | 2018 | 147 | 439–453 doi: 10.1111/jnc.14558

REVIEW

DARPP-32 in the orchestration of responses to positive natural stimuli

Simona Scheggi, Maria Graziella De Montis and Carla Gambarana

Department of Molecular and Developmental Medicine, University of Siena, Siena, Italy

Abstract

Dopamine- and cAMP-regulated phosphoprotein (M_r 32 kDa, DARPP-32) is an integrator of multiple neuronal signals and plays a crucial role particularly in mediating the dopaminergic component of the systems involved in the evaluation of stimuli and the ensuing elaboration of complex behavioral responses (e.g., responses to reinforcers and stressors). Dopamine neurons can fire tonically or phasically in distinct timescales and in specific brain regions to code different behaviorally relevant information. Dopamine signaling is mediated mainly through the regulation of adenylyl cyclase activity, stimulated by D1-like or inhibited by D2-like receptors, respectively, that modulates cAMP-dependent protein kinase (PKA) function. The activity of DARPP-32 is finely regulated by its phosphorylation at multiple sites. Phosphorylation at the threonine (Thr) 34 residue by PKA converts DARPP-32 into an inhibitor of protein phosphatase 1, while the phosphorylation at the Thr75 residue turns it into an inhibitor of PKA. Thus, DARPP-32 is critically implicated in regulating striatal output in response to the convergent pathways that influence signaling of the cAMP/PKA pathway. This review summarizes some of the landmark and recent studies of DARPP-32-mediated signaling in the attempt to clarify the role played by DARPP-32 in the response to rewarding natural stimuli. Particularly, the review deals with data derived from rodents studies and discusses the involvement of the cAMP/PKA/DARPP-32 pathway in: 1) appetitive food-sustained motivated behaviors, 2) motivated behaviors sustained by social reward, 3) sexual behavior, and 4) responses to environmental enrichment.

Keywords: dopamine, environmental enrichment, food, nucleus accumbens, sexual behavior, social stimuli.

J. Neurochem. (2018) **147**, 439–453.

Dopamine- and cAMP-regulated phosphoprotein-32 kDa (DARPP-32, also known as proteinphosphatase-1 regulatory subunit, PPP1R1B) was first identified as a major target of dopamine D1 receptor-activated adenylyl cyclase in dopaminoceptive neurons by Greengard and collaborators (Walaas and Greengard 1984). Over the last 30 years, DARPP-32 has been established to have a prominent role in mediating the biochemical, electrophysiological, transcriptional, and behavioral effects of dopamine. This review summarizes some of the relevant studies on DARPP-32-mediated signaling mainly in striatal medium spiny neurons (MSNs) and highlights the crucial role played by DARPP-32 in the integration of the responses to rewarding natural stimuli.

Dopamine and DARPP-32 signaling pathways

Brain dopaminergic circuit

Brain dopaminergic neuronal pathways play a critical role in multiple functions, including motor activation, cognition, emotion, reward, and response to stress. The main

Received June 1, 2018; revised manuscript received July 9, 2018; accepted July 16, 2018.

Address correspondence and reprint requests to Scheggi Simona, Department of Molecular and Developmental Medicine, University of Siena, Via A. Moro 2 53100 Siena, Italy. E-mail: scheggi9@unisi.it

Abbreviations used: AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; BOLD, blood-oxygen-level dependent; BP, breaking point; cAMP, cyclic adenosine monophosphate; Cdk5, cyclin-dependent kinase; CK1, casein kinase 1; CK2, casein kinase 2; CPu, caudate–putamen; DARPP-32, dopamine- and cAMP-regulated phosphoprotein-32 kDa; EE, environmental enrichment; FR1, fixed ratio 1; FR5, fixed ratio 5; GABA, γ-aminobutyric acid; HD, Huntington disease; icv, intracerebroventricular; KO, knock-out; LTD, long-term depression; LTP, long-term potentiation; mPFC, medial prefrontal cortex; MPOA, medial preoptic area; MSN, medium spiny neuron; NAcC, nucleus accumbens core; NAc, nucleus accumbens; NAcS, nucleus accumbens shell; NMDA, *N*-methyl-D-aspartic acid; PKA, cAMP-dependent protein kinase; PP-1, protein phosphatase-1; PP2A/B56™, protein phosphatase 2A regulatory subunit B 56δ; PP2A/PR72, protein phosphatase 2A regulatory subunit B PR72; PP2A, protein phosphatase 2A; PP2B, protein phosphatase 2B; PPP1R1B, proteinphosphatase-1 regulatory subunit; Ser, serine; SNP, single nucleotyde polimorphism; SN, substantia nigra; Thr, threonine; VCS, vaginal cervix stimulation; VTA, ventral tegmental area.

dopaminergic neuronal pathways arise from midbrain nuclei, ventral tegmental area (VTA), and substantia nigra (SN) that, through the medial forebrain bundle, project to several forebrain regions. The dopaminergic neurons in the SN project to the dorsal striatum (Caudate–Putamen, CPu) via the nigrostriatal pathway and are involved in the control of movement. Dopaminergic neurons in the VTA predominantly innervate the ventromedial striatum (nucleus accumbens, NAc), which acts as a limbic-motor interface (Mogenson *et al.* 1980). In a more contemporary view, the NAc function may be regarded as a filter mechanism that facilitates an efficient approach to reward-related stimuli (Floresco 2015). Midbrain dopaminergic neurons exhibit functional heterogeneity and operate in distinct modes with tonic and phasic pattern of activity to differentiate behaviorally relevant information (Schultz 2007). Tonic activity is sustained by dopaminergic discharge at low frequencies without bursts (Grace and Bunney 1984) and generates basal levels of dopamine (Grace 2016). Phasic burst firing induces greater extracellular dopamine release (Gonon 1988; Grace 1991; Floresco *et al.* 2003) and is elicited by salient inputs (Peoples and West 1996; Shi *et al.* 2000; Stuber *et al.* 2008; Tsai *et al.* 2009; Cacciapaglia *et al.* 2011). Accordingly, transient increases in extraneuronal dopamine levels are observed in the ventral striatum after exposure of animals to relevant stimuli (Yoshida *et al.* 1992; Cabib and Puglisi-Allegra 1994; Pfaus *et al.* 1995; Pontieri *et al.* 1995; Bassareo *et al.* 2002).

About 90% of striatal neurons are GABAergic MSNs expressing dopamine D1-like or D2-like receptors, while the remaining cells are large cholinergic and GABAergic interneurons (Meredith *et al.* 1993). The tonic activity of cholinergic interneurons expressing high levels of dopamine D2 receptors (Alcantara *et al.* 2003) regulates midbrain dopaminergic neurons firing (Threlfell *et al.* 2012) and studies performed in monkeys indicate that cholinergic interneurons participate in signaling reward-related events in close interaction with reward-related responses of dopaminergic neurons (Morris *et al.* 2004). MSNs sending projections to the basal ganglia output nuclei form part of the direct pathway, while MSNs sending projections to basal ganglia output nuclei via the globus pallidus external segment and the subthalamic nucleus form part of the indirect pathway. (Zahm 2000; Voorn *et al.* 2004). According to a canonical view, in the dorsal striatum the direct pathway is distinguished by the prevailing expression of dopamine D1 receptors along with dynorphin and substance P, while the indirect pathway by the predominant expression of dopamine D2 receptors and enkephalin (Gerfen *et al.* 1990; Surmeier *et al.* 2007). This organization has been considered more complex in the ventral striatum (Zahm 1989). Indeed, the NAc can be differentiated into at least two anatomically distinct regions, the core (NAcC) and the shell (NAcS), with different connectivity and functional properties (Zahm 2000; Voorn *et al.* 2004). The NAcC shows a more-striatal like organization. Recent studies show that the direct and indirect pathways are not strictly coded by the MSN cell type in the NAcC. While part of MSNs expressing dopamine D1-like receptors participate in a indirect pathway, targeting ventral pallidum neurons that send projections to the ventral mesencephalon, a portion of MSNs expressing dopamine D2-like receptors contribute to a direct pathway and synapse on ventral pallidum neurons that directly project to the thalamus (Kupchik *et al.* 2015; Kupchik and Kalivas 2017). Moreover, a similar organization has also been suggested in the dorsal striatum (Cazorla *et al.* 2014; Saunders *et al.* 2015). A division into direct and indirect pathway is even more difficult to define in the NAcS (Sesack and Grace 2010), where a higher expression of dopamine D3 receptors (Le Moine and Bloch 1996) and some degree of dopamine D1 and D2 receptors co-expression were reported (Surmeier *et al.* 2007; Bertran-Gonzalez *et al.* 2008), although the exact proportion of dopamine D1 and D2 receptors co-expression is still debated. Dopamine exerts its complex effects in MSNs acting on D1-like (D1 and D5) and D2-like (D2, D3, and D4) receptors, which regulate the cAMP-dependent protein kinase (PKA) cascade in opposite ways. A further level of complexity is suggested by the reported expression of dopamine receptor heteromers, with pharmacological properties distinct from those of individual receptors (Ferré *et al.* 2009; Frederick *et al.* 2015; Hasbi *et al.* 2018).

Dopamine in the NAc plays a crucial role in the acquisition and expression of appetitive responses and motivation (Montague *et al.* 2004). An increase in extracellular dopamine is thought to encode reward predictions, enhance reinforcement learning, and signal the motivational salience of a stimulus (see Schultz 2016 for review). In this context, the NAcS and NAcC have a different responsiveness to natural or pharmacological stimuli (Pontieri *et al.* 1995; Bassareo and Di Chiara 1999) and seem to play different roles in reward-related behaviors. The NAcS has been mainly implicated in encoding reward outcome and magnitude (Stopper and Floresco 2011; Saddoris *et al.* 2015; Sackett *et al.* 2017), while the NAcC is likely to have a major role in locomotor aspect of reward responses (Ito *et al.* 2004). However, so far, no data have shown a complete segregation of function between these two regions. Moreover, recent evidences suggest novel more complex views of the regulation of the neuronal circuitries involved in the processing and execution of motivated behaviors by ventral striatal outputs and sustain a crucial role of the ventral pallidum (Kupchik *et al.* 2015; Kupchik and Kalivas 2017).

Molecular properties of DARPP-32

In the striatum, DARPP-32 is expressed in the majority of MSNs, but not in the cholinergic and GABAergic interneurons (Ouimet *et al.* 1984). At the ultrastructural level,

DARPP-32 expression has been observed in the soma, both in the cytoplasm and nucleus, in dendrites and axon terminals (Ouimet and Greengard 1990).

The activity of DARPP-32 depends on the state of phosphorylation at multiple regulatory sites, including Thr34, Thr75, Ser97, and Ser130, and the phosphorylation pattern is dependent on the dynamic balance between activation of protein kinases and phosphatases. Phosphorylation at Thr34 by PKA converts DARPP-32 into an inhibitor of protein phosphatase-1 (PP-1) (Hemmings *et al.* 1984); phosphorylation at Thr75 by cyclin-dependent kinase 5 (Bibb *et al.* 1999) converts DARPP-32 in an inhibitor of PKA (Nishi *et al.* 2002). Additional sites on Ser97/102 or Ser130/137 (mouse and rat sequence, respectively) phosphorylated by casein kinase 2 and 1 (CK1), regulate DARPP-32 activity (Walaas *et al.* 2011).

