Commentary

Dopamine, Opioids, and Positron Emission Tomography Imaging of the Human Brain: Contrasting Findings in Opioid Use Disorder and Healthy Volunteers

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The ability of drugs of abuse to increase synaptic dopamine plays a central role in explaining how substances exert their reinforcing properties. This was first demonstrated in rodent studies with microdialysis and later corroborated in humans using positron emission tomography (PET) to image dopamine type 2/3 receptor availability (1). PET imaging with a dopamine type 2/3 radiotracer before and after the administration of a substance of abuse provides an indirect measure of dopamine release in the brain. In humans, nearly all major drugs of abuse except opioids have been shown to increase endogenous dopamine. In this issue of *Biological Psychiatry*, Spagnolo *et al.* (2) report their pivotal study demonstrating that morphine increases dopamine transmission in the nucleus accumbens and globus pallidus in healthy human volunteers.

Although stimulants such as cocaine and amphetamines directly act on the dopamine transporter in the synapse, PET studies have shown that alcohol, nicotine, and cannabis also increase endogenous dopamine levels in the human brain (1). Dopamine has been shown to significantly modulate reward-driven behavior, particularly the reinforcing effect of drugs and alcohol. However, a class of substances most clearly associated with drug-seeking behavior—opioids—were not previously shown to affect dopamine levels in humans. Although dopamine release after opioid administration has been demonstrated using microdialysis in rodents (3), this effect had not been seen in human volunteers. Two studies (4,5) in subjects with opioid use disorder (OUD) who were maintained on methadone or buprenorphine showed that intravenous diamorphine injection did not significantly change [^{11}C]raclopride binding. These findings led to questions about the role of dopamine in the mechanism behind opioid reinforcement and OUD.

Spagnolo *et al.* (2) revisited this question by investigating opioid-induced dopamine release in healthy volunteers who had previous experience with opioids. The rationale was that if OUD itself has an impact on striatal dopamine, this may have masked the ability of opioids to change endogenous levels measured with PET. Spagnolo *et al.* (2) studied the subjective and neurobiologic effects of 10 mg/70 kg of intravenous morphine, compared with placebo, in healthy opioid-exposed men. Wisely, Spagnolo *et al.* (2) began with volunteers who were given the morphine challenge under controlled conditions, not in the scanner, to exclude subjects who could not tolerate the morphine dose.

After the morphine session to confirm tolerability, the participants were scanned on two separate occasions with PET— after an intravenous infusion of either morphine or saline—in a counter-balanced design. The physiological response to the morphine dose was confirmed by pupilometer. The PET results showed that morphine decreased binding potential by 9.0% in the globus pallidus and 8.8% in the nucleus accumbens. Drug wanting was negatively correlated with the change in binding potential in the caudate and putamen, and subjective ratings of a "high" and feeling of drug effect were negatively correlated with the change in radiotracer binding in the pallidum. Conversely, dopaminergic changes did not predict drug-liking scores.

These results indicate that opioid administration increases endogenous dopamine levels in the human brain to a level that is detectable with PET in nonaddicted individuals (2). This is an important finding that adds to our understanding of the neurobiology of substances of abuse. However, as Spagnolo *et al.* (2) note, this study also highlights the loss of sensitivity that comes with imaging dopamine in the human brain. A series of animal studies combining microdialysis with PET have shown that radiotracer displacement is significantly blunted compared with the increase in dopamine measured in dialysate [for review, see Finnema *et al.* (6)]. From these studies it can be estimated that a 1% reduction in radiotracer binding correlates with a 40% increase in endogenous dopamine levels (7). These results indicate that there is a lower limit when using PET to detect changes in dopamine, even though these changes are likely occurring in the brain. Notably, recent human PET studies have shown that agonist radiotracers, such as [^{11}C]PHNO and [^{11}C]NPA, may have a greater sensitivity for measuring changes in dopamine levels and could be used in future studies to investigate this question (8,9).

Comparing the results of Spagnolo *et al.* (2) with those of Daglish *et al.* (4) and Watson *et al.* (5) raises two possibilities. The first is that that OUD (in the setting of opioid maintenance) is associated with blunted striatal dopamine to a point where any changes may be below a detectable limit using PET imaging with [^{11}C]raclopride. Previous PET studies have shown that other substance use disorders are associated with a blunted dopamine release in response to a pharmacologic challenge, such as cocaine use disorder and stimulant administration (10). The second option is that dopamine is released in response to an opioid challenge in healthy

volunteers but that this effect is not present in OUD. At this point, neither possibility can be ruled out.

Spagnolo *et al.* (2) highlight the importance of participant characteristics when imaging the effects of substances of abuse. By design and necessity, this study included subjects who could tolerate the dose of morphine. Based on the results presented on the subjective response to morphine [Figure 1 in Spagnolo *et al.* (2)], the study volunteers felt "high" and liked the drug—although fortunately indicated that they were not interested in taking more, despite the positive response. An interesting corollary to this finding would be an imaging study in subjects who find opioids aversive, in order to investigate whether the dopamine response would be different. Of course, given the logistics of PET scanning, such an experiment would be quite burdensome to both the research participants and the investigators.

In summary, Spagnolo *et al.* (2) have addressed a question that needed an answer and showed that acute opioid administration is associated with an increase in dopaminergic signaling. With these findings, this group has also demonstrated that individuals with a history of opioid use, without an OUD, differ from subjects with an OUD on maintenance therapy. As Spagnolo *et al.* (2) also posit, increased dopamine may be reinforcing during the initiation of substance use, while other factors, such as negative reinforcers (e.g., prevention of withdrawal symptoms), may be reinforcing with sustained use. Given the challenges that come with PET imaging and the issues that arise with a complicated pharmacologic intervention, the field has benefitted tremendously by the effort behind this important publication.

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Article Information

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