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| The Role of Dopamine in the Reward System (with relevance for addiction) |  |
| Sian Duss, Jonas Fullin & Nima Yassini |  |

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opamine, a tyrosine derived monoamine of the catecholamine family, has similar to the other two important members of the catecholamine family, noradrenaline and adrenaline, a pivotal role in our body. Although the dopaminergic system in the mammalian nervous system does not possess many neurons, its functions are essential and can evoke life-threatening behaviors when disrupted.

An important function of dopamine is its involvement in the reward system. This system promotes and reinforces behavior that eventually helps increasing the evolutionary fitness of an organism. Although not being the only neurotransmitter involved, dopamine is the main substance associated with reward signaling, for example by linking the two important reward areas in the brain, the ventral tegmental area (VTA) and the nucleus accumbens (NAc). The idea of dopamine-involvement in addiction exists since the last century, but only recently, evidence for the sufficiency of specific dopamine neurons in the midbrain to trigger addiction have been provided. All known addictive drugs somehow interfere with the dopamine circuit and thereby elicit changes in the neuronal plasticity. How cocaine affects long term potentiation will be discussed in more detail. Two recent discoveries provide more detailed insights in hallmarks drug addiction.

With a constant increase in bodyweight among the world population, the obesity epidemic has become an undeniable problem of the modern world’s society. Drug addiction studies in regards to the dopaminergic system and behavioral observations of adipose individuals have indicated a possible connection of these two seemingly different aspects of life. Here we discuss some properties of the dopaminergic system having a role in the contemplation and experience of eating palatable food, another reward sensations evoking medium.

# GENERAL ASPECTS OF DOPAMINE IN THE NERVOUS SYSTEM

## Neuroanatomy and Functions

With the discovery of catecholamines being used as neurotransmitters in the nervous system, a new naming system for cells using these neurotransmitters was introduced. So far, twenty different cell groups in the mammalian nervous system have been identified and named A1–A17 and C1–C3. Ten cell groups among these twenty have been linked to dopamine (A8–A17), which together with noradrenaline constitute the two primary members of the catecholamine family.

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| **FIGURE 1 |** Projections of dopaminergic neurons from the nigrostriatal and mesocorticolimbic system in a human brain (Arias-Carrión et al., 2010). |
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Besides A16 and A17 neurons, which are located in the olfactory bulb and the retina respectively, the dopaminergic cell groups reside in the midbrain and hypothalamus (Björklund and Dunnett, 2007; Kandel et al., 2012). Cells in the substantia nigra pars compacta (SNc) form the A9 group and project together with the closely located A8 group to the striatum. This nigrostriatal system is known to be important for the initiation and inhibition of locomotion. Typical degradation in these areas are observed in patients with Parkinson’s disease, where the dopaminergic system is disrupted and the voluntary movement is rigid and tremorous (Arias-Carrión et al., 2010; Kandel et al.,2012).

The mesolimbic and mesocortical systems arise from the A10 group and are often referred to as mesocorticolimbic system, due to their overlapping location in the ventral tegmental area (VTA), which can be found in the mesencephalon. With the projections to the amygdala, hippocampus, olfactory tubercule, nucleus accumbens and the cortex, this system is known to be important for its functions in motivation, reward, emotion and memory (Arias-Carrión and Pöppel, 2007; Kandel et al.,2012).

Neurons from the A12, A14 and A15 group are part of the tuberoinfundibular system and project to the pituitary, where together with the hypothalamus the hormonal homeostasis is a core function. The remaining A11 and A13 cells are located in the hypothalamus and have their targets in brainstem and spinal cord, where they can have a regulatory function in the sympathetic system (Kandel et al., 2012; Vucetic and Reyes, 2010).

## Biosynthesis and Uptake

Important aspects that lead to the expansion of the initial twelve catecholamine cell groups were the knowledge of their bio

synthesis and the discovery of novel biochemical techniques in the 1970s. This allowed the use of enzymes involved in the production of noradrenaline and dopamine as markers, which lead to a more accurate categorization of neurons facilitating catecholamines as neurotransmitters (Björklund and Dunnett, 2007).

Catecholamines share a common biosynthesis, in which the beginning is marked by the hydroxylation of the amino acid tyrosine. This first step is the rate-limiting reaction in the biosynthesis and is carried out by the enzyme tyrosine hydroxylase. The resulting L-dihydroxyphenylalanine (or more commonly known as L-DOPA) will then get decarboxylated by an enzyme called amino acid decarboxylase, from which dopamine emerges. Another hydroxylation would lead to noradrenaline and a methyl-transfer after that would yield adrenaline, but this last reaction only happens in the medulla of the adrenal glands (Kandel et al., 2012).

Once the dopamine or noradrenaline has been synthesized, their distribution between cytosol and vesicular storage is then determined by a transporter termed vesicular monoamine transporter-2 (VMAT-2). Should the dopamine find itself in the synaptic cleft due to a vesicular release, its reuptake is then mediated through the monoamine transporter dopamine transporter (DAT). This transporter takes advantage of the electrochemical ion gradient ensured by the Na+/K+-ATPase, since it functions as a symporter, meaning more specifically the use of two Na+-ions and one Cl--ion as co-transporter to facilitate the uptake of the extracellular dopamine. DAT has shown to be an important target for pharmacological and addictive compounds (Brown et al., 2000; Vaughan and Foster, 2013; Torres et al., 2003).