Dopamine regulation of DARPP-32 phosphorylation pattern

DARPP-32 plays a pivotal role in dopamine transmission. Under basal conditions, DARPP-32 is mainly phosphorylated at Thr75, Ser97, and Ser130 residues (Nishi *et al.* 2017) and acts as a PKA inhibitor (Fig. 1a). Activation of the dopamine D1 receptor/PKA pathway increases phospho-Thr34 DARPP-32 levels, turning DARPP-32 into a PP-1 inhibitor, and stimulating the PKA-sensitive protein phosphatase 2A regulatory subunit B56δ (PP2A/B56δ) that, in turn, dephosphorylates the Thr75 and Ser97 residues (Fig. 1b). Dephosphorylation of the Thr75 residue relieves inhibition of PKA itself, thus amplifying dopamine D1 receptor transmission by a positive feedback loop. The phospho-Thr34 DARPP-32-mediated inhibition of PP-1 increases the levels of phosphorylation of several substrates and modulates the activity of some ion channels (Greengard *et al.* 1999; Svenningsson *et al.* 2004; Scheggi *et al.* 2009). In particular, dopamine D1 receptor activation increases the phosphorylation of NMDA NR1, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) GluR1 and $GABA_A$ β1/β3 subunits, resulting in increased AMPA and NMDA receptor-mediated currents and inhibition of $GABA_A$ receptor-mediated currents. Conversely, when phosphorylated at Thr75 by cyclin-dependent kinase, DARPP-32 antagonizes the PKA/phosphoThr34 DARPP-32/PP-1 cascade, reducing the efficacy of dopamine D1 receptor signaling through a negative feedback mechanism (Nishi *et al.* 2002).

Phospho-Thr34 DARPP-32 is mainly dephosphorylated by PP2B (calcineurin), activated by glutamate-induced increases in intracellular Ca^{2+} levels (Nishi *et al.* 2002); phospho-Thr75 and phospho-Ser97 DARPP-32 are mainly dephosphorylated by the heterotrimeric forms of PP2A PP2A/B56δ and Ca^{2+}-sensitive PP2A regulatory subunit PR72 (PP2A/PR72; Ahn *et al.* 2007; Nishi *et al.* 2002). Dephosphorylation of the Ser97 residue facilitates DARPP-32 nuclear translocation (Stipanovich *et al.* 2008) and nuclear accumulation would favor the phosphorylation of histone H3 at the Ser10 residue, a PP-1 dephosphorylation site. In this way, DARPP-32 could also have a role in the regulation of gene expression (Yger and Girault 2011), (Fig. 1b). DARPP-32 cytonuclear shuttling can also be regulated by glutamate through the influence on Ser97 phosphorylation levels.

Glutamate regulation of DARPP-32 phosphorylation pattern

Among the mechanisms that regulate DARPP-32 phosphorylation pattern, glutamate-induced increases in intracellular Ca^{2+} levels play a crucial role (Fig. 1c). As previously mentioned, activation of glutamate NMDA and AMPA receptors induces PP2B-mediated dephosphorylation of phospho-Thr34 DARPP-32 (Halpain *et al.* 1990). Thus, dopamine through D1 receptor activation and glutamate through NMDA/AMPA receptors/Ca^{2+}/PP2B activation seem to exert a mutual antagonistic regulation of phospho-Thr34 DARPP-32 levels (Nishi *et al.* 2005). Glutamate, through the influence on Ser97 phosphorylation levels, also controls the nuclear localization of dephospho-Thr34 and dephospho-Ser97 DARPP-32 (Fig. 1b). *In vitro* experiments on striatal neurons have recently revealed that dephosphorylation at the Thr34, Thr75, and Ser97 residues by PP2A/PR72 leads to nuclear accumulation of an inactive form of DARPP-32 (Nishi *et al.* 2017). Thus, glutamate transmission may counteract dopamine D1 receptor signaling also through this mechanism.

However, higher levels of complexity in the regulation of DARPP-32 function have been reported. Studies based on kinetic models suggest that DARPP-32 does not merely act as a molecular switch between PP-1 and PKA activity, but as a temporal integrator of dopamine and glutamate signals. In particular, the two signals can be integrated in a downstream response only if they are temporally close and occur in a defined order (dopamine after glutamate-calcium signal) (Fernandez *et al.* 2006). The temporal coincidence of these two stimuli potentiates the increase in phospho-Thr34 DARPP-32 levels (Lindskog *et al.* 2006), represents a switch for inducing long-term depression or long-term potentiation, and is crucial for synaptic plasticity and reinforcement learning (Nakano *et al.* 2010; Qi *et al.* 2010; Nair *et al.* 2016).

Altogether, DARPP-32 appears as a sensitive hub of neuronal inputs different in terms of source, amplitude, and timescale, able to integrate and convey biochemical, cellular, and physiological signals by changing the functional state of ion channels, influencing transcription factors levels, down-regulating genes, modifying reward processing, and motor activity. Moreover, thanks to its fine-tuned mechanisms of regulation, DARPP-32 contributes to enhance the reliability of signaling processes and increase the signal/noise ratio in MSNs that receive dense innervation and direct inputs from multiple regions (Barbano *et al.* 2007).

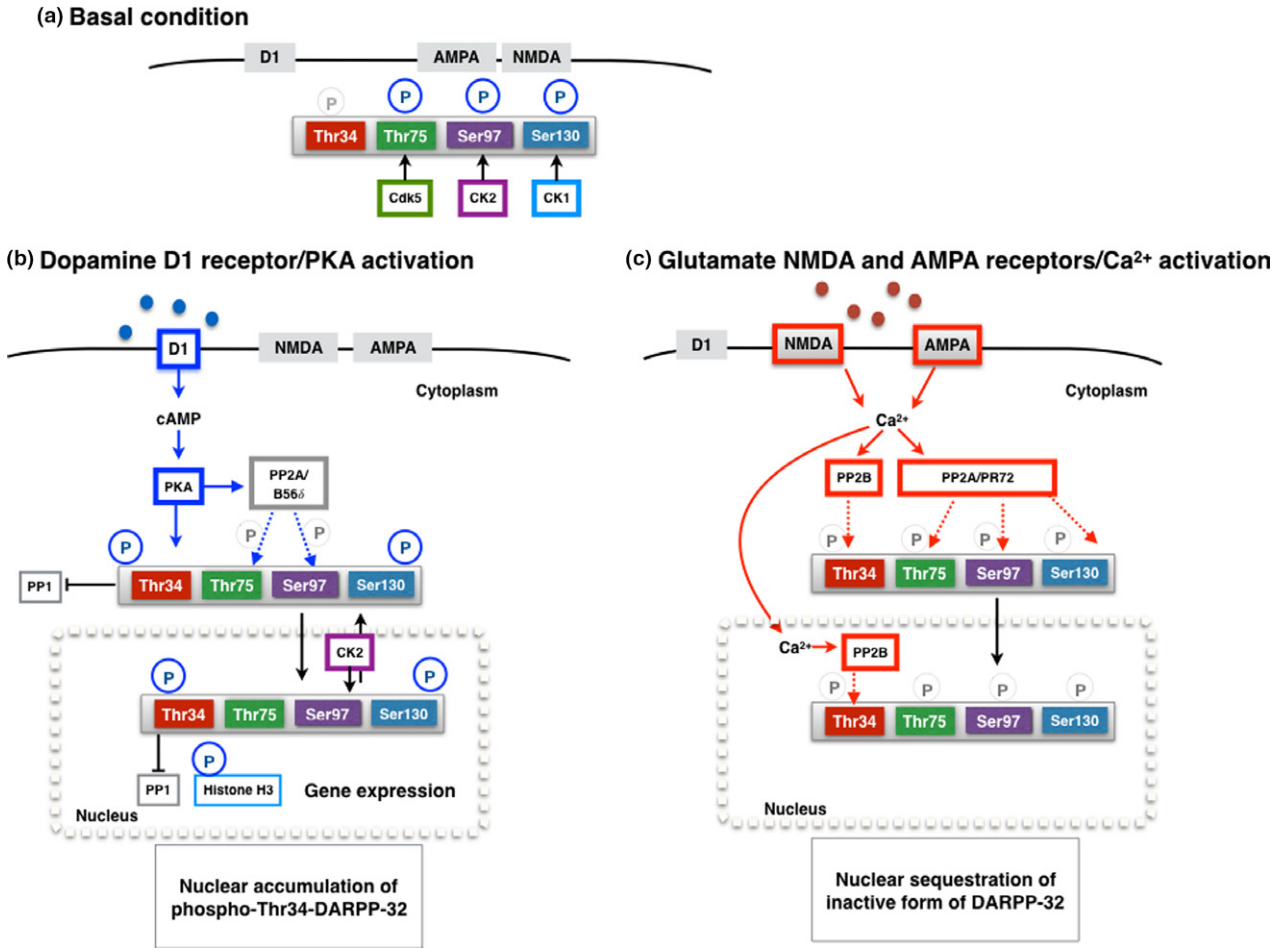

Fig. 1 DARPP-32 phosphorylation pattern in basal conditions, and after activation of dopamine D1 or ionotropic glutamate receptors. (a) Under basal conditions, DARPP-32 is mainly phosphorylated at Thr75 by cyclin-dependent kinase 5 (Cdk5), at Ser97 by casein kinase (CK) 2 and at Ser-130 by CK1. (b) Dopamine D1 receptor stimulation induces DARPP-32 phosphorylation at Thr34 by cAMP-dependent protein kinase (PKA) and dephosphorylation of Thr75 and Ser97 by PP2A/B56δ. The phosphorylation at Thr34 leads to inhibition of protein phosphatase-1 (PP1). Dephosphorylation of Ser97 facilitates phospho-Thr34 DARPP-32 nuclear localization, which favors inhibition of nuclear PP1, phosphorylation of histone H3, and transcriptional activation. (c) Ionotropic glutamate receptors stimulation increases intracellular calcium levels that induce dephosphorylation of Thr34 by PP2B, and Thr75, Ser 97, and Ser 130 by PP2A/PR72. Dephosphorylation of Ser97 facilitates DARPP-32 nuclear export but since DARPP-32 is dephosphorylated at Thr34, this leads to nuclear accumulation of an inactive form of DARPP-32.

Natural rewards, dopamine transmission, and DARPP-32 phosphorylation in mesolimbic areas

Natural reinforcers, such as food, water, and a receptive sexual partner, are key stimuli for the survival of the individual and the species and activate the neuronal pathways that code for reward and motivation.

1) Appetitive drive and dopaminergic responses

Food intake is influenced by multiple and coordinated interactions between brain areas that regulate homeostatic signals and circuits involved in reinforcement and motivational drive. Homeostatic signals provide information related to caloric and nutritional requirements and are coordinated mainly by hypothalamic nuclei via regulatory neuropeptides and through the sensing of nutrients (Volkow *et al.* 2011). However, homeostatic signals can be overridden by inputs arising from reward circuits that could promote food intake even in the absence of metabolic needs. Highly caloric foods rich in sugars are potent natural rewards and their consumption may become disengaged from homeostatic control (Lenoir *et al.* 2007), and sweet-dense food and beverages may have addictive properties in humans. Among natural reinforcers, food is often used in order to elicit responses that are easily investigated in experimental animals and humans.

