14 Beyond Wise et al.: Neuroleptic-induced "anhedonia" in rats: Pimozide blocks reward quality of food

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INTRODUCTION TO DOPAMINE (DA)

Of all the neurotransmitters in the brain the one that is best known to the lay public, by far, is dopamine (DA). To the public, and much of the media, DA is the brain's "pleasure transmitter." By this popular view, it is a burst of DA that produces the pleasure associated with the receipt or anticipation of natural rewards – a chocolate cake, sex, even social rewards – as well as the euphoria produced by addictive drugs, such as amphetamine, cocaine or heroin. In the popular media it is often suggested that it is pursuit of this DA "rush" that leads to a variety of impulse control disorders, such as over-eating, gambling and addiction. Of all the ideas, in all of neuroscience, this is one of the most widely known, and its origin can be traced to the 1978 paper by Roy Wise, Joan Spindler, Harriet deWit and Gary Gerber, that is the topic of this chapter. This paper is an excellent example of how the interpretation of a seemingly simple experimental finding can profoundly influence the thinking and trajectory of an entire field, and the public imagination, for decades – even if it is wrong.

But before getting to that conclusion, we should step back and consider the time leading up to the publication of this extremely influential paper. It was only a little over a decade earlier that DA was first recognized as a neurotransmitter in its own right (rather than just being a precursor of norepinephrine). This came about from a series of important studies by researchers in Sweden who developed a histofluorescence method to identify and map monoamine neurotransmitters in the brain (including DA). They thus effectively created the field of chemical neuroanatomy, as well as vividly mapping the location of dopamine in the brain. They also produced useful methods to selectively lesion monoamine-containing cells with neurotoxins, such as 6-hydroxydopamine (6-OHDA), which would help reveal dopamine's psychological functions via behavioral consequences. As a result of these studies it became clear that DA-producing neurons located in the midbrain (the substantia nigra and ventral tegmental area) send dense projections to the dorsal and ventral striatum (the caudate-putamen and nucleus accumbens) in the

forebrain, where DA is released. It also became clear that the loss of this dopamine projection, especially in the striatum, produces severe motor impairments similar to Parkinson's disease in humans. Indeed, early studies on the role of DA in extrapyramidal movement disorders led to the Nobel Prize much later (in 2000) for one of these Swedish researchers, Arvid Carlsson.

Much of the early work on the functions of DA focused on its role in sensorimotor control related to Parkinson's symptoms. However, an additional role for DA in motivation and reward was revealed in 1971 when Urban Ungerstedt (one of the group of influential Swedes mentioned above) published a paper reporting that 6-OHDA-induced degeneration of nigrostriatal DA neurons produced severe aphagia and adipsia; that is, the rats no longer ate or drank. This behavioral starvation syndrome was very similar to the aphagia/adipsia described following lateral hypothalamic lesions years before by Anand and Brobeck (1951), and studied in detail by Phillip Teitelbaum and his colleagues, as well as others. It turned out that these lateral hypothalamic lesions cut the nigrostriatal DA projection, depleting striatal dopamine (in addition to destroying neurons within lateral hypothalamus), leading Ungerstedt (1971) to suggest that perhaps the lateral hypothalamic syndrome was due to loss of striatal DA. To study that, John Marshall, Steven Richardson and Phillip Teitelbaum (1972) directly compared the behavioral deficits produced by lateral hypothalamic lesions and by selective 6-OHDA lesions of the nigrostriatal DA pathway that spared hypothalamic neurons. They found that these two procedures produced very similar effects on feeding behavior, similar sensorimotor disturbances, and similar patterns of recovery of function. Importantly, they also concluded that "Like lateral hypothalamic rats, these [DA depleted] animals have persistent motivational and regulatory deficits in feeding and drinking which cannot easily be attributed to their sensorimotor disturbances." In other words, the role of dopamine in motivation for food and drink was different from its role in movement or sensorimotor function.