## Dopamine Receptors

The practical importance of the dopamine receptors cannot be denied, considering the fact that virtually all clinically used antipsychotics have the ability to block the D2 receptor, one member of the five known dopamine receptors. Just like the other four, the D2 receptor belongs to the family of G-protein coupled receptors (GPCRs). These GPCRs act, as the name suggests, through a trimeric

G-protein, which upon receptor activation switches from its inactive state, where a GDP is bound, to an active state, where the binding of the GDP-replacing GTP leads to the dissociation of the Gα-subunit from the βγ-subunit. Depending on the type of the Gα-subunit, the downstream effectors and/or effects can vary and even be completely antagonistic.

Due to their similarities in regards of pharmacology and biochemistry, the five different dopamine receptors are divided into two subfamilies: D1-class and D2-class receptors. The D1-class receptors, which comprises D1- and D5-receptors, are known to act through Gαs/olf, after which the cyclic AMP (cAMP) concentrations rise, due to the activation of adenylyl cyclase. This rise in cAMP, which is considered as second messenger, leads to the activation of the important downstream effector protein kinase A (PKA). PKA can then phosphorylate signal-specific proteins and give rise to the needed response. The remaining D2-, D3- and D4-receptors, which belong to the D2-class, generally use Gαi/o and thus reduce the cAMP concentrations by inhibiting the adenylyl cyclase.

An important aspect that has to be mentioned is that the dopamine receptors not only reside on the postsynaptic side, but can also be found presynaptically. This opens up the possibility of having negative feedback loops upon autoactivation and allows for a more versatile dopaminergic system (Beaulieu and Gainetdinov, 2011; Vallone et al., 2000).

For a more complete description of the downstream signaling of the D1- and D2-class receptors, as well as alternative signaling methods by these dopamine receptors, consider the review from 2015 by Beaulieu et al.

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| **FIGURE 2 |** Schematic view of the dopa-mine synthesis, vesicular uptake (yellow: VMAT-2) and cellular reuptake (Torres et al., 2003). |
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# THE REWARD SYSTEM

## Introduction to reward and its importance

If one talks about reward in everyday life, he might refer to the medal he won for his great performance in a cycling race or the delicious meal he granted himself after a long and exhausting workday. In science however, reward is not defined just as the bonus for a good effort, but rather by the behavior that it induces in the organism. In this context, reward has three different functions.

First of all, an important function of reward is to cause positive emotions, especially pleasure. We only consider a stimulus to be rewarding, if it elicits a feeling of pleasure. And if we once have experienced this feeling, we crave to relive it by seeking the triggering stimulus again.

This brings us to the second function of reward, which is decision making. Rewards have a big influence on the way we live, by directing our behavior and our decisions towards actions that make us experience positive emotions again. We decide to go dining in a nice restaurant rather than consuming the leftovers from the day before, because we know that it will improve our mood and bring us this rewarding feeling of pleasure and contentment. But how do we know this in beforehand? Because we already experienced the connection between a behavior like that and a positive feeling in other moments of our lives. This shows, that as its third function, reward can produce learning (Schultz, 2015).

Thorndike`s famous “puzzle box” experiments, where a cat in a cage first randomly discovers the mechanism to get food, but later intentionally triggers the same mechanism over and over again, only worked because the cat validated the food as a reward and craved it again which resulted in learning (Thorndike, 1911).

So one might ask oneself, why this concept of reward seems to play such an influential role in our lives. The answer may lie, as it is often the case, in an evolutionary benefit. When we think of things that we consider to be rewarding, eating, drinking and sex probably will be among the things we will come up with first. Exactly those things are also crucial to achieve a high fitness, because without eating and drinking there is no survival and without intercourse there is no offspring. Thus, the eventual function of reward is to promote behavior leading to better survival and reproduction and hence to an increase in evolutionary fitness (Schultz, 2015).

How reward is processed in the brain and how this system brings different structures together, will be discussed in the following.

## Anatomy and physiology of the reward system

The anatomy of the reward system in the brain is quite complex as many different structures are involved and interconnected. The reward pathway often is also referred to as the mesolimbic dopaminergic system (Trainor, 2011). This name not only indicates the important role of the neurotransmitter dopamine in this pathway, but also the general brain region, where the different involved structures are located. A central part of the system is the ventral tegmental area located in the midbrain. When a person is exposed to a stimulus which is associated with a reward, such as food or sex, dopaminergic neurons in the VTA are activated and start to release its neurotransmitter dopamine (Pignatelli and Bonci, 2015). Although the VTA consists only of more or less 5000 neurons, thanks to their extensive projections they are able to communicate with many different structures in the brain (Arias-Carrión et al., 2010).