Food consumption and DARPP-32 phosphorylation pattern

In rodents, palatable food consumption induces a phasic increase in extraneuronal dopamine levels in mesolimbic areas that confer incentive salience to it (Berridge 2007). The ingestion of a food of unexpected palatability induces in rats a consistent dopaminergic response in the NAcS, NAcC, and medial prefrontal cortex (mPFC) in terms of increased extraneuronal dopamine levels (Bassareo and Di Chiara 1999). In the NAcS, but not in the NAcC or mPFC, this response undergoes rapid adaptive regulation and blunted increases in dopamine levels are observed with repeated exposure to the same palatable stimulus. Thus, it has been proposed that the transient dopaminergic response in the NAcS represents the integration of motivational valence and novelty of the stimulus, and may be involved in associative learning, while in the NAcC or mPFC it encodes a generic motivational value (Bassareo *et al.* 2002). Administration of a dopamine D1 receptor antagonist impairs learning of conditioned taste aversion to a palatable food able to elicit a transient increase in NAcS dopamine levels (Fenu *et al.* 2001). Consistent with these findings, dopamine D1 receptor-PKA-DARPP-32-dependent signaling is affected by palatable food consumption (Gambarana *et al.* 2003; Rauggi *et al.* 2005; Danielli *et al.* 2010). In non-food-deprived rats, the first consumption of palatable sweets, independently of the caloric content (i.e., sucrose or saccharin), triggers a sequence of changes in DARPP-32 phosphorylation pattern in the NAcS. In fact, levels of phospho-Thr34 DARPP-32 increase 30 min after sweets consumption and decrease at 2–3 h, when phospho-Thr75 DARPP-32 levels increase (Rauggi *et al.* 2005; Danielli *et al.* 2010; Scheggi *et al.* 2013). Repeated exposure to the same palatable food elicits blunted dopaminergic responses in terms of dopamine levels and modifications in DARPP-32 phosphorylation pattern (Bassareo and Di Chiara 1999; Gambarana *et al.* 2003; Danielli *et al.* 2010), (Fig. 2 a-c). However, when rats are subjected to an acute mild food deprivation (a 18-h fast), re-exposure to the same palatable food still elicits the dopaminergic responses (Danielli *et al.* 2010; Scheggi *et al.* 2013). Intriguingly, in this condition of mild food deprivation a second consumption of saccharin does not induce significant changes in extraneuronal dopamine levels and DARPP-32 phosphorylation pattern in the NAcS, while changes are observed after the first and second consumption of standard caloric food (Danielli *et al.* 2010; Scheggi *et al.* 2013), (Fig. 2d–g). These results on changes in DARPP-32 phosphorylation pattern in response to palatable food in conditions of satiety or mild caloric deficit suggest that the phenomenon of blunted dopaminergic response ('habituation') in the NAcS may signal an unnecessary food stimulus. Thus, in the absence of a caloric need changes in DARPP-32 phosphorylation pattern could transiently signal the value of food represented by palatability and novelty, while in a condition of food deprivation they signal the primary biological value of the food stimulus that is its caloric content, and this response is maintained after repeated consumption. In line with this hypothesis, the dopaminergic responses in the NAcS seem to correlate with the motivation to operate in order to obtain the food. In experiments of sucrose or saccharin self-administration on a progressive ratio schedule of reinforcement, rats are trained to press a lever at progressively increasing rate to obtain the reinforcer and the value that represent the maximal effort exerted, defined breaking point (BP), is considered an index of motivation (Hodos 1961). Non-food-deprived rats show lower BP scores than fasted rats when sucrose is the reinforcer; conversely, when saccharin is the reinforcer, non-food-deprived and fasted rats show similar BP scores (Scheggi *et al.* 2013) (Fig. 2h). Thus, the motivation to operate for a food reward in the absence of caloric deprivation is mainly controlled by palatability and correlates with transient modifications in dopamine levels and DARPP-32 phosphorylation pattern in the NAcS, while during fasting it is dependent on the caloric content of the food stimulus and correlates with the dopaminergic responses elicited (Fig. 2d–h).

The hypothesis that in non-food-deprived rats changes in DARPP-32 phosphorylation pattern are related to the motivation to pursue palatable food as a positive reinforcer is also indirectly supported by the results obtained in a rat model of depressive symptoms. Exposure to a chronic stress protocol abolishes in non-food-deprived rats the NAcS dopaminergic responses to palatable food consumption (Marchese *et al.* 2013). We investigated whether differences in DARPP-32 phosphorylation pattern had a behavioral correlate that is whether they would consistently segregate with differences in motivation to operate for the positive stimulus. Indeed, stress exposure disrupts lever pressing for sucrose and repeated treatments that restore in stress-exposed rats the NAcS dopaminergic responses to sucrose also reinstate operant responding for it, while treatments that do not restore the NAcS responses to sucrose do not reinstate the motivation to operate for it (Grappi *et al.* 2011; Scheggi *et al.* 2011, 2015, 2016, 2017; Marchese *et al.* 2013). Further support for a role of DARPP-32 phosphorylation changes in the integration of signaling that underlies responses to the food stimulus comes from conditioned taste aversion experiments, in which sucrose consumption is paired to a negative stimulus. In this condition, DARPP-32 phosphorylation pattern is unmodified, suggesting that it translates appetitive motivation, but it is likely not crucial in aversive associative learning (Marotta *et al.* 2014).

DARPP-32 phosphorylation in food-sustained operant behavior

Increases in dopaminergic transmission in animals that perform food-sustained instrumental behaviors have been reported as increases in dopamine levels in striatal areas

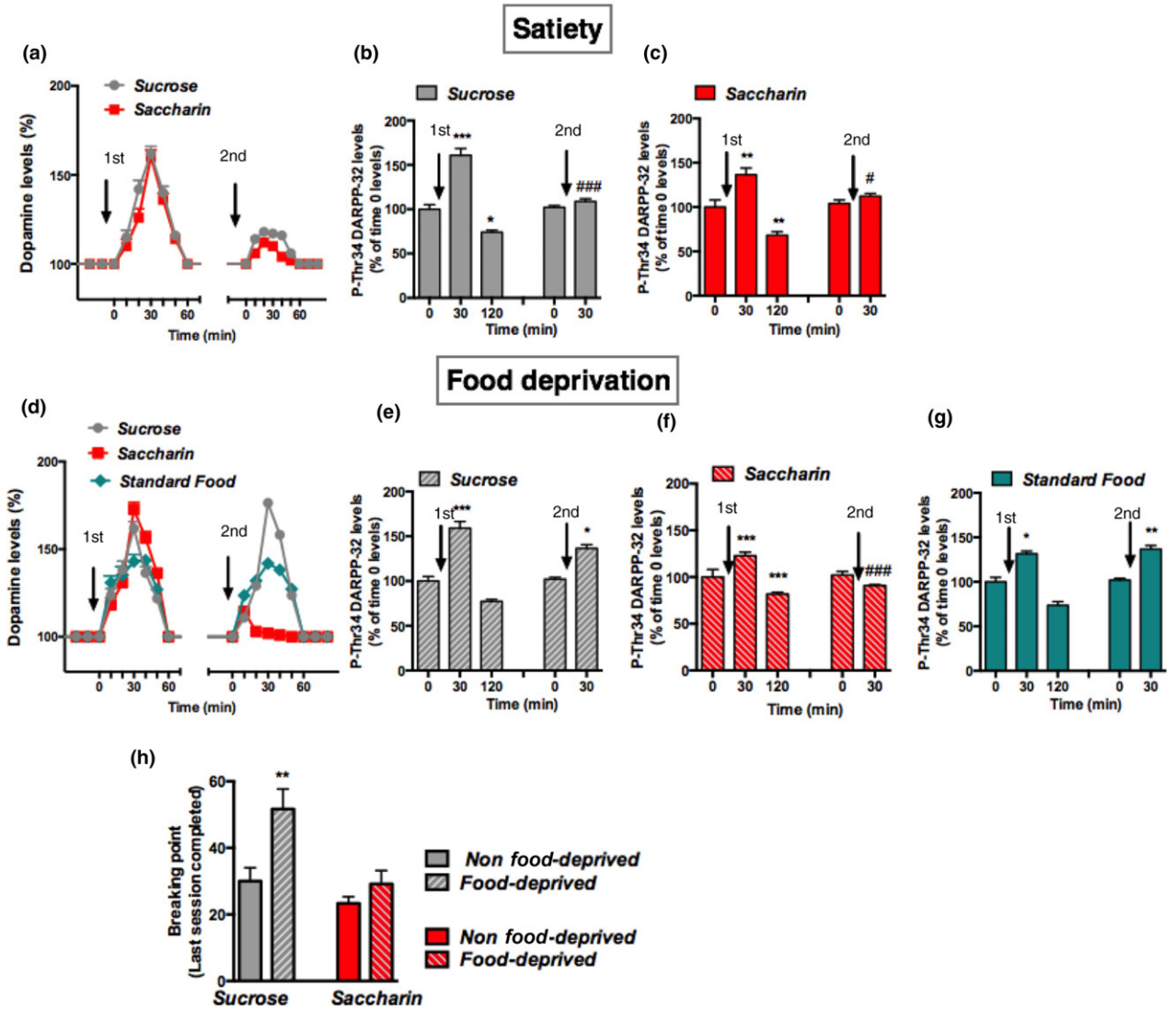

Fig. 2 Dopamine levels and DARPP-32 phosphorylation in the NAcS in response to repeated food consumption and appetitive motivation in rats. (a and d) *Extraneuronal dopamine levels.* In non-food-deprived rats (Satiety), dopamine levels increase after the first but not the second consumption of palatable sweets (a). In 18-h food-deprived rats (food deprivation), dopamine levels increase after the first consumption of sucrose, saccharin, and standard food but after the second consumption only caloric foods (sucrose or standard food) elicit a dopaminergic response (d). (b, c, e, f and g) *Time-dependent changes in DARPP-32 phosphorylation levels.* In non-food-deprived rats the first consumption of sucrose (b) or saccharin (c) triggers a sequence of early and delayed changes in Thr34-DARPP-32 phosphorylation levels, while no changes are observed upon re-exposure to the same palatable stimulus ($^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ vs. time 0 levels; $^{\#}p < 0.05$, $^{\#\#\#}p < 0.001$ vs. 1st time 30 min levels, Bonferroni's test). In 18-h food-deprived rats, Thr34-DARPP-32 phosphorylation levels are modified by re-exposure to sucrose (e) or standard food (g), while no changes are observed upon re-exposure to saccharin (f). (h) *Responding for palatable food on a progressive ratio schedule of reinforcement.* When sucrose is the reinforcer, non-food-deprived rats show breaking point (BP) scores markedly lower than fasted rats ($^{**}p < 0.01$, Bonferroni's test); when saccharin is the reinforcer, non-food-deprived and fasted rats show similar BP scores. (Modified from Scheggi *et al.* 2013).

(Sokolowski *et al.* 1998; Ostlund *et al.* 2011; Segovia *et al.* 2011), VTA dopamine neurons firing (Kosobud *et al.* 1994), and phasic dopamine release in the NAc (Cacciapaglia *et al.* 2011). The hypothesis that DARPP-32 signaling is involved in encoding and strengthening the valence and motivational value of food is supported by the phosphorylation changes observed in the NAc subregions at different stages of food self-administration in rats (Segovia *et al.* 2012). Food-restricted rats trained to self-administer standard food that is working to maintain an homeostatic caloric balance, in the transition from the fixed ratio (FR) 1 schedule (1 response – 1 reward) to the fixed ratio 5 (FR5) schedule that requires a

higher effort level (5 responses – 1 reward), show higher dopamine release on the first FR5 training day in the NAcS and on the second FR5 training day in the NAcC (Segovia *et al.* 2011). In line with these observations, phospho-Thr34-DARPP-32 expression is increased on the first FR5 training day in the NAcS, while its expression is increased on the second FR5 training day in the NAcC; in rats exposed to extended FR-5 training increases in phospho-Thr34-DARPP-32 levels are mainly observed in dorsal striatum (Segovia *et al.* 2012). The fact that phosphorylation changes occur with a subregion-specificity in the transition from FR1 to FR5 confirms that modifications in DARPP-32 phosphorylation pattern may mediate motivation and behavioral activation, with the NAcS and NAcC playing different roles in the response to positive stimuli (Corbit *et al.* 2001; Corbit and Balleine 2011) and the dorsolateral striatum being primarily involved in the process of habit formation (Furlong *et al.* 2014). Moreover, when food-restricted rats have the choice between obtaining a carbohydrate-rich food on a progressive ratio schedule or eating the standard food available on the cage, variability in individual responses is observed. Two populations of rats can be identified, one showing high levels of lever pressing with relative low standard diet consumption (high responders) and one showing low levels of lever pressing with high standard diet consumption (low responders) (Randall *et al.* 2012). Phospho-Thr34-DARPP-32 expression is higher in the NAcC of high responders compared to low responders (Randall *et al.* 2012), suggesting that NAcC dopamine transmission and dopamine D1 receptor signal transduction are related to the effort spent.