DOPAMINE AS THE 'PLEASURE TRANSMITTER'

The evidence above was consistent with a role of DA in the motivation to eat, and possibly even in food reward. However, the nature of the "motivational deficits" produced by DA depletion remained unclear. Just what was the role of DA in motivation and reward? This brings us to Wise et al.'s (1978) paper, as it was the first to provide a clear and concise answer to this question. Their key experiment in this paper was devilishly simple. First, hungry rats were trained to press a lever to get a food pellet, which they avidly did. After all the rats had acquired lever-pressing for food, the experimental manipulations took place over four subsequent days. In one group food was simply not provided when the lever was pressed. In these animals responding was maintained on the first day of testing, but not surprisingly, over the next few days responding decreased to very low levels (i.e. the rats underwent extinction in the absence of the reward). Rats in the other key group continued to receive food when they lever pressed; however,

before the test session they were treated with a drug, pimozide, which blocked DA receptors. The behavior of these animals was identical to the group that underwent extinction – responding decreased over the four days of testing, as if the food was no longer rewarding. A number of control groups were included to eliminate the possibility that the decrease in responding under pimozide was simply due to sensorimotor dysfunction – (it was not) – as the animals treated with pimozide were clearly capable of responding, they just didn't.

A couple of years before this Wise and his colleagues had also reported that blockade of DA receptors (but not norepinephrine receptors) reduced the rewarding effects of the psychostimulant drug amphetamine, as well as that produced by rewarding electrical brain stimulation. However, it was in this 1978 paper that a reason for this was first proposed in a single powerful sentence. Tying these studies together, Wise et al. suggested that "neuroleptics [DA blockers] appear to take the pleasure out of normally rewarding brain stimulation, take the euphoria out of normally rewarding amphetamine, and take the 'goodness' out of normally rewarding food." In this one sentence, near the end of the paper, the idea was born that DA is a neurotransmitter in the brain that mediates pleasure. Wise elaborated on this idea several later papers. For example, in a 1980 *Trends in Neuroscience* review he concluded, ". . . it may yet be of heuristic value to think of pleasure centers in the brain and to think of these centers located . . . at the synapses of one or another dopamine terminal field." "The dopamine synapse might be the place where the cold information regarding the physical dimensions of a stimulus is translated into the warm experience of pleasure."

This notion – that DA is the brain's "pleasure transmitter" – immediately had an enormous impact on the field and quickly became the dominant theoretical framework guiding research on dopamine and reward, an influence still evident today, nearly 40 years later. The influence is evident in many papers published decades later (for reviews see Berridge and Robinson, 1998; Berridge, 2007). For example, as recently as 2012 it was stated, "Currently throughout the neuroscience literature dopamine is considered both a 'pleasure molecule' and an 'antistress molecule'" (Blum et al., 2012). The influence of this notion is even more evident today in the popular media. A Google search for dopamine will reveal many examples of DA presented as a "pleasure molecule." It is quite remarkable that an idea launched by one sentence in a short paper (and supported by dozens of similar experiments by Wise and others over the next decade) could have such a strong and enduring influence, and reach a level of public awareness that arguably surpasses any other conceptual advance in neuroscience.

A CHALLENGE TO THE NOTION OF DA AS A "PLEASURE TRANSMITTER"

The pervasive influence of the DA "hedonia hypothesis" is also a testament as to how entrenched a simple and seductive idea can become, even after most