An important structure that gets activated by dopaminergic signaling from the VTA is the nucleus accumbens (NAc) in the basal forebrain (Ranaldi, 2014). In the 1950s, Olds and Milner observed, that animals would carry out different tasks, when they were rewarded with the stimulation of the brain region, now linked to the nucleus accumbens, which implied its function as the possible “pleasure center” in the brain and its important role in the reward system (Olds and Milner, 1954). The NAc is mainly composed by medium spiny neurons expressing dopamine receptors (Salgado and Kaplitt, 2015). Whenever dopamine neurons of the VTA are activated upon rewarding stimuli, the released dopamine binds to the corresponding receptors on the NAc neurons. The exact role of the NAc is still not fully understood yet, but it appears to be important for different components of reward processing. When the release of dopamine from the VTA occurs, not only the medium spiny neurons of the NAc get activated, but also a change in the responsiveness of said NAc neurons for excitatory stimuli coming concurrently from other parts of the brain, especially the amygdala and the orbital-medial prefrontal cortex, is promoted. Following to its activation, the NAc neurons project to an area near the globulus pallidus, which is called the ventral pallidum (VP) (Purves, 2012).

Studies could show that inducing lesions to this brain region in rats caused an elimination of the normal liking behavior towards sucrose, indicating its role in the mediation of reward (Cromwell and Berridge, 1993). There are even some indications that activation of the circuit through the VP alone can be sufficient for the activation of a reward-induced behavior, showed by experiments similar to the ones by Olds and Milner mentioned earlier, where animals pressed a lever repeatedly when they were rewarded with electrical stimulation of the VP area (Smith et al., 2009). The VP normally effectuates a tonic inhibition of the mediodorsal nucleus, which is located in the thalamus. When NAc neurons are activated however, their GABAergic signaling leads to a suppression of this tonic inhibition and therefore to an overall activation of the mediodorsal nucleus (Purves, 2012).

The mediodorsal nucleus is thought to contribute to decision making and object-reward associations (Chakraborty et al., 2016). A recent study about the function of this structure revealed that monkeys with a damaged mediodorsal nucleus failed in making logical decisions based on previous decisions that were rewarded. This suggests that this region is necessary to make the link between recent decisions that resulted in reward and new decisions about the same topic (Chakraborty et al., 2016). The activation of this nucleus by NAc mediated disinhibition, induces further signaling to the medial prefrontal cortex (Purves, 2012). This signal gets enhanced by projections of dopaminergic neurons which reach from the VTA directly into the same cortical region (Purves, 2012). The medial prefrontal cortex not only gets inputs from different areas, but has also a back signaling function by bringing sensomotoric information back to both, VTA and NAc by glutamatergic projections (Kandel et al., 2012).

As described here, many anatomical structures have a relevant role in the reward system, however, the exact way they interact with each other and the exact role of every area is still not fully understood.

A question that impels itself as well is, which stimuli really activate this whole cir-

cuit and which do not. Possible answers regarding this issue are discussed in the following paragraph.

## Stimuli which activate the reward system

As outlined earlier, rewarding stimuli like sex, food or even social interactions (Krach et al., 2010) activate the reward system in our brain by first releasing dopamine in the VTA. But how does the brain know whether a stimulus is rewarding or not?

Stimuli of primary rewards, such as the discovering of food during exploration of an environment or even just the offering of a nutrient without any prior task completion, activates 70% of the dopaminergic neurons in the reward system (Schultz, 2002). There is no significant difference in neuronal response between different foods or drinks, but there is a clear contrast to non-rewarding or even aversive stimuli (Romo and Schultz, 1990). The phasic activation of dopamine neurons upon aversive stimuli, such as drinking of hypertonic salt solutions, namely occurred only in 14% of the neurons (Mirenowicz and Schultz, 1996). This however does not mean that this system and its dopaminergic neurons is not also involved importantly in processing aversion, indicated for example by rats which showed activation of dopaminergic neurons in the NAc upon electrical shocks (Schultz, 2002). The exact role of the system regarding aversion is generally discussed quite controversially, whereby newer studies suggest, that many of the dopaminergic neurons indeed are inhibited by stimuli of aversion, but there is a small subgroup that in contrast gets excited (Volman et al., 2013).

When conditioned stimuli are used which predict rewards, similar to the famous conditioning experiments by Pavlov, still 55-70% of the dopaminergic neurons are activated (Schultz, 2002). The mechanisms of reward processing in learning and conditioning are generally an interesting topic with rather surprising findings. When an unconditioned, primary stimulus is presented, the dopaminergic signaling fires directly after perceiving the stimulus (Schultz, 2002). However, if a conditioned stimulus, which earlier has been connected to a later occurring reward by classical conditioning, is presented, this stimulus already triggers dopaminergic firing, even before the presentation of the connected reward. The reward itself afterwards does not evoke an additional firing (Mirenowicz and Schultz, 1994). When the conditioned reward after the stimulus is removed, there is not only no additional firing, but even a depression of activity. This depression happens exactly at the time, at which the reward normally occurred during conditioning, suggesting that there is some sort of internal clock which tracks the timing of the reward delivery (Schultz et al., 1993).