The possible involvement of DARPP-32 in operant responding for food stimuli has also been studied taking advantage of mutant mouse lines. The first studies used DARPP-32 knock-out mice, which likely have non-selective impairments in their behavioral repertoire. Food-restricted DARPP-32 knock-out mice acquire a food-reinforced operant task (Heyser *et al.* 2000; Risinger *et al.* 2001). However, they exhibit impaired reversal learning, suggesting that DARPP-32 is involved in the processes underlying learning and memory (Heyser *et al.* 2000). The involvement of DARPP-32 in food-directed instrumental behavior has also been studied using a knock-in mouse line carrying a Ser-97 to alanine (S97A) point mutation in the DARPP-32 sequence (S97A-DARPP-32 mouse) that is characterized by inhibition of DARPP-32 cytonuclear shuttling (Stipanovich *et al.* 2008). In mildly food-deprived wild-type mice, earning food in self-administration protocols triggers phospho-Thr34 DARPP-32 nuclear accumulation in the dorsal striatum, NAcS, and NAcC. This effect is mediated by dopamine D1 receptor stimulation and influences phosphorylation of nuclear proteins, such as histone H3 (Stipanovich *et al.* 2008). In S97A-DARPP-32 mice, the motivation to operate for food, measured as BP, is reduced, while learning is normal (Stipanovich *et al.* 2008). Interestingly, levels of phosphorylation of Thr34 DARPP-32 and DARPP-32-dependent proteins are reduced in these mice. These results suggest the involvement of DARPP-32 in mediating transcription-dependent long-term plasticity and reward learning elicited by increased dopamine D1 receptor transmission.

In summary, there are evidences for a correlation between changes in DARPP-32 phosphorylation pattern in the NAcS that imply changes in its functional activity and the consumption of foods with different characteristics (palatable or standard, with or without caloric content) by animals in different physiological states (food-deprived or non-food-deprived). The modifications in DARPP-32 phosphorylation pattern observed seem to correlate with the motivation to operate for the food stimuli. However, experiments aimed at demonstrating that modifications in DARPP-32 phosphorylation pattern play a necessary role in the motivation to operate for food, in particular for a palatable food in rats that do not have a homeostatic caloric drive, are warranted. In fact, the majority of studies on DARPP-32 and food-sustained instrumental behavior used food-restricted rats or mice that operate for standard food in a condition of caloric deficit and are subjected to different tasks before sacrifice. Moreover, often total DARPP-32 expression levels and/or its phosphorylation at only one site have been analyzed.

2) Social rewards and DARPP-32 phosphorylation pattern

Social behavior is subserved by high cognitive functions and is fundamental to improve survival in dynamic and complex environments. The ability to procreate and raise the offspring, engage in, and manage relationships requires successful social interactions with peers. Evidence from animal and human studies indicates that socioemotional stimuli are processed in the same brain areas involved in reward and motivation. In particular, maternal care, social play behavior, and sexual behavior are highly rewarding for humans (Izuma *et al.* 2008; Spreckelmeyer *et al.* 2009) and animals (Trezza *et al.* 2011) since they induce a condition of well-being, pleasure, motivation, and associative learning (Berridge and Kringelbach 2008). Their relevance is evident in psychiatric disorders like autism and schizophrenia where difficulties in establishing social interactions are core symptoms of the disease (Couture *et al.* 2006; Chevallier *et al.* 2012).

Maternal care and social behaviors in animals

Nursing and maternal care are among the most primal social interactions in mammals and the oxytocin-mesolimbic dopamine systems play a relevant role in their expression (Pedersen *et al.* 1994; Numan and Sheehan 1997). In lactating dams, the interaction with pups induces an increase in the NAcS dopamine signal (measured by voltammetry) that is particularly pronounced in high-licking/grooming mothers, and is accompanied by increased levels of

dopamine D1 and D3 receptors in the same brain region (Champagne *et al.* 2004). A further support for the role of mesolimbic dopamine transmission in maternal behavior comes from studies linking maternal neglect (among other mechanisms) to a dysregulation of dopamine transmission that impairs the normal ability of the mother to experience hedonic reward from caring for the offspring (Numan 2007). In this context, a naturally neglectful mouse line characterized by little or no care of the offspring displays increased phospho-Thr34 DARPP-32 levels in the NAc and CPu at baseline (Gammie *et al.* 2008). The modified DARPP-32 phosphorylation pattern could impair the responsiveness to significant stimuli during maternal–pups interactions, leading to neglect. The increase in phospho-Thr34 DARPP-32 observed in the striatum of neglectful mothers in comparison to nurturing dams has been related to an altered steroid signaling; however, neglect could also be the result of hyperactive/impulsive and inattentive behavior in the neglectful mothers (Gammie *et al.* 2008).

Several studies indicate that social behavior is a natural reward and the activation of NAc dopamine D1 receptors is one important mechanism involved. In single-housed male rats, a brief interaction with a conspecific induces an increase in the release of extracellular dopamine in the NAc (Robinson *et al.* 2002, 2011), and social interaction in mice elicits increased activity of VTA dopamine neurons (Gunaydin *et al.* 2014). In mice, optogenetic activation of the VTA dopamine neurons projecting to the NAc increases social interaction and this increase is prevented by the infusion of a dopamine D1 receptor-antagonist in the NAc. In addition, optogenetic enhancement of dopamine D1 signaling restores social interaction and hedonic behaviors disrupted by chronic social defeat stress, while chemogenetic inhibition of VTA dopamine neurons projecting to the NAc increases depressive-like behaviors (Francis *et al.* 2015). In mice exposed to chronic social defeat stress, levels of total DARPP-32 and phospho-Thr34 and Thr75-DARPP-32 are increased in the mPFC and amygdala (Jin *et al.* 2015), although the exact mechanisms and functional relevance of these modifications are yet to be elucidated.

Role of PPP1R1B gene in the response to social stimuli in humans

In humans, the processing of social stimuli, such as attractive faces, positive emotional expressions, social reputation, or monetary reinforcers, is able to activate the reward circuitry in the ventral striatum and orbitofrontal cortex (Aharon *et al.* 2001; Izuma *et al.* 2008; Rademacher *et al.* 2010). The possible role of DARPP-32 in regulating reward circuits in response to social cues in humans has been indirectly explored taking advantage of genetic analysis. DARPP-32 is encoded by the *PPP1R1B* gene in humans and there is evidence that genetic variations in *PPP1R1B* affect DARPP-32 mRNA levels and neuronal connectivity. Studies performed in post-mortem brains associated the major alleles G, T, and A at three SNPs (rs879606, rs907094, and rs3764352, respectively) to higher DARPP-32 mRNA expression in the dorsolateral prefrontal cortex (Meyer-Lindenberg *et al.* 2007). Moreover, carriers of these genetic variations of *PPP1R1B* associated to higher DARPP-32 mRNA levels display greater activation of frontostriatal circuits (Meyer-Lindenberg *et al.* 2007), better performance in tests of episodic memory (Persson *et al.* 2017b), and increased functional connectivity between the prefrontal cortex, CPu, and hippocampus during associative emotional learning tasks (Ćurcić-Blake *et al.* 2012). These data suggest that genetic variations in *PPP1R1B* play a role in the modulation of cognitive processes (Meyer-Lindenberg *et al.* 2007) and associative emotional learning (Ćurcić-Blake *et al.* 2012). Further studies evaluating changes in blood-oxygen-level dependent activation show a correlation between *PPP1R1B* genetic variations (rs879606, rs907094, and rs3764352) and the response to socially relevant stimuli (Persson *et al.* 2017a). In fact, carriers of these haplotypes that have been associated to higher expression of DARPP-32 display increased functional connectivity in cortical-subcortical circuits in dorsal prefrontal cortex, fusiform gyrus, and the midbrain in response to happy faces, while no association was observed between genetic variations and the responses to angry faces (Persson *et al.* 2017a). Moreover, genetic variations in *PPP1R1B* may also affect reinforcement learning (Frank *et al.* 2007, 2009) and predict choice bias as a function of expected value (Cockburn *et al.* 2014), influencing individual differences on motivated behavior. Thus, although current results in humans are still limited, the data on *PPP1R1B* genetic variants seem to suggest that DARPP-32 plays a role in the response to social reward signaling cues.

3) Sexual behavior and DARPP-32 phosphorylation pattern

Mating or vaginal cervix stimulation (VCS) induces in rodents several responses including progesterone release and facilitation of lordosis, the characteristic posture that permit mating to occur. VCS induces lordosis in estrogen primed rats, even in the absence of progesterone and this progesterone-independent, but progestin receptor-dependent, effect has been ascribed to dopamine that is released in several brain areas (e.g., the NAc, CPu, and ventromedial hypothalamus) after mating or VCS (Foreman and Moss 1979; López and Carrer 1982; Pfaus *et al.* 1995). Moreover, in ovariectomized, estrogen-primed rats, lordosis is induced by the intracerebroventricular (icv) administration of a dopamine D1 receptor agonist that also increases phospho-Thr34 DARPP-32 positive cells in the medial preoptic area (MPOA), caudal ventromedial hypothalamic nucleus, posterodorsal medial amygdala, and bed nucleus of stria terminalis (Meredith *et al.* 1998). These brain regions, crucial for the hormonal regulation of sexual behavior, are

rich in estradiol-induced progestin receptors. The facilitatory effect of dopamine D1 receptor agonists on female sexual behavior can be blocked by progesterone antagonists (Mani *et al.* 1994). In ovariectomized, estradiol-primed rats both progesterone and dopamine facilitate the expression of female sexual behavior and these effects are consequent to the increased cAMP/PKA/phospho-Thr34 DARPP-32 signaling in the medial basal hypothalamic nuclei (Mani 2000). The progesterone and dopamine facilitatory effect on sexual receptivity in female rats and mice is blocked by infusion of antisense oligonucleotides to DARPP-32 (Mani 2000; Frye and Walf 2010), suggesting that DARPP-32 phosphorylation may be a necessary step in progestin receptor regulation of sexual receptivity. Furthermore, homozygous mice carrying a null mutation for the DARPP-32 gene exhibit a reduction in progesterone-facilitated sexual receptivity in comparison to their wild-type littermates (Mani 2000). The progesterone-induced activation of PKA and the increase in cAMP levels in the hypothalamus of female rats is not prevented by the icv administration of a dopamine D1 receptor antagonist, suggesting that these effects do not require a modulation of dopamine receptors by progesterone (Mani 2000). Dopamine through the PKA-mediated DARPP-32 phosphorylation modulates the activation of nuclear progesterone receptors by a ligand-independent mechanism. Thus, reproductive behavior in female rodents can be modulated by the cross talk between signaling mediated by the intracellular progesterone receptors and the G protein-coupled dopamine D1 receptors (Mani 2000; Mani and Blaustein 2012).