people working in the field no longer accept it, including the person who first proposed it. The first real challenge to the idea came from a study by us in 1989, based on what was essentially our failed attempt to find additional support for anhedonia after dopamine loss. At the time, Kent Berridge and his colleagues had published a series of papers using a "taste reactivity" procedure to assess the pleasurable impact of tastes, from sweet to bitter. It turns out that many species (from rats to monkeys to human babies) make very characteristic and quantifiable oral-facial and other movements in response to different tastes squirted directly into the mouth, which are essentially hedonic facial expressions. Many studies established that these expressions reflect affective judgments as to the "goodness" or "badness" of tastes, such as when hunger makes sweetness taste more pleasant than when full, or when a learned taste aversion after becoming nauseous makes an originally pleasant taste become disgusting. So, in the late 1980s Berridge thought this would be a good way to add one more bit of evidence to the large amount already available in support of Wise's notion that DA mediates the pleasurable effects of foods, but using a more direct measure of affective reactions. He teamed up with Terry Robinson who was studying dopamine in the brain, and who had techniques available to measure brain dopamine and to produce dopamine-depleting lesions (along with an honors undergraduate student, Isabel Venier). Our working hypothesis going into this study was that a loss of DA would render good tastes less pleasurable and this would be reflected by a decrease in positive affective reactions to the taste, and perhaps an increase in negative reactions – thus confirming Wise's idea. But that is not what we found. In this study Berridge et al. (1989) used the neurotoxin 6-OHDA to destroy DA neurons and severely deplete DA in the striatum. The depletion was so great that many rats became profoundly aphagic and adipsic and had to be kept alive by tube feeding. Nevertheless, when sweet or bitter tastes were squirted into their mouth they reacted exactly the same as control animals. The loss of DA seemed to have no influence on their experience of the tastes as good or bad, despite the fact they showed no motivation to eat. This contradicted the previous conclusion of Wise and colleagues that rewards became worthless without dopamine. However, as a key to explanation, in all previous studies by Wise and others the tests for reward involved instrumental responding, i.e. the willingness of animals to work for a reward, which of course is not a direct measure of hedonic responses.

Two years later Berridge and Valenstein (1991) used a manipulation to change DA in the opposite direction, i.e. they *increased* feeding behavior by use of rewarding electrical brain stimulation in the lateral hypothalamus that can stimulate dopamine release. Contrary to predictions of hedonic hypotheses at the time, they showed the increased motivation to eat was not because the food tasted better, again using the taste reactivity procedure. In addition, one limitation of the 1989 study was that DA levels were measured in the entire striatum, and it was possible that DA in the ventral striatum (nucleus accumbens) was relatively spared and this was why hedonic reactions were also spared – at the time it was becoming increasingly accepted that it was DA in the ventral as opposed to dorsal striatum that was

especially important in reward. Therefore, in a later paper Berridge and Robinson (1998) conducted a similar study that included rats that had essentially complete (+99%) DA depletions in both the ventral and dorsal striatum. Although profoundly aphagic and adipsic, these rats also showed normal taste reactivity. In this latter study it was also shown that DA depleted rats could learn new hedonic values of a taste when a previously good taste was rendered bad by pairing it with an aversive state (taste aversion learning), which indicated that the facial reactions reliably reflected the hedonic value perceived by the entire brain.

A MOTIVATIONAL INTERPRETATION

In writing the original 1989 paper (Berridge et al., 1989) we were faced with a dilemma: DA depletion greatly decreased food reward in the sense of the motivation to feed, consistent with many studies showing that a decrease in DA neurotransmission decreases the willingness of animals to *work* for rewards (including the Wise et al., 1978 study), but this was not accompanied by any apparent change in the ability of DA depleted rats to generate normal hedonic reactions to the pleasure of sweetness, as assessed with taste reactivity. How to explain this discrepancy between the earlier anhedonia evidence and our observation of normal hedonic impact? It was done by proposing the notion of *incentive salience* attribution, as an admittedly post hoc hypothesis to make sense of these and the earlier data (guided also by other evidence and theory about how incentive motivation works). Simply put, the hypothesis we proposed was that "dopamine neurons belong to a system that assigns salience or motivational significance to the perception of intrinsically neutral events." This notion was further elaborated by Berridge and Valenstein (1991), and then more extensively in a larger review paper by Berridge and Robinson (1998), in which it was proposed that neural systems that mediate "wanting" rewards are dissociable from those that mediate "liking" rewards, and that DA is important for "wanting" rewards, the extent to which animals are motivated to obtain them, but not for "liking" them.