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| **FIGURE 3 |** The firing of dopaminergic reward system neurons after an unpredicted reward (1), after a predicting conditioned stimulus with following reward presenting (2) and after a predicting conditioned stimulus where the reward is omitted (Schultz et al., 1997). |
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Together, these finding indicated a different role for dopaminergic reward signaling than what was originally proposed. Not just any reward related stimulus activates the reward circuit unconditionally, but there is rather a reporting of the reward, relative to its prediction (Schultz, 2002). When the reward is as expected and predicted by previous learning, there is no signaling when the reward is presented, but only after the receiving of the conditioned stimulus. When the reward is better than predicted or was not predicted at all, there is an increased dopaminergic signaling upon reward obtaining. However, when the reward is removed after the conditioned stimulus or it is worse than predicted, the signaling is depressed (Schultz, 2002). Concluding, the reward system is activated upon deviation of the actual reward in comparison to the prediction, the so called prediction error of reward (Schultz et al., 1997).

Unfortunately, the reward system does not only help to reinforce behavior which is necessary for survival and reproduction, but can also be manipulated by a large group of drugs and contributes thereby to addiction, as we will see in the following.

# DOPAMINE AND ADDICTION

## Addiction in General

Drug addiction, a substance-dependence on a psychological and physical level (Purves, 2012), leads to interfering physiological modification in the dopamine system. An addict shows a compulsive drug-taking behavior even though it may provoke consequences regarding health, social standing and even law enforcement.

Discontinued drug intake after abuse leads to substance-characteristic withdrawal syndromes, generally opposite effects (Purves, 2012) manifesting themselves physically and emotionally. Although there are many environmental and psychological factors involved, addiction is a biological process that affects not only humans but also other laboratory animals, including primates and rodents (Purves, 2012). Epidemiological studies display a significantly high genetic risk-component (40 – 60 %) (Nestler and Landsman, 2001) for an individual in developing addictive behavior.

The progression to addiction involves three consecutive steps, starting with occasional and recreational drug intake. In a second step, drug use gets more frequently and intensified and is ultimately followed by loss of control.

After intake of the agent of abuse, the rewarding and reinforcing effects lead to continuation and consolidation of this demeanor. But as persistent drug exposure eventually induces tolerance, i.e. a reduced sensitivity to the substance of dependence, the afflicted individual enters a vicious circle of an increased dose needed for the desired effect, leading again to an intensified dependence and tolerance. The opposite effect of tolerance, after continuously drug taking, is sensitization. Such increased effects include behavioral alterations, often locomotion (Keiflin and Janak, 2015), and augmented amount of dopamine in the synaptic cleft and induction of a set of immediate early genes (White, 1998).

As addiction is a chronic disease, even after treatment, craving for the abused drug accompanies the process of rehabilitation for years. Statistics of the Yale University in USA show that more than two thirds of the individuals relapse during the first year of treatment (Osborn, 2017) , and a high risk remains even after years of abstinence. On top of this, drug abuse could lead to cognitive consequences that impede the rehabilitation process beyond quitting drug intake and seeking (Robbins and Everitt, 1999).

## Drug Targets in General

Especially circuits in the evolutionarily old brain, i.e. the mesolimbic system, are affected by drug-mediated addiction. The previously discussed reward system that responds to natural reinforcers, including food and sex, is hijacked and can lead to a loss of control in regard to drug seeking (Nestler and Landsman, 2001). The euphoric rewarding effects of cocaine are also linked to dopaminergic projections to the nucleus accumbens in the forebrain (White, 1998).

## Classification of Drugs

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| C:\Users\siand\AppData\Local\Packages\Microsoft.MicrosoftEdge_8wekyb3d8bbwe\TempState\Downloads\journal.pmed.0030437.g001.TIF | **FIGURE 4 |** Addictive drugs induce an increased dopamine level via three main mechanisms and are classified by them. Class I: through disinhibition by interacting with G-protein coupled receptors (G) on GABAergic neurons. Class II: interaction with ion channels or ionotropic receptors (i), Class I and II drugs operate in the ventral tegmental area (VTA). Class III: blocking transporters (T) for the monoamine reuptake leads directly to a raised dopamine level in the nucleus accumbens (NAc) (Lüscher and Ungless, 2006) |
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There is a huge diversity of addictive substances, yet, many of them commonly target G-protein-coupled receptors. Cannabinoids and opioids are agonists for cannabinoid and opioid receptors, respectively and cocaine acts indirectly on dopamine receptors, which belong to the family of G-protein coupled receptors, too (Nestler and Landsman, 2001).

More precisely, by the molecular mechanisms of action through which dopamine is increased, most of the common drugs can be assigned to one of three groups (Nugent et al., 2007) (figure 4). Class I contains substances that directly bind G protein-coupled receptors, including the just mentioned opioids and cannabinoids. They are commonly agonists of the GPCRs on GABA neuron and raise dopamine levels via disinhibition (Lüscher and Ungless, 2006). The second group has a more diverse effect on dopamine neurons (excitation, disinhibition), but generally acts on ionotropic receptors. This class consists of socially more accepted drugs like nicotine and alcohol and also the prescription drug benzodiazepine (Lüscher and Ungless, 2006). Monoamine transporters for neurotransmitter uptake are blocked by addictive substances of class III, and as a consequence, dopamine concentrations are increased. Mostly party drugs like ecstasy, amphetamines and cocaine operate on this pathway. While class I and II drugs affect neurons in the ventral tegmental area, the effects of substances from the third group elicit a direct increase of dopamine in the nucleus accumbens. Besides these differences, all addictive drugs commonly lead on one hand to a higher mesolimbic dopamine levels, and on the other hand, strengthen dopaminergic neurons in the VTA, i.e. increasing the AMPA/NMDA ratio by inserting AMPA receptors into the postsynaptic neuron (Nugent et al., 2007).