Dopamine has a facilitatory role also in male sexual behavior (reviewed by Melis and Argiolas 1995; Giuliano and Allard 2001). Dopamine agonists in rodents promote mount and copulatory behaviors, while dopamine antagonists inhibit sexual motivation (Hull *et al.* 1995; Phillips-Farfán and Fernández-Guasti 2009; Simonsen *et al.* 2016). Dopamine levels increase in the NAcS in response to odors emitted by estrus female and during copulation (Pfaus *et al.* 1990; Wenkstern *et al.* 1993; Fumero *et al.* 1994). In addition, extraneuronal dopamine increases before copulation in the MPOA, a crucial region in the regulation of male sexual behavior, and this increase is likely associated to sexual drive (Hull *et al.* 1995; Dominguez and Hull 2005). Copulation induces an increase in phospho-Thr34-DARPP-32 levels specifically in the MPOA of previously sexually experienced male rats, suggesting that in this region DARPP-32 phosphorylation is involved in mediating sexual learning. Thus, the dopamine D1 receptor/PKA/DARPP-32 signaling seems to be important in male rats for the experience-induced consolidation of sexual behavior (McHenry *et al.* 2012). Conversely, in female rats, phospho-Thr34 DARPP-32 levels increase only after the first VCS, suggesting sex differences in the phosphorylation response to sexual cues.

4) Environmental enrichment and DARPP-32 phosphorylation pattern

Environmental enrichment (EE), originally defined as a combination of complex inanimate and social stimulation (Rosenzweig *et al.* 1978), exerts deep effects on behavior, brain development and plasticity (Sale 2018). Rodents maintained in EE conditions are housed in cages larger than standard cages that allow physical activity and formation of social groups and they are provided with inanimate objects that are periodically changed or moved around the cage. A large number of studies performed in rodents showed that, at a behavioral level, EE improves spatial and non-spatial learning and memory (van Praag *et al.* 2000; Nithianantharajah and Hannan 2006), reduces anxiety and increases exploratory activity (Fernández-Teruel *et al.* 2002; Galani *et al.* 2007; Harati *et al.* 2013), induces antidepressant-like effects, and decreases cocaine self-administration (Green *et al.* 2010). However, all these effects are not consistently observed, perhaps because of the different EE protocols used across studies (Rogers *et al.* 2017). EE protocols may differ for the developmental age in which they are applied, their duration, the introduction of running wheels as sources of physical activity. EE-related behavioral effects are accompanied at the anatomical level by robust increases in neurogenesis, axonal sprouting, and dendritic arborization, particularly in the hippocampus (Hebb 1949; Diamond *et al.* 1972; Greenough and Volkmar 1973; van Praag *et al.* 2000; Nithianantharajah and Hannan 2006). At the molecular level, EE affects the expression of genes involved in synaptic function (Rampon *et al.* 2000), levels of neurotrophic factors, thus perhaps modulating neuronal plasticity (Pham *et al.* 1999; Young *et al.* 1999), and signaling pathways of different neurotransmitters, including dopamine. EE seems to produce long-lasting functional changes in mesolimbic dopamine transmission that may contribute to protective effects on vulnerability to drugs of abuse (Darna *et al.* 2015). In particular, EE has been associated with decreased dopamine D1 receptor expression in PFC and striatum (Del Arco *et al.* 2007; Gill *et al.* 2013) and down-regulation of the dopamine transporter in PFC (Kim *et al.* 2016). Moreover, in rats exposed to EE, reduced baseline levels of phospho-Thr34 DARPP-32 have been reported in PFC and interpreted as the result of a modified balance between dopamine D1 receptor- and NMDA receptor-mediated signaling (Gomez *et al.* 2012).

A role for DARPP-32 and its interaction with adducins in the response to environmental factors has been proposed. The molecular and cellular mechanisms underlying EE effects are not fully elucidated and modifications in DARPP-32 phosphorylation pattern have been proposed to mediate EE effects by interaction with adducins. Adducins are actin-capping proteins that stabilize the cortical cytoskeleton and regulate synaptic stability (Engmann *et al.* 2015). In particular, β-adducin is essential for the stability of dendritic spines and is involved in learning and memory processes through the regulation of actin- and spectrin-based

Table 1 DARPP-32 involvement in responses to natural positive stimuli

Type of natural stimulus	Potential roles	References
Food	Encoding the value of food in rats	Rauggi *et al.* (2005), Danielli *et al.* (2010), Scheggi *et al.* (2013)
	Different facets of motivation in mice and rats	Stipanovich *et al.* (2008), Segovia *et al.* (2012), Randall *et al.* (2012), Scheggi *et al.* (2015, 2016, 2017)
Social interaction	Maternal behavior in mice	Gammie *et al.* (2008)
	Emotional associative learning in humans (indirect evidence)	Meyer-Lindenberg *et al.* (2007), Curcik-Blake *et al.* (2012), Persson *et al.* (2017a,b)
	Reinforcement learning in humans (indirect evidence)	Frank *et al.* (2007, 2009), Cockburn *et al.* (2014)
Sexual partner	Sexual receptivity in female rodents	Meredith *et al.* (1998), Mani (2000), Frye and Walf (2010)
	Experience-induced enhancement of sexual behavior in male rats	McHenry *et al.* (2012)
Enriched environment	Neural plasticity and dendritic spines remodeling in mice and rats	Engmann *et al.* (2015)
	Reduction of cognitive deficits and depressive-like symptoms in Huntington's Disease mouse models	Spires *et al.* (2004), Bibb *et al.* (2000), Dellen *et al.* (2000)

synapse formation (Bednarek and Caroni 2011; Pielage *et al.* 2011). In mice striatum, phospho-Thr75 DARPP-32 promotes the phosphorylation of the Ser713 residue of β-adducin and this modification prevents β-adducin interaction with actin and spectrin, destabilizing the cytoskeleton of spines and dendrites. This destabilization seems to be crucial for synaptic plasticity to occur and may explain the rapid effects of EE on dendritic spines of NAc neurons. Thus, DARPP-32 could have an important role in regulating striatal MSN activity also by modulating β-adducin function and, consequently, new spine formation.

Studies in rodents have increased our knowledge of the influence of gene–environment interactions on the plasticity of the normal brain and may further the understanding of the possible relevance of these interactions in the dysfunctional brain. EE-induced enhanced neuronal plasticity could be beneficial for some neurological disorders, such as Alzheimer, Huntington, Parkinson diseases (Nithianantharajah and Hannan 2006). In particular, EE behavioral and neurochemical effects, including those on dopamine D1 receptor/DARPP-32 signaling pathway, have been extensively studied in transgenic mouse models of Huntington disease (HD). EE has been shown to delay disease progression in HD models improving motor symptoms and reducing cognitive deficits (Dellen *et al.* 2000; Hockly *et al.* 2002). Deficits in HD mice may be underpinned by an impairment in dopamine D1 receptor signaling, as reduced levels of dopamine D1 receptors, DARPP-32, and other markers of the dopaminergic signaling cascade have been reported in striatal and cortical areas (Bibb *et al.* 2000; Spires *et al.* 2004). Thus, it is of interest that EE rescues in HD mice the reduced cortical levels of DARPP-32 (Bibb *et al.* 2000) that, by altering monoaminergic signaling, may contribute to the dysfunctions characteristic of HD models (Bibb *et al.* 2000; Dellen *et al.* 2000). The restored DARPP-32 expression levels in the frontal cortex of HD mice exposed to EE may contribute to the reduction of cognitive deficits and symptoms of psychiatric-like conditions.

Concluding remarks

This review provides an overview on the role of DARPP-32 signaling cascade in the integration of the responses to natural reinforcing stimuli, with a focus on food as a natural reinforcer (Table 1). DARPP-32 is largely conserved across vertebrates (Ung and Teoh 2014) and its pathway is involved in physiological functions and pharmacological responses. A dissection of DARPP-32 role in specific physiological responses would greatly benefit of sophisticated animal models, yet rodents with region-specific or temporally restricted knock-out or knock-down of DARPP-32 or its phosphorylation-site mutated forms are not available. Moreover, selective activation of DARPP-32-mediated signaling in striatonigral and striatopallidal neurons has only been studied in response to pharmacological stimuli.

The evidence reported here shows that DARPP-32 phosphorylation pattern and function are differently modified in response to natural stimuli, and a large body of literature also demonstrates modifications in DARPP-32 phosphorylation induced by pharmacological stimuli. These results are apparently at variance with the studies in mouse models that indicate that DARPP-32 deletion or modifications at phosphorylation sites do not conspicuously affect development, adult phenotype, and spontaneous behaviors (Fienberg and Greengard 2000; Heyser *et al.* 2000). However, we must

consider that the animals born, raised and performing behavioral tasks in our laboratories are not exposed to the challenges of the complex, rapidly changing and often hostile natural environment. Thus, the role of DARPP-32 may not be necessary for responding to simple stimuli, but it may become significant in orchestrating complex adaptive responses. Accordingly, DARPP-32 function may enhance the reliability of responses to incentive cues by filtering concurrent stimuli. This hypothesis is relevant in a phylogenetic perspective since appropriate responses to natural stimuli are fundamental for the survival of the organism and the species in a complex challenging environment.

References

Aharon I., Etcoff N., Ariely D., Chabris C. F., O'Connor E. and Breiter H. C. (2001) Beautiful faces have variable reward value: fMRI and behavioral evidence. *Neuron* **32**, 537–551.

Ahn J. H., Sung J. Y., McAvoy T., Nishi A., Janssens V., Goris J., Greengard P. and Nairn A. C. (2007) The B''/PR72 subunit mediates Ca2 + -dependent dephosphorylation of DARPP-32 by protein phosphatase 2A. *Proc. Natl Acad. Sci.* **104**, 9876–9881.

Alcantara A. A., Chen V., Herring B. E., Mendenhall J. M. and Berlanga M. L. (2003) Localization of dopamine D2 receptors on cholinergic interneurons of the dorsal striatum and nucleus accumbens of the rat. *Brain Res.* **986**, 22–29.

Barbano P. P. E., Spivak M., Flajolet M., Nairn A. C., Greengard P. and Greengard L. (2007) A mathematical tool for exploring the dynamics of biological networks. *Proc. Natl Acad. Sci. USA* **104**, 19169–19174.

Bassareo V. and Di Chiara G. (1999) Modulation of feeding-induced activation of mesolimbic dopamine transmission by appetitive stimuli and its relation to motivational state. *Eur. J. Neurosci.* **11**, 4389–4397.

Bassareo V., De Luca M. A. and Di Chiara G. (2002) Differential expression of motivational stimulus properties by dopamine in nucleus accumbens shell versus core and prefrontal cortex. *J. Neurosci.* **22**, 4709–4719.

Bednarek E. and Caroni P. (2011) β-adducin is required for stable assembly of new synapses and improved memory upon environmental enrichment. *Neuron* **69**, 1132–1146.

Berridge K. C. (2007) The debate over dopamine's role in reward: the case for incentive salience. *Psychopharmacology* **191**, 391–431.

Berridge K. C. and Kringelbach M. L. (2008) Affective neuroscience of pleasure: reward in humans and animals. *Psychopharmacology* **199**, 457–480.

Bertran-Gonzalez J., Bosch C., Maroteaux M., Matamales M., Herve D., Valjent E. and Girault J. A. (2008) Opposing patterns of signaling activation in dopamine D1 and D2 receptor-expressing striatal neurons in response to cocaine and haloperidol. *J. Neurosci.* **28**, 5671–5685.

Bibb J. A., Snyder G. L., Nishi A. *et al.* (1999) Phosphorylation of DARPP-32 by Cdk5 modulates dopamine signalling in neurons. *Nature* **402**, 669–671.

Bibb J. A., Yan Z., Svenningsson P., Snyder G. L., Pieribone V. A., Horiuchi A., Nairn A. C., Messer A. and Greengard P. (2000) Severe deficiencies in dopamine signaling in presymptomatic Huntington's disease mice. *Proc. Natl Acad. Sci.* **97**, 6809–6814.