The idea that "wanting" is not the same as "liking" has since been investigated extensively and has become reasonably well accepted in the literature. Furthermore, additional evidence accumulated in 1990s suggesting the role of DA in reward was not to mediate pleasure. For example, studies by Wolfram Shultz established that once presentation of a reward was predicted by a cue preceding it, DA neurons discharged upon presentation of the cue, not during consumption of the food reward, when presumably they would experience the pleasure of its taste. This was consistent with many studies using microdialysis or in vivo voltammetry showing that DA is released in *anticipation* of rewards, be they food, sex or drug rewards (e.g. Phillips et al., 2008). Other studies established that DA is released and some DA neurons discharge during aversive/stressful events (like footshock) and cues that predict them, which would presumably not be experienced as pleasurable. Importantly, studies in humans emerged addressing this question (e.g. Leyton, 2010). In one example, Brauer and deWit (1997) reported

that DA receptor blockade with pimozide in humans given amphetamine reduced ratings of how much they wanted more, but had no effect on how much they liked it. Indeed, 16 years after his seminal 1978 paper Wise (1994) himself wrote, ". . . my assumption was that subjective pleasure usually accompanied reward and would be blunted by treatments that blunt reward; I no longer make this assumption . . .". Nevertheless, although no longer held by most researchers in the field, the notion of DA as the brain's "pleasure transmitter" still holds sway in the public's imagination.

In the scientific literature the debate as to the role of DA in reward has not gone away, but it has shifted to consider other aspects of reward. It has become increasingly recognized that "reward" is a multifaceted concept consisting of a number of psychologically and neurobiologically dissociable processes. Berridge and Robinson (2003) argued that reward has three major components, each of which can be further subdivided: (1) *learning* about rewards and the cues that predict their availability; (2) *motivation* for these and cues associated with them (wanting and "wanting"); (3) *affective* (hedonic) responses to the actual pleasure of rewards (liking and "liking"). Thus, as it became accepted that DA is not involved in mediating the affective (pleasurable) component of reward after all, the debate has shifted as to whether DA mediates either learning about rewards or a motivational component such as incentive salience, discussed above. This debate is quite complicated and can only be very briefly discussed here, but it has been the topic of a number of comprehensive reviews (Schultz et al., 1997; Berridge, 2007, 2012).

LEARNING INTERPRETATIONS

There are a number of different ways DA has been proposed to contribute to learning. For example, it has been suggested that it may reinforce or 'stamp-in' learned associations, such as those between two stimuli (S-S associations) or between stimuli and responses (S-R associations). A more sophisticated way is the well-known idea called the "prediction error learning hypothesis" derived from elegant electrophysiological studies in monkeys during the 1990s by Wolfram Schultz. In a series of studies Schultz and his colleagues recorded from DA neurons and found that, prior to learning, those neurons discharged upon receipt of the reward. However, as the monkeys learned that a given signal predicted the reward, DA neurons came to fire upon presentation of the cue and stopped firing upon receipt of the reward. If the cue was presented but the reward omitted there was a brief dip in DA activity. Similar results have now been found using other techniques, where DA release is measured directly in DA terminal fields. This pattern of activity is consistent with what is called a "prediction error signal," which is central to most computational models of learning, and therefore it has been hypothesized that phasic DA activity comprises a "teaching signal" necessary for learning (e.g. Schultz et al., 1997). This hypothesis has been widely adopted in the computational modeling literature.

Learning versus motivation

However, others have challenged this learning interpretation. Most notably, Berridge (2007) has argued that "dopamine is not needed for new learning, and not sufficient to directly mediate learning by causing teaching or prediction signals." For example, a number of studies suggest DA does not appear to be necessary for much new reward learning. In the paper mentioned above showing that rats with complete striatal DA depletions showed normal hedonic reactions to tastes, Berridge and Robinson (1998) also reported these rats could learn normally about changes in the value of tastes. Normal learning has also been described in mutant mice that cannot synthesize DA (e.g. Cannon and Palmiter, 2003; Robinson et al., 2005) and following DA receptor blockade (e.g. Calaminus and Hauber, 2007). In addition, DA elevation does not appear to be sufficient to enhance new learning either. Mutant mice in which DA signaling is elevated do not appear to learn new Pavlovian or instrumental associations better than controls (e.g. Cagniard et al., 2006). Similar conclusions have been reached in studies with humans, i.e. Parkinson's patients on or off their dopaminergic medication. These latter researchers concluded that "dopaminergic drug state (ON or OFF) did not impact learning", but ". . . the critical factor was drug state during the performance phase" (Shiner et al., 2012). Although the DA manipulations discussed above did not seem to influence learning, they did influence behavior (performance) in ways consistent with a motivational interpretation. Thus, Robinson et al. (2005) concluded, ". . . dopamine is not necessary for mice to like or learn about rewards but it is necessary for mice to seek (want) rewards during goal-directed behavior." Similarly, Cagniard et al. (2006) concluded, "DA directly scales behavioral performance in the absence of new learning." In their study using DA antagonists, Calaminus and Hauber (2007) concluded that DA receptor signals in the core of the accumbens "seem to be unnecessary in updating the reward-predictive significance of cues, rather, they serve to activate instrumental behavior."