## LTP Induction

The progress of addiction is comparable to a habit-based learning (Robbins and Everitt, 1999). As its chronicity indicates, frequent drug abuse induces persistent synaptic adaptations. For example, upon repeated cocaine exposure of rats, their dopamine neurons in the ventral tegmental area become significantly more susceptible to long-term potentiation (Liu et al., 2005). More precisely, cocaine not only inhibits dopamine and other monoamine transporters in the nucleus accumbens and by interfering with the neurotransmitter reuptake, prolongs the neurotransmission (Pascoli et al., 2015), the drug mediates a disinhibitory effect on dopamine neurons in the ventral tegmental area, too (Liu et al., 2005).

The experiments of Qing-song Liu, Lu Pu & Mu-ming Poo in the year 2005 suggest that cocaine leads to a reduction of the of GABAA (-aminobutyric acid) receptor-mediated inhibition, thereby leading to more active dopamine neurons. The enhanced synaptic plasticity facilitates long-term potentiation and may play an important role in memory formation in regard to addiction.

Looking at dopaminergic neurons in midbrain slices obtained from rats that were exposed to either cocaine dissolved in saline or saline only, effects on the long-term potentiation induction were studied. Using whole-cell recordings from VTA dopamine neurons, the stimulation-evoked excitatory postsynaptic potentials (EPSPs) were measured. Since these excitatory postsynaptic potentials were fully abrogated in presence of an AMPA (-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid) and NMDA (N-methyl-D-aspartate) receptor antagonist, the neurotransmitter in charge must be glutamate. Both of these receptors are crucial for learning and memory formation and the activity-dependent changes in the structure of a synapse. NMDA receptor are responsible for long-term potentiation induction, they sense correlated

pre- and postsynaptic activity and hence act

as a coincidence detector. By mimicking the EPSP-pattern observed in reward-related stimuli, the researchers could induce a stimulus for long-term potentiation. The obtained data show significant differences not only in rats treated with cocaine or saline, but as well in rats treated only once or multiple times with the drug. Neither rats treated with saline for one or more days nor the ones treated to cocaine for a single day showed any significant alterations, whereas the rats exposed to cocaine for 5-7 days exhibited an increased EPSP amplitude in ventral tegmental area dopamine neurons (Figure 5). This suggests a facilitated induction of long-term potentiation in the respective neurons, mediated by repeated cocaine-presence.

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|  | **FIGURE 5 |** Facilitated long-term potentiation induction in rat midbrain slices after stimulation (mimicked reward-related stimuli)  b, c, top: examples of excitatory postsynaptic potentials (EPSP), after stimulation  bottom: normalized EPSP amplitude  left: rats treated with saline for 5-7 days  right: rats treated with cocaine dissolved in saline for 5-7 days  the arrow indicates the start of the long-term potentiation (LTP) induction protocol  d: rats treated for one day with saline, after stimulation  e: rats treated for one day with cocaine dissolved in saline, after stimulation  (Liu et al., 2005) |
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Given that LTP induction at excitatory synapses is often prevented by GABA-mediated inhibition, in absence of this inhibitory signal, LTP induction should be facilitated. Using the substances bicuculline methiodide (BMI) and picrotoxin (PTX), blockers for the GABAA receptor, the experimental outcome looked, as expected, completely differently. The amplitude of ESPS increased not only in repeatedly cocaine-treated rat brain slices (like before), but also to a similar extend in rats treated with time-matched saline injections, and in rats given a single dose of cocaine or saline, too (figure 6).

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|  | **FIGURE 6 |** Facilitated LTP induction in rat midbrain slices after stimulation, due to blocking GABA-mediated inhibition  a, b, top: examples of EPSP in presence of bicuculline methiodide (BMI), after stimulation  bottom: normalized EPSP amplitude in presence of BMI  left: rats treated with saline for 5-7 days  right: rats treated with cocaine dissolved in saline for 5-7 days  the arrow indicates the start of the long-term potentiation (LTP) induction protocol  c: EPSP amplitude of rats treated for one day with saline, in presence of picrotoxin (PTX)  d: EPSP amplitude of rats treated for one day with cocaine dissolved in saline, in presence of picrotoxin (PTX)  (Liu et al., 2005) |
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Evidence that the magnified excitatory postsynaptic potential is due to long-term potentiation are firstly, that concurrent treatment with AP5 (D-2-amino-5-phosphonopentanoic acid), a NMDA antagonist, abolishes the effect of bicuculline methiodide, and inducing no LTP. Secondly, the presence of these receptor blockers had no influence on LTP if applied after the stimulus. And thirdly, addition of a GABAA receptor enhancer, thus increased inhibition, prevents long-term potentiation formation in rats that have been treated for 5-7 days with cocaine.