Cabib S. and Puglisi-Allegra S. (1994) Opposite responses of mesolimbic dopamine system to controllable and uncontrollable aversive experiences. *J. Neurosci.* **14**, 3333–3340.

Cacciapaglia F., Wightman R. M. and Carelli R. M. (2011) Rapid dopamine signaling differentially modulates distinct microcircuits within the nucleus accumbens during sucrose-directed behavior. *J. Neurosci.* **31**, 13860–13869.

Cazorla M., deCarvalho F., Chohan M. M. O., Shegda M., Chuhma N., Rayport S., Ahmari S. S. E., Moore H. and Kellendonk C. (2014) Dopamine D2 receptors regulate the anatomical and functional balance of basal ganglia circuitry. *Neuron* **81**, 153–164.

Champagne F. A., Chretien P., Stevenson C. W., Zhang T. Y., Gratton A. and Meaney M. J. (2004) Variations in nucleus accumbens dopamine associated with individual differences in maternal behavior in the rat. *J. Neurosci.* **24**, 4113–4123.

Chevallier C., Kohls G., Troiani V., Brodkin E. S. and Schultz R. T. (2012) The social motivation theory of autism. *Trends in Cogn. Sci.* **16**, 231–239.

Cockburn J., Collins A. G. E. and Frank M. J. (2014) A reinforcement learning mechanism responsible for the valuation of free choice. *Neuron* **83**, 551–557.

Corbit L. H. and Balleine B. W. (2011) The general and outcome-specific forms of Pavlovian-Instrumental Transfer are differentially mediated by the nucleus accumbens core and shell. *J. Neurosci.* **31**, 11786–11794.

Corbit L. H., Muir J. L. and Balleine B. W. (2001) The role of the nucleus accumbens in instrumental conditioning: evidence of a functional dissociation between accumbens core and shell. *J. Neurosci.* **21**, 3251–3260.

Couture S. M., Roberts D. L., Penn D. L., Cather C., Otto M. W. and Goff D. (2006) Do baseline client characteristics predict the therapeutic alliance in the treatment of schizophrenia? *J. Nerv. Ment. Dis.* **194**, 10–14.

Ćurcić-Blake B., Swart M., Horst G. J., Ter Langers D. R. M., Kema I. P. and Aleman A. (2012) Variation of the gene coding for DARPP-32 (PPP1R1B) and brain connectivity during associative emotional learning. *NeuroImage* **59**, 1540–1550.

Danielli B., Scheggi S., Grappi S., Marchese G., Montis M. G., De Tagliamonte A. and Gambarana C. (2010) Modifications in DARPP-32 phosphorylation pattern after repeated palatable food consumption undergo rapid habituation in the nucleus accumbens shell of non-food-deprived rats. *J. Neurochem.* **112**, 531–541.

Darna M., Beckmann J. S., Gipson C. D., Bardo M. T. and Dwoskin L. P. (2015) Effect of environmental enrichment on dopamine and serotonin transporters and glutamate neurotransmission in medial prefrontal and orbitofrontal cortex. *Brain Res.* **1599**, 115–125.

Del Arco A., Segovia G., Canales J. J., Garrido P., Blas M. De., García-Verdugo J. M. and Mora F. (2007) Environmental enrichment reduces the function of D1 dopamine receptors in the prefrontal cortex of the rat, in *J. Neural. Transm.* **114**, 43–48.

vanDellen A., Blakemore C., Deacon R., York D. and Hannan A. J. (2000) Delaying the onset of Huntington's in mice. *Nature* **404**, 721–722.

Diamond M. C., Rosenzweig M. R., Bennett E. L., Lindner B. and Lyon L. (1972) Effects of environmental enrichment and impoverishment on rat cerebral cortex. *J. Neurobiol.* **3**, 47–64.

Dominguez J. M. and Hull E. M. (2005) Dopamine, the medial preoptic area, and male sexual behavior. *Physiol. Behav.* **86**, 356–368.

Engmann O., Giralt A., Gervasi N. *et al.* (2015) DARPP-32 interaction with adducin may mediate rapid environmental effects on striatal neurons. *Nat. Commun.* **6**, 10099.

Fenu S., Bassareo V. and Di Chiara G. (2001) A role for dopamine D1 receptors of the nucleus accumbens shell in conditioned taste aversion learning. *J. Neurosci.* **21**, 6897–6904.

Fernandez E., Schiappa R., Girault J. A. and Le Novère N. (2006) DARPP-32 is a robust integrator of dopamine and glutamate signals. *PLoS Comput. Biol.* **2**, 1619–1633.

Fernández-Teruel A., Giménez-Llort L., Escorihuela R. M., Gil L., Aguilar R., Steimer T. and Tobea A. (2002) Early-life handling stimulation and environmental enrichment: are some of their effects mediated by similar neural mechanisms*? Pharmacol. Biochem. Behav.* **73**, 233–245.

Ferré S., Baler R., Bouvier M. *et al.* (2009) Building a new conceptual framework for receptor heteromers. *Nat. Chem. Biol.* **5**, 131–134.

Fienberg A. A. and Greengard P. (2000) The DARPP-32 knock out mouse. *Brain Res. Brain Res. Rev.* **31**, 313–319.

Floresco S. B. (2015) The nucleus accumbens: an interface between cognition, emotion, and action. *Annu. Rev. Psychol.* **66**, 25–52.

Floresco S. B., West A. R., Ash B., Moore H. and Grace A. A. (2003) Afferent modulation of dopamine neuron firing differentially regulates tonic and phasic dopamine transmission. *Nat. Neurosci.* **6**, 968–973.

Foreman M. M. and Moss R. L. (1979) Role of hypothalamic dopaminergic receptors in the control of lordosis behavior in the female rat. *Physiol. Behav.* **22**, 283–289.

Francis T. C., Chandra R., Friend D. M. *et al.* (2015) Nucleus accumbens medium spiny neuron subtypes mediate depression-related outcomes to social defeat stress. *Biol. Psychiatry* **77**, 212–222.

Frank M. J., Moustafa A. A., Haughey H. M., Curran T. and Hutchison K. E. (2007) Genetic triple dissociation reveals multiple roles for dopamine in reinforcement learning. *Proc. Natl Acad. Sci.* **104**, 16311–16316.

Frank M. J., Doll B. B., Oas-Terpstra J. and Moreno F. (2009) Prefrontal and striatal dopaminergic genes predict individual differences in exploration and exploitation. *Nat. Neurosci.* **12**, 1062–1068.

Frederick A. L., Yano H., Trifilieff P. *et al.* (2015) Evidence against dopamine D1/D2 receptor heteromers. *Mol. Psychiatry* **20**, 1373–1385.

Frye C. A. and Walf A. A. (2010) Infusions of anti-sense oligonucleotides for DARPP-32 to the ventral tegmental area reduce effects of progesterone- and a dopamine type 1-like receptor agonist to facilitate lordosis. *Behav. Brain Res.* **206**, 286–292.

Fumero B., Fernandez-Vera J. R., Gonzalez-Mora J. L. and Mas M. (1994) Changes in monoamine turnover in forebrain areas associated with masculine sexual behavior: a microdialysis study. *Brain Res.* **662**, 233–239.

Furlong T. M., Jayaweera H. K., Balleine B. W. and Corbit L. H. (2014) Binge-like consumption of a palatable food accelerates habitual control of behavior and is dependent on activation of the dorsolateral striatum. *J. Neurosci.* **34**, 5012–5022.

Galani R., Berthel M. C., Lazarus C., Majchrzak M., Barbelivien A., Kelche C. and Cassel J. C. (2007) The behavioral effects of enriched housing are not altered by serotonin depletion but enrichment alters hippocampal neurochemistry. *Neurobiol. Learn. Mem.* **88**, 1–10.

Gambarana C., Masi F., Leggio B., Grappi S., Nanni G., Scheggi S., Montis M. G. and De Tagliamonte A. (2003) Acquisition of a palatable-food-sustained appetitive behavior in satiated rats is dependent on the dopaminergic response to this food in limbic areas. *Neuroscience* **121**, 179–187.

Gammie S. C., Edelmann M. N., Mandel-Brehm C., D'Anna K. L., Auger A. P. and Stevenson S. A. (2008) Altered dopamine signaling in naturally occurring maternal neglect. *PLoS ONE* **3**, e1974.

Gerfen C., Engber T., Mahan L., Susel Z., Chase T., Monsma F. and Sibley D. (1990) D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science* **250**, 1429–1432.

Gill K. E., Beveridge T. J. R., Smith H. R. and Porrino L. J. (2013) The effects of rearing environment and chronic methylphenidate administration on behavior and dopamine receptors in adolescent rats. *Brain Res.* **1527**, 67–78.

Giuliano F. and Allard J. (2001) Dopamine and male sexual function. *Eur. Urol.* **40**, 601–608.

Gomez A. M., Midde N. M., Mactutus C. F., Booze R. M. and Zhu J. (2012) Environmental enrichment alters nicotine-mediated locomotor sensitization and phosphorylation of DARPP-32 and CREB in rat prefrontal cortex. *PLoS ONE* **7**, e44149.

Gonon F. G. (1988) Nonlinear relationship between impulse flow and dopamine released by rat midbrain dopaminergic neurons as studied by in vivo electrochemistry. *Neuroscience* **24**, 19–28.

Grace A. A. (1991) Phasic versus tonic dopamine release and the modulation of dopamine system responsivity: a hypothesis for the etiology of schizophrenia. *Neuroscience* **41**, 1–24.

Grace A. A. (2016) Dysregulation of the dopamine system in the pathophysiology of schizophrenia and depression. *Nat. Rev. Neurosci.* **17**, 524–532.

Grace A. A. and Bunney B. S. (1984) The control of firing pattern in nigral dopamine neurons: burst firing. *J. Neurosci.* **4**, 2877–2890.

Grappi S., Marchese G., Secci M. E., Montis M. G., De Gambarana C. and Scheggi S. (2011) Morphine sensitization as a model of mania: comparative study of the effects of repeated lithium or carbamazepine administration. *Pharmacol. Biochem. Behav.* **99**, 749–758.

Green T. A., Alibhai I. N., Roybal C. N. *et al.* (2010) Environmental enrichment produces a behavioral phenotype mediated by low cyclic adenosine monophosphate response element binding (CREB) activity in the nucleus accumbens. *Biol. Psychiatry* **67**, 28–35.

Greengard P., Allen P. B. and Nairn A. C. (1999) Beyond the dopamine receptor: the DARPP-32/protein phosphatase-1 cascade. *Neuron* **23**, 435–447.

Greenough W. T. and Volkmar F. R. (1973) Pattern of dendritic branching in occipital cortex of rats reared in complex environments. *Exp. Neurol.* **40**, 491–504.

Gunaydin L. A., Grosenick L., Finkelstein J. C. *et al.* (2014) Natural neural projection dynamics underlying social behavior. *Cell* **157**, 1535–1551.

Halpain S., Girault J. A. and Greengard P. (1990) Activation of NMDA receptors induces dephosphorylation of DARPP-32 in rat striatal slices. *Lett. to Nat.* **343**, 369–372.

Harati H., Barbelivien A., Herbeaux K., Muller M. A., Engeln M., Kelche C., Cassel J. C. and Majchrzak M. (2013) Lifelong environmental enrichment in rats: impact on emotional behavior, spatial memory vividness, and cholinergic neurons over the lifespan. *Age (Omaha).* **35**, 1027–1043.

Hasbi A., Perreault M. L., Shen M. Y. F. *et al.* (2018) Activation of dopamine D1-D2 receptor complex attenuates cocaine reward and reinstatement of cocaine-seeking through inhibition of DARPP-32, ERK, and ΔFosB. *Front. Pharmacol.* **8**, 924.