Instead, dopamine elevation does more reliably scale with motivation for rewards, including even addictive or compulsive levels of motivation. Sensitized DA release in Parkinson's patients with dopamine dysregulation syndrome, leading to pathological drug use, is correlated with "compulsive drug 'wanting' but not 'liking'", and in healthy people DA release correlates well with ratings of drug wanting but not with changes in affective state (see Leyton, 2010, for a review). Finally, individuals vary in the extent to which they attribute incentive salience to reward predictive cues. DA activity is increased in response to reward cues in rats that attribute incentive salience to such cues, but not in those for whom the cue has predictive but not incentive value (Flagel et al., 2010).

All of these studies are consistent with the incentive salience or motivational interpretation of dopamine's primary role in reward described earlier. That is, DA is critical in mediating the extent to which rewards are "wanted," but not the extent to which they are "liked" or the ability to learn about them. As put by Berridge and Robinson (2003), "Incentive salience is a motivational, rather than an affective,

component of reward. Its attribution transforms mere sensory information about rewards and their cues (sights, sounds and smells) into attractive, desired, riveting incentives":

> The sight of food, drugs or other incentives is merely a sensory configuration of shape and color that is not intrinsically motivating. Attribution of incentive salience to a percept or other representation is what is suggested to make it a "wanted" target of motivation. Incentive salience or "wanting", unlike "liking", is particularly influenced by dopamine neurotransmission.

As with most debates in science, consensus is never achieved quickly but only over time, with the gradual accumulation of evidence for and against various positions. And this is the case concerning the role of dopamine in reward. We can probably safely conclude that the "hedonia hypothesis" of DA function first raised by Wise et al. (1978) that is the target of this commentary is no longer held by most researchers in the field – although it lives on in the popular media. As to learning versus motivational interpretations, these are still the subject of debate. It is obvious from the above that we think the weight of the evidence favors a motivational interpretation, but it would be presumptuous in 2016 to conclude this is an overwhelmingly consensus opinion, and so this debate will likely continue until more evidence accumulates.

NEURAL BASIS OF PLEASURE

Going back to the question as to what neural systems mediate pleasurable experiences – if not DA systems, then what? This is a difficult question to address in non-human animals, but it has been a focus of investigation of one of us (KB) over the last few decades, and considerable progress has been made, especially concerning systems that mediate the sensory pleasures associated with tastes (Berridge and Kringelbach, 2013). These results suggest that hedonic "liking" is generated by a more restricted brain substrate than DA, via a set of small "hedonic hotspots" nestled within mesocorticolimbic structures. Each hotspot uses opioid (natural heroin-type neurotransmitters), endocannabinoid (natural marijuana-type neurotransmitters) and related neurochemicals to amplify "liking" reactions, but never DA. Hedonic hotspots are relatively tiny – each is only a cubic millimeter or so in rats and probably about a cubic centimeter or so in humans. For example, one hotspot constitutes about just 10% of the entire nucleus accumbens, and there are other hotspots in the ventral pallidum, in the limbic regions of the prefrontal cortex, and in the brainstem. Hedonic hotspots appear to act together as a unified system to enhance a sensory pleasure, recruiting each other into activation, and requiring unanimous activation of several simultaneously to create an intense pleasure. So, there are "pleasure centers" in the brain – they just do not use dopamine to function.

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