Records of the inhibitory postsynaptic current (IPSC) of the ventral tegmental area neurons provided more insights into the GABA-mediated inhibition and its alteration due to cocaine. In slices of repeatedly cocaine-treated rats, there was a significant reduction of the mean amplitude of maximal IPSP. Moreover, this reduction was cell-type specific (figure 7). While dopaminergic VTA neurons exhibited a reduced IPSC amplitude, there was no alteration in non-dopamine neurons. On top of this, after seven days of cocaine-injection, the decreased amplitude remained at a reduced level for more than 12 days, leading to a persistent synaptic adaptation. As the amplitude of the GABA-mediated synaptic currents is decreased, the postsynaptic responsiveness to GABA is reduced, and as a consequence, the spike-probability is increased.

This facilitatory effect on LTP induction caused by cocaine, as well as BMI and PTX, is suggested to be due to disinhibition on the dopamine neurons in the VTA, which is further supported by previous studies. They suggest that by blocking GABA-mediated inhibition during repetitive stimulation of afferents, temporal summation of excitatory postsynaptic potentials is enhanced (Pouille and Scanzani, 2001) and the NMDA receptor is more active (Herron et al., 1985). Furthermore, back-propagation of the action potential is enhanced (Larkum et al., 1999), too, which may be part of the important retrograde signal that initiates long-term sensitization.

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| **FIGURE 7 |** Dopamine neurons specifically show a decreased IPSC after cocaine treatment.  a: ventral tegmental area (VTA) dopamine neurons, treated with cocaine (black) or only saline (white) for 7 days. The mean maximal inhibitory postsynaptic current (IPSC) amplitude decreases during cocaine treatment and stays low even 12 days after withdrawal  b: mean amplitude of IPSCs in VTA non-dopamine neurons, treated with cocaine (black) or only saline (white) for 7 days  (Liu et al., 2005) |
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## Sufficiency of Dopamine in Progression to Addiction

Apparently, dopamine plays a fundamental role addiction, but is it sufficient to elicit addictive behavior? Using an optogenetic approach, Pascoli et al. allowed mice a specific self-stimulation of only dopaminergic neurons in the VTA, and thereby test sufficiency. The experiment consisted of mice in an operant box and after pressing an active lever, they received laser stimulation of the VTA neurons. The stimulation pattern (bursts) mimicked the firing pattern observed in natural reward. A flashing cue light preceded the laser stimulation and, to imitate the delay of raised dopamine levels occurring after drug intake, the laser stimulation onset was only 5 s after the required lever pressing. As the laser-evoked bursts in the dopamine neurons elicited self-stimulation in all mice, dopamine signaling seems to be sufficient to initiate reinforcement.

After cocaine injections prior to self-stimulation sessions, mostly in the first 30 minutes – consistent with cocaine pharmacokinetics – the active lever pressing decreased by 75%, indicating that reinforcement by cocaine and optogenetic stimulation, respectively, hinge on similar underlying brain circuits.

With the optogenetic approach and thereby only specific dopaminergic neuron stimulation in the VTM, another hallmark of addiction was observed. Even after a relatively long abstinent time, in this experiment 30 days of withdrawal after 12 days of self-stimulation, seeking of the very same behavior was still apparent. Relapse can be triggered by the drug itself, a stress situation or a conditioned stimulus that predicts drug availability in a cue-associative fashion (Robbins and Everitt, 1999). Just by re-exposing the mice to the operant chamber, robust cue-associated behavior could be triggered and mice pressed the lever repeatedly, triggering only the cue light and not the actual stimulus. Most importantly, the changes in plasticity seen in the optogenetic mice cannot be distinguished from mice treated with cocaine injections.

To take another core feature into account, a mild electric shock, coincident with every third laser stimulation, cocaine or sucrose injection, displays the negative consequences following consumption, in this case self-administration. While in mice treated with sucrose, the shock occluded any repetition in lever pressing, in optogenetic or cocaine self-stimulated mice, two different behavioral responses became apparent. Punishment triggered a sensitive behavior in some mice, defined by a decrease of self-stimulation by at least 80%. Mice classified as resistant preserved and did not alter the number of self-stimulation, although they had to endure punishment. Furthermore, resistant mice had the tendency to augment the number of futile lever presses, i.e. presses that are unnecessary for a stimulation initiation, mostly between the cue and onset of stimulation. This may be interpreted as an impatient and impulsive response. Altogether, these observations give rise to the assumption that activation VTA dopamine neurons are important to drive resistance to punishment in drug abuse, but more importantly, self-stimulation of only VTA dopamine neurons is sufficient to trigger compulsivity and govern progression through the tree consecutive steps to addiction. The specific activation of midbrain neurons achieved by the optogenetic approach seems to be potently addictive, even more than drugs – in this case cocaine – as shown by the proportion of punishment-resistant mice. While two thirds of previously optogenetically stimulated mice maintained self-stimulation, only about a quarter of mice with cocaine self-administration continued a drug seeking-behavior. A possible explanation may be the specific and proximate dopaminergic activation. Cocaine targets as well other cellular mechanisms and thereby may trigger counteracting behavior.