Hebb D. O. (1949) The organization of behavior: a Neuropsychological Approach. *Am. J. Psychol.* **63**, 633.

Hemmings H. C., Williams K. R., Konigsberg W. H. and Greengard P. (1984) DARPP-32, a dopamine- and adenosine 3':5'-monophosphate-regulated neuronal phosphoprotein. I. Amino acid sequence around the phosphorylated threonine. *J. Biol. Chem.* **259**, 14486–14490.

Heyser C. J., Fienberg A. A., Greengard P. and Gold L. H. (2000) DARPP-32 knockout mice exhibit impaired reversal learning in a discriminated operant task. *Brain Res.* **867**, 122–130.

Hockly E., Cordery P. M., Woodman B., Mahal A., Dellen A., Van Blakemore C., Lewis C. M., Hannan A. J. and Bates G. P. (2002)

Environmental enrichment slows disease progression in R6/2 Huntington's disease mice. *Ann. Neurol.* **51**, 235–242.

Hodos W. (1961) Progressive ratio as a measure of reward strength. *Science*. **134**, 943–944.

Hull E. M., Du J., Lorrain D. S. and Matuszewich L. (1995) Extracellular dopamine in the medial preoptic area: implications for sexual motivation and hormonal control of copulation. *J. Neurosci.* **15**, 7465–7471.

Ito R., Robbins T. W. and Everitt B. J. (2004) Differential control over cocaine-seeking behavior by nucleus accumbens core and shell. *Nat. Neurosci.* **7**, 389–397.

Izuma K., Saito D. N. and Sadato N. (2008) Processing of social and monetary rewards in the human striatum. *Neuron* **58**, 284–294.

Jin H. M., Shrestha Muna S., Bagalkot T. R., Cui Y., Yadav B. K. and Chung Y. C. (2015) The effects of social defeat on behavior and dopaminergic markers in mice. *Neuroscience* **288**, 167–177.

Kim M. S., Yu J. H., Kim C. H. *et al.* (2016) Environmental enrichment enhances synaptic plasticity by internalization of striatal dopamine transporters. *J. Cereb. Blood Flow Metab.* **36**, 2122–2133.

Kosobud A. E. K., Harris G. C. and Chapin J. K. (1994) Behavioral associations of neuronal activity in the ventral tegmental area of the rat. *J. Neurosci.* **14**, 7117–7129.

Kupchik Y. M. and Kalivas P. W. (2017) The direct and indirect pathways of the nucleus accumbens are not what you think. *Neuropsychopharmacology* **42**, 369–370.

Kupchik Y. M., Brown R. M., Heinsbroek J. A., Lobo M. K., Schwartz D. J. and Kalivas P. W. (2015) Coding the direct/indirect pathways by D1 and D2 receptors is not valid for accumbens projections. *Nat. Neurosci.* **18**, 1230–1232.

Le Moine C. and Bloch B. (1996) Expression of the D3 dopamine receptor in peptidergic neurons of the nucleus accumbens: comparison with the D1 and D2 dopamine receptors. *Neuroscience* **73**, 131–143.

Lenoir M., Serre F., Cantin L. and Ahmed S. H. (2007) Intense sweetness surpasses cocaine reward. *PLoS ONE* **2**, e698.

Lindskog M., Kim M., Wikström M. A., Blackwell K. T. and Kotaleski J. H. (2006) Transient calcium and dopamine increase PKA activity and DARPP-32 phosphorylation. *PLoS Comput. Biol.* **2**, 1045–1060.

López H. S. and Carrer H. F. (1982) Investigation of peripeduncular-hypothalamic pathways involved in the control of Lordosis in the rat. *Brain Res.* **253**, 287–302.

Mani S. K. (2000) Requirement for DARPP-32 in Progesterone-facilitated sexual receptivity in female rats and mice. *Science* **287**, 1053–1056.

Mani S. K. and Blaustein J. D. (2012) Neural progestin receptors and female sexual behavior. *Neuroendocrinology* **96**, 152–161.

Mani S. K., Allen J. M. C., Clark J. H., Blaustein J. D. and Omalley B. W. (1994) Convergent pathways for steroid hormone- and neurotransmitter- induced rat sexual behavior. *Science* **265**, 1246–1249.

Marchese G., Scheggi S., Secci M. E., Montis M. G. and De Gambarana C. (2013) Anti-anhedonic activity of long-term lithium treatment in rats exposed to repeated unavoidable stress. *Int. J. Neuropsychopharmacol.* **16**, 1611–1621.

Marotta R., Fenu S., Scheggi S., Vinci S., Rosas M., Falqui A., Gambarana C., De Montis M. G. and Acquas E. (2014) Acquisition and expression of conditioned taste aversion differentially affects extracellular signal regulated Kinase and glutamate receptor phosphorylation in rat prefrontal cortex and nucleus accumbens. *Front. Behav. Neurosci.* **8**, 153.

McHenry J. A., Bell G. A., Parrish B. P. and Hull E. M. (2012) Dopamine D1 receptors and phosphorylation of dopamine- and cyclic AMP-regulated phosphoprotein-32 in the medial preoptic area are involved in experience-induced enhancement of male sexual behavior in rats. *Behav. Neurosci.* **126**, 523–529.

Melis M. R. and Argiolas A. (1995) Dopamine and sexual behavior. *Neurosci. Biobehav. Rev.* **19**, 19–38.

Meredith G. E., Pennartz C. M. A. and Groenewegen H. J. (1993) The cellular framework for chemical signalling in the nucleus accumbens. *Prog. Brain Res.* **99**, 3–24.

Meredith J. M., Moffatt C. A., Auger A. P., Snyder G. L., Greengard P. and Blaustein J. D. (1998) Mating-related stimulation induces phosphorylation of dopamine- and cyclic AMP-regulated phosphoprotein-32 in progestin receptor-containing areas in the female rat brain. *J. Neurosci.* **18**, 10189–10195.

Meyer-Lindenberg A., Straub R. E., Lipska B. K. *et al.* (2007) Genetic evidence implicating DARPP-32 in human frontostriatal structure, function, and cognition. *J. Clin. Invest.* **117**, 672–682.

Mogenson G. J., Jones D. L. and Yim C. Y. (1980) From motivation to action: functional interface between the limbic system and the motor system. *Prog. Neurobiol.* **14**, 69–97.

Montague P. R., Hyman S. E. and Cohen J. D. (2004) Computational roles for dopamine in behavioural control. *Nature* **431**, 760–767.

Morris G., Arkadir D., Nevet A., Vaadia E. and Bergman H. (2004) Coincident but distinct messages of midbrain dopamine and striatal tonically active neurons. *Neuron* **43**, 133–143.

Nair A. G., Bhalla U. S. and Hellgren Kotaleski J. (2016) Role of DARPP-32 and ARPP-21 in the emergence of temporal constraints on striatal calcium and dopamine integration. *PLoS Comput. Biol.* **12**, e1005080.

Nakano T., Doi T., Yoshimoto J. and Doya K. (2010) A kinetic model of dopamine- and calcium-dependent striatal synaptic plasticity. *PLoS Comput. Biol.* **6**, e1000670.

Nishi A., Bibb J. A., Matsuyama S., Hamada M., Higashi H., Nairn A. C. and Greengard P. (2002) Regulation of DARPP-32 dephosphorylation at PKA- and Cdk5-sites by NMDA and AMPA receptors: distinct roles of calcineurin and protein phosphatase-2A. *J. Neurochem.* **81**, 832–841.

Nishi A., Watanabe Y., Higashi H., Tanaka M., Nairn A. C. and Greengard P. (2005) Glutamate regulation of DARPP-32 phosphorylation in neostriatal neurons involves activation of multiple signaling cascades. *Proc. Natl Acad. Sci. USA* **102**, 1199–1204.

Nishi A., Matamales M., Musante V., Valjent E., Kuroiwa M., Kitahara Y., Rebholz H., Greengard P., Girault J. A. and Nairn A. C. (2017) Glutamate counteracts dopamine/PKA signaling via dephosphorylation of DARPP-32 Ser-97 and alteration of its cytonuclear distribution. *J. Biol. Chem.* **292**, 1462–1476.

Nithianantharajah J. and Hannan A. J. (2006) Enriched environments, experience-dependent plasticity and disorders of the nervous system. *Nat. Rev. Neurosci.* **7**, 697–709.

Numan M. (2007) Motivational systems and the neural circuitry of maternal behavior in the rat. *Dev. Psychobiol.* **49**, 12–21.

Numan M. and Sheehan T. P. (1997) Neuroanatomical circuitry for mammalian maternal behavior. *Ann. N. Y. Acad. Sci.* **807**, 101–125.

Ostlund S. B., Wassum K. M., Murphy N. P., Balleine B. W. and Maidment N. T. (2011) Extracellular dopamine levels in striatal subregions track shifts in motivation and response cost during instrumental conditioning. *J. Neurosci.* **31**, 200–207.

Ouimet C. C. and Greengard P. (1990) Distribution of DARPP-32 in the basal ganglia: an electron microscopic study. *J. Neurocytol.* **19**, 39–52.

Ouimet C., Miller P., Hemmings H. C., Walaas S. and Greengard P. (1984) DARPP-32, a dopamine- and adenosine 3':5'-monophosphate-regulated phosphoprotein enriched in dopamine-innervated brain regions. III. Immunocytochemical Localization. *J. Neurosci.* **4**, 111–124.

Pedersen C. A., Caldwell J. D., Walker C., Ayers G. and Mason G. A. (1994) Oxytocin activates the postpartum onset of rat maternal behavior in the ventral tegmental and medial preoptic areas. *Behav. Neurosci.* **108**, 1163–1171.

Peoples L. L. and West M. O. (1996) Phasic firing of single neurons in the rat nucleus accumbens correlated with the timing of intravenous cocaine self-administration. *J. Neurosci.* **16**, 3459–3473.

Persson N., Lavebratt C., Ebner N. C. and Fischer H. (2017a) Influence of DARPP-32 genetic variation on BOLD activation to happy faces. *Soc. Cogn. Affect. Neurosci.* **12**, 1658–1667.

Persson N., Persson J., Lavebratt C. and Fischer H. (2017b) Effects of DARPP-32 genetic variation on prefrontal cortex volume and episodic memory performance. *Front. Neurosci.* **11**, 244.

Pfaus J. G., Damsma G., Nomikos G. G., Wenkstern D. G., Blaha C. D., Phillips A. G. and Fibiger H. C. (1990) Sexual behavior enhances central dopamine transmission in the male rat. *Brain Res.* **530**, 345–348.

Pfaus J. G., Damsma G., Wenkstern D. and Fibiger H. C. (1995) Sexual activity increases dopamine transmission in the nucleus accumbens and striatum of female rats. *Brain Res.* **693**, 21–30.

Pham T. M., Ickes B., Albeck D., Soderstrom S., Granholm A. C. and Mohammed A. H. (1999) Changes in brain nerve growth factor levels and nerve growth factor receptors in rats exposed to environmental enrichment for one year. *Neuroscience* **94**, 279–286.

Phillips-Farfán B. V. and Fernández-Guasti A. (2009) Endocrine, neural and pharmacological aspects of sexual satiety in male rats. *Neurosci. Biobehav. Rev.* **33**, 442–455.

Pielage J., Bulat V., Zuchero J. B., Fetter R. D. and Davis G. W. (2011) Hts/adducin controls synaptic elaboration and elimination. *Neuron* **69**, 1114–1131.

Pontieri F. E., Tanda G. and Chiara G. Di. (1995) Intravenous cocaine, morphine, and amphetamine preferentially increase extracellular dopamine in the "shell" as compared with the "core" of the rat nucleus accumbens. *Proc. Natl Acad. Sci. USA* **92**, 12304–12308.

van Praag H., Kempermann G. and Gage F. H. (2000) Neural consequences of environmental enrichment. *Nat. Rev. Neurosci.* **1**, 191–198.

