Acute Administration of Haloperidol Does Not Influence \(^{123}\)I-FP-CIT Binding to the Dopamine Transporter

Jan Booij\(^1\), Guus van Loon\(^1,2\), Kora de Bruin\(^1\), and Pieter Voorn\(^2\)

\(^1\)Department of Nuclear Medicine, University of Amsterdam, Academic Medical Center, Amsterdam, The Netherlands; and \(^2\)Department of Anatomy and Neurosciences, Vrije Universiteit Medical Centre, Neuroscience Campus Amsterdam, Amsterdam, The Netherlands

E-mail: j.booij@amc.uva.nl

DOI: 10.2967/jnumed.113.132340

Clear \(^{123}\)I-FP-CIT binding was visible in the striatum and nucleus accumbens, both in saline-treated rats and in haloperidol-treated rats (Fig. 1).

RESULTS
Clear \(^{123}\)I-FP-CIT binding was visible in the striatum and nucleus accumbens, both in saline-treated rats and in haloperidol-treated rats (Fig. 1).
haloperidol (as executed in the present experiment as well as in the study by Nikolaus et al. (7)) is high enough to induce changes in $^{123}$I-FP-CIT binding to DAT. A previous study showed that acute administration of a 1 mg/kg dose of haloperidol