By looking at c-Fos expression – indicating neural activity – Pascoli et al. found a noticeable increase in the orbitofrontal cortex (OFC) only in resistant mice. In slices prepared 24h after the last punishment session, the intrinsic excitability of OFC neuron was enhanced only in mice that showed resistance to punishment before and probably is due to raised c-Fos levels. An indication for a causal relationship between c-Fos expression and resistance is provided by an experiment that exhibited a reduction of the resistant to sensitive mice ration. In presence of an OFC inhibitor, significantly less mice continued the compulsive self-stimulation in presence of the punishing electro shock. As a conclusion, OFC neurons seem to be involved in the decision to maintain self-administration regardless of negative consequences, which is a hallmark of the disease progressing to addiction.

There are not only similarities between chronic drug users and people with cortex-damage in regard to decision making (Robbins and Everitt, 1999), impaired cost-benefit decisions and compulsivity have been linked to dysfunctions of the orbitofrontal cortex.

Yet, the cellular mechanism that drives an increased c-Fos expression in the orbitofrontal cortex, eventually enhance resistance to punishment and thereby foster addiction, remains unknown.

## Reward prediction error

As already mentioned, phasic dopamine signals play an important role in reward prediction errors (RPE) due to reporting rather the discrepancy between the real and expected reward than just the presence of the reward itself (Purves, 2012). Of importance is, that during associative learning, this reward prediction error shifts the neural activation from responding to the presence of the natural reward to the presence of the associated cue (Keiflin and Janak, 2015), as seen in figure 8, A. This system allows learning and modulation until an accordance of the predicted and actual reward is achieved, leading to a stable cue value (figure 8, C).

Contrariwise, cocaine self-administration elicits a delayed phasic dopamine release that does not decrease with cue-learned reward prediction and remains unmodified. Similar to the response to food, the cue itself triggers as well a time-locked increase in dopamine in the nucleus accumbens (figure 8, B). But as the long-lasting dopamine signal remains unaltered by the error-correcting RPE, the cue value continuously increases and therefore never reaches gets stable (figure 8, C).

By producing a value-prediction, RPE contribute to the behaviors of an individual and can lead to reinforcement. Drugs like cocaine seem to evoke long-lasting increases in dopamine signal amplitude and frequency, in response to the reward itself – and not only the cue – and thereby may be responsible for repeated drug-taking (Keiflin and Janak, 2015).

# DOPAMINE AND OBESITY

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| **FIGURE 8 |**  Reward prediction error in natural reward and after cocaine self-administration.  A: A phasic dopamine release is triggered by unexpected food, but after cue-associated learning, only the cue elicits a neural response.  B: As in natural rewards, learning leads to a cue-associated response. Contrarily, persistent bursts of dopamine release are evoked by cocaine injections and they do not decrease with learning.  C: RPE allows adjustment until the reward prediction matches the real occurring reward, leading to a constant cue value. Cocaine, on the contrary, never elicits matching values and consequently, the cue value constantly increases (Keiflin and Janak, 2015). |
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As the obesity epidemic continues and more and more people are affected by the increased health risks that accompanies obesity, our society is in dire need of a solution to ameliorate the current situation, as this trend has global health and economic implications. In this section we will discuss one aspect of the dopaminergic reward circuitry that adds yet another facet to obesity, a condition that is in the current consensus view more complicated than the simplistic surplus of energy due to an imbalance of energy intake and energy need.

## Regulations of Food Intake

Dopamine in the lateral and ventromedial hypothalamus has been shown to have a regulatory function in regards to food intake. While lesions in the ventromedial hypothalamus resulted in overeating behavior (hyperphagia), destruction of the lateral area of the hypothalamus showed a reduced food intake (hypophagia). Further investigations showed, that dopamine is one key factor in these areas. In satiety, the dopamine levels in the ventromedial are decreased, but during the transition towards fastening, dopamine levels are elevated. Furthermore, a dopamine injection in that area resulted in an increased meal size.

While there is decreased amount of dopamine in the ventromedial hypothalamus, the concentration rises in the lateral area, once the organism starts eating. It has been shown that there is a proportional increase of dopamine compared to meal size. As soon as the organism is in the post-prandial state, the dopamine decreased in the lateral hypothalamus. Pharmacological activation of this area lead to a decreased eating behavior. These findings suggest that dopamine in the ventromedial hypothalamus promotes food intake, while it prevents the intake when elevated in the lateral hypothalamus (Vucetic and Reyes, 2010).

## Motivational Eating

When it comes to reward based research, the terms “wanting” and “liking” have been established, with the former being more motivation based and the latter acting through reinforcement (Volkow et al., 2011; Vucetic and Reyes, 2010).

So far, two different areas have been discovered to be important for the “want”-based rewarding: nucleus accumbens (NAc) and caudate putamen (CPu). As it was thought that the mesolimbic system is more responsible for the motivation based circuit, it was earlier detected that NAc plays a vital role in the reward based behavior. Studies have shown that a clear external stimulus with motivational significance (such as palatable food) causes a burst-like firing of dopamine in NAc. However, disruptions in this area did not cause for a decrease in meal size or frequency, but a clear decrease in efforts to get to the desired food. Pharmacological activation of this area showed supporting results, as the meal size, in contrast to the willingness to obtain the food, did not increase.