Qi Z., Miller G. W. and Voit E. O. (2010) Internal state of medium spiny neurons varies in response to different input signals. *BMC Syst. Biol.* **4**, 26.

Rademacher L., Krach S., Kohls G., Irmak A., Gründer G. and Spreckelmeyer K. N. (2010) Dissociation of neural networks for anticipation and consumption of monetary and social rewards. *NeuroImage* **49**, 3276–3285.

Rampon C., Jiang C. H., Dong H., Tang Y. P., Lockhart D. J., Schultz P. G., Tsien J. Z. and Hu Y. (2000) Effects of environmental enrichment on gene expression in the brain. *Proc. Natl Acad. Sci. USA* **97**, 12880–12884.

Randall P. A., Pardo M., Nunes E. J., López Cruz. L., Vemuri V. K., Makriyannis A., Baqi Y., Müller C. E., Correa M. and Salamone J. D. (2012) Dopaminergic modulation of effort-related choice behavior as assessed by a progressive ratio chow feeding choice task: pharmacological studies and the role of individual differences. *PLoS ONE* **7**, e47934.

Rauggi R., Scheggi S., Cassanelli A., De Montis M. G., Tagliamonte A. and Gambarana C. (2005) The mesolimbic dopaminergic response to novel palatable food consumption increases dopamine-D1 receptor-mediated signalling with complex modifications of the DARPP-32 phosphorylation pattern. *J. Neurochem.* **92**, 867–877.

Risinger F. O., Freeman P. A., Greengard P. and Fienberg A. A. (2001) Motivational effects of ethanol in DARPP-32 knock-out mice. *J. Neurosci.* **21**, 340–348.

Robinson D. L., Heien M. L. A. V. and Wightman R. M. (2002) Frequency of dopamine concentration transients increases in dorsal and ventral striatum of male rats during introduction of conspecifics. *J. Neurosci.* **22**, 10477–10486.

Robinson D. L., Zitzman D. L., Smith K. J. and Spear L. P. (2011) Fast dopamine release events in the nucleus accumbens of early adolescent rats. *Neuroscience* **176**, 296–307.

Rogers J., Li S., Lanfumey L., Hannan A. J. and Renoir T. (2017) Environmental enrichment reduces innate anxiety with no effect on depression-like behaviour in mice lacking the serotonin transporter. *Behav. Brain Res.* **332**, 355–361.

Rosenzweig M. R., Bennett E. L., Hebert M. and Morimoto H. (1978) Social grouping cannot account for cerebral effects of enriched environments. *Brain Res.* **153**, 563–576.

Sackett D. A., Saddoris M. P. and Carelli R. M. (2017) Nucleus Accumbens Shell dopamine preferentially tracks information related to outcome value of reward. *eNeuro* **4**, e0058.

Saddoris M. P., Cacciapaglia F., Wightman R. M. and Carelli R. M. (2015) Differential dopamine release dynamics in the Nucleus Accumbens Core and Shell reveal complementary signals for error prediction and incentive motivation. *J. Neurosci.* **35**, 11572–11582.

Sale A. (2018) A systematic look at environmental modulation and its impact in brain development. *Trends Neurosci.* **41**, 4–17.

Saunders A., Oldenburg I. A., Berezovskii V. K., Johnson C. A., Kingery N. D., Elliott H. L., Xie T., Gerfen C. R. and Sabatini B. L. (2015) A direct GABAergic output from the basal ganglia to frontal cortex. *Nature* **521**, 85–89.

Scheggi S., Crociani A., De Montis M. G., Tagliamonte A. and Gambarana C. (2009) Dopamine D1 receptor-dependent modifications in the dopamine and cAMP-regulated phosphoprotein of Mr 32 kDa phosphorylation pattern in striatal areas of morphine-sensitized rats. *Neuroscience* **163**, 627–639.

Scheggi S., Marchese G., Grappi S., Secci M. E., De Montis M. G. and Gambarana C. (2011) Cocaine sensitization models an anhedonia-like condition in rats. *Int. J. Neuropsychopharmacol.* **14**, 333–346.

Scheggi S., Secci M. E., Marchese G., De Montis M. G. and Gambarana C. (2013) Influence of palatability on motivation to operate for caloric and non-caloric food in non food-deprived and food-deprived rats. *Neuroscience* **236**, 320–331.

Scheggi S., Pelliccia T., Ferrari A., De Montis M. G. and Gambarana C. (2015) Impramine, fluoxetine and clozapine differently affected reactivity to positive and negative stimuli in a model of motivational anhedonia in rats. *Neuroscience* **291**, 189–202.

Scheggi S., Melis M., Felice M., De Aroni S., Muntoni A. L., Pelliccia T., Gambarana C., De Montis M. G. and Pistis M. (2016) PPARα modulation of mesolimbic dopamine transmission rescues depression-related behaviors. *Neuropharmacology* **110**, 251–259.

Scheggi S., Pelliccia T., Gambarana C. and De Montis M. G. (2017) Aripiprazole relieves motivational anhedonia in rats. *J. Affect. Disord.* **227**, 192–197.

Schultz W. (2007) Multiple dopamine functions at different time courses. *Annu. Rev. Neurosci.* **30**, 259–288.

Schultz W. (2016) Dopamine reward prediction-error signalling: a two-component response. *Nat. Rev. Neurosci.* **17**, 183–195.

Segovia K. N., Correa M. and Salamone J. D. (2011) Slow phasic changes in nucleus accumbens dopamine release during fixed ratio acquisition: a microdialysis study. *Neuroscience* **196**, 178–188.

Segovia K. N., Correa M., Lennington J. B., Conover J. C. and Salamone J. D. (2012) Changes in nucleus accumbens and neostriatal c-Fos and DARPP-32 immunoreactivity during different stages of food-reinforced instrumental training. *Eur. J. Neurosci.* **35**, 1354–1367.

Sesack S. R. and Grace A. A. (2010) Cortico-basal ganglia reward network: microcircuitry. *Neuropsychopharmacology* **35**, 27–47.

Shi W. X., Pun C. L., Zhang X. X., Jones M. D. and Bunney B. S. (2000) Dual effects of D-amphetamine on dopamine neurons mediated by dopamine and nondopamine receptors. *J. Neurosci.* **20**, 3504–3511.

Simonsen A. L., Danborg P. B. and Gøtzsche P. C. (2016) Persistent sexual dysfunction after early exposure to SSRIs: systematic review of animal studies. *Int. J. Risk Saf. Med.* **28**, 1–12.

Sokolowski J. D., Conlan A. N. and Salamone J. D. (1998) A microdialysis study of nucleus accumbens core and shell dopamine during operant responding in the rat. *Neuroscience* **86**, 1001–1009.

Spires T. L., Grote H. E., Varshney N. K., Cordery P. M., van Dellen A., Blakemore C. and Hannan A. J. (2004) Environmental enrichment rescues protein deficits in a mouse model of Huntington's disease, indicating a possible disease mechanism. *J. Neurosci.* **24**, 2270–2276.

Spreckelmeyer K. N., Krach S., Kohls G., Rademacher L., Irmak A., Konrad K., Kircher T. and Gründer G. (2009) Anticipation of monetary and social reward differently activates mesolimbic brain structures in men and women. *Soc. Cogn. Affect. Neurosci.* **4**, 158–165.

Stipanovich A., Valjent E., Matamales M. *et al.* (2008) A phosphatase cascade by which rewarding stimuli control nucleosomal response. *Nature* **453**, 879–884.

Stopper C. M. and Floresco S. B. (2011) Contributions of the nucleus accumbens and its subregions to different aspects of risk-based decision making. *Cogn. Affect. Behav. Neurosci.* **11**, 97–112.

Stuber G. D., Klanker M., de Ridder B., Bowers M. S., Joosten R. N., Feenstra M. G. and Bonci A. (2008) Reward-predictive cues enhance excitatory synaptic strength onto midbrain dopamine neurons. *Science* **321**, 1690–1692.

Surmeier D. J., Ding J., Day M., Wang Z. and Shen W. (2007) D1 and D2 dopamine-receptor modulation of striatal glutamatergic signaling in striatal medium spiny neurons. *Trends Neurosci.* **30**, 228–235.

Svenningsson P., Nishi A., Fisone G., Girault J. A., Nairn A. C. and Greengard P. (2004) DARPP-32: an integrator of neurotransmission. *Annu. Rev. Pharmacol. Toxicol.* **44**, 269–296.

Threlfell S., Lalic T., Platt N. J., Jennings K. A., Deisseroth K. and Cragg S. J. (2012) Striatal dopamine release is triggered by synchronized activity in cholinergic interneurons. *Neuron* **75**, 58–64.

Trezza V., Damsteegt R., Achterberg E. J. and Vanderschuren L. J. (2011) Nucleus Accumbens μ-opioid receptors mediate social reward. *J. Neurosci.* **31**, 6362–6370.

Tsai H. C., Zhang F., Adamantidis A., Stuber G. D., Bond A., Lecea L. and De Deisseroth K. (2009) Phasic firing in dopaminergic neurons is sufficient for behavioral conditioning. *Science* **324**, 1080–1084.

Ung C. Y. and Teoh T. C. (2014) The evolutionary strata of DARPP-32 tail implicates hierarchical functional expansion in higher vertebrates. *J. Biosci.* **39**, 493–504.

Volkow N. D., Wang G. J. and Baler R. D. (2011) Reward, dopamine and the control of food intake: implications for obesity. *Trends Cogn. Sci.* **15**, 37–46.

Voorn P., Vanderschuren L. J. M. J., Groenewegen H. J., Robbins T. W. and Pennartz C. M. A. (2004) Putting a spin on the dorsal-ventral divide of the striatum. *Trends Neurosci.* **27**, 468–474.

Walaas S. I. and Greengard P. (1984) DARPP-32, a dopamine- and adenosine 3':5'-monophosphate-regulated phosphoprotein enriched in dopamine-innervated brain regions. I. Regional and cellular distribution in the rat brain. *J. Neurosci.* **4**, 84–98.

Walaas S. I., Hemmings H. C., Greengard P. and Nairn A. C. (2011) Beyond the dopamine receptor: regulation and roles of serine/threonine protein phosphatases. *Front. Neuroanat.* **5**, 50.

Wenkstern D., Pfaus J. G. and Fibiger H. C. (1993) Dopamine transmission increases in the nucleus accumbens of male rats during their first exposure to sexually receptive female rats. *Brain Res.* **618**, 41–46.

Yger M. and Girault J. A. (2011) DARPP-32, Jack of All Trades? Master of Which? *Front. Behav. Neurosci.* **5**, 56.

Yoshida M., Yokoo H., Mizoguchi K., Kawahara H., Tsuda A., Nishikawa T. and Tanaka M. (1992) Eating and drinking cause increased dopamine release in the nucleus accumbens and ventral tegmental area in the rat: measurement by *in vivo* microdialysis. *Neurosci. Lett.* **139**, 73–76.

Young D., Lawlor P. A., Leone P., Dragunow M. and During M. J. (1999) Environmental enrichment inhibits spontaneous apoptosis, prevents seizures and is neuroprotective. *Nat. Med.* **5**, 448–453.

Zahm D. S. (1989) The ventral striatopallidal parts of the basal ganglia in the rat-II. Compartmentation of ventral pallidal efferents. *Neuroscience* **30**, 33–50.

Zahm D. S. (2000) An integrative neuroanatomical perspective on some subcortical substrates of adaptive responding with emphasis on the nucleus accumbens. *Neurosci. Biobehav. Rev.* **24**, 85–105.