It was later found that a depleted CPu can be lethal in regards to nutritional intake. Mice lacking neuronal activity in this region did not have a high enough food intake. When both NAc and CPu were depleted and then only the NAc function restored, mice showed a motivated behavior in respect to palatability but had still troubles with taking in the needed energy amounts. On the other hand, a restored CPu with a still disrupted NAc was enough for the mice to survive. These observations suggest that the mesolimbic NAc contributes to hedonic motivations for food consumptions, while CPu serves as an area, where the motivation for the intake of sufficient amounts of food comes from.

Another property of the reward system seems to be that subjects can like the reward for being a reward. This idea of “liking” applied with respect to food consumption has been shown to have its neural basis not only in the mesolimbic system but also in cortical regions. The dopaminergic system seems to be interconnected with the endogenous opioid system. Activation of the opioid receptors resulted in an overeating behavior of palatable food, while the antagonistic intervention showed the vice versa. When the opioid system was activated, dopamine was increasingly observed in the NAc (Vucetic and Reyes, 2010).

## Modulating the Circuit

Hormones responsible for maintaining the homeostasis of the bodies energy needs can also have an effect on non-energy related systems. For example, insulin, as a hormone released when glucose levels are high, can decrease the response to food stimuli in brain regions correlating with the reward system. Type-II diabetes patients, who have become insensitive to insulin, show a higher brain activity in those regions, compared to non-diabetic subjects, when confronted with food stimuli.

Leptin, another hormone increasingly secreted in satiety, has similar effects. Leptin deficient patients were shown images of meals after they had eaten and still had active responses in the mesolimbic dopamine

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| **FIGURE 9 |** Left: Response to food stimuli in congenital leptin deficient patients (Leptin is produced by adipocytes in normal physiology). Right: The response after one week of treatment with leptin (Volkow et al., 2011). |
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system. After one week of leptin treatment the response was decreased (Figure 9).

The gastral hormone ghrelin on the other hand shows a positive effect to the reward system. This hormone, that is secreted by the

endocrine cells in the stomach in higher concentrations during fastening, enhanced the activity in the mesocorticolimbic areas, when exposed to food stimuli (Pape et al., 2014; Volkow et al., 2011).

## Obesity and Compulsive eating

A functional magnetic resonance imaging study performed with obese and lean individuals in 2008 showed, that when the conditioned stimulus for obese individuals (palatable food) was presented to the participants, the brain activity in the obese group was higher compared to the group with the lower BMI. This increased activity was observed in the somatosensory cortex (presumably because the processing of palatable food takes place in that area). However, when the actual food was given to the participants, the response in the dopaminergic reward areas was lower than in lean individuals (Stice et al., 2008; Volkow et al., 2011).

In their experiments with rats, Johnson and Kenny showed, that rodents with extended access to the so called “cafeteria diet” (a form of palatable food for rats) had decreased D2 receptor levels in the striatum. These rats then showed a compulsive eating behavior, even when negative stimuli were also accompanied with the access to the cafeteria diet. This compulsive behavior and hyperphagia might be explained by an attempt to reach the rewarding state, which is desensitized, and thus needs increased food intake as a compensation. (Johnson and Kenny, 2010; Volkow et al., 2011).

Together with the delay discounting aspect of obesity and hyperphagia, these results seem to indicate, that obesity and addictive drug behavior show neural similarities and that an altered dopamine reward system might play a vital role in this regard (Volkow et al., 2011).

# CONCLUSION

## Reward and Addiction

During the last century, many studies have been done regarding the reward system and its function. Different brain areas and neurotransmitters have been proposed to have a role in reward processing. However the exact mechanisms – as well in regard to addiction – are still not fully understood and further research will be necessary for a more detailed understanding of both, molecular interactions between and specific functions of the different structures. Nevertheless, recent studies already made progresses in describing the way in which the reward system is activated, highlighting the important function of comparing reward prediction with effective reward presentation for circuit activation by dopamine release. By understanding the reward system, conclusions to addiction can be drawn and a better understanding is crucial to enable better treatments.

Especially cocaine is a widely researched drug and a lot of effects caused by it are known, for example facilitated LTP induction, monoamine transporter blocking and altered RPE. But on a molecular basis, many mechanisms remain unknown.

## Reward and Obesity

In the hypothalamus, two areas have been identified to be important for regulating food ingestion. By lesion and intervention studies the role of the ventromedial hypothalamus in meal size determination has been demonstrated, while in the lateral hypothalamus a termination function for food intake was observed.

With depletion of the dopaminergic system and reactivation of the caudate putamen, the essential role of this dopaminergic area to perceive nutritional needs as an incentive to pursue food was discovered. The hedonic aspects of eating and its motivational drive on the other hand has been linked to the nucleus accumbens. However, the dopaminergic system is not the single leader in the role of motivating the organism. Endogenous opiates have also an important part in this regard and seem to have a interconnective relation to the dopaminergic system.

Lastly, the plasticity of the D2 receptors in the striatum, more specifically its downregulation in obese individuals compared to lean subjects, has been correlated to a compulsive eating behavior, not unlike the compulsivity observed in drug-seeking individuals. All in all, dopamine seems to have a quite important role in regards to food intake and these behavioral and molecular similarities between obesity and addiction indicate a possible and partial explanation of the rising numbers in overweight and obese individuals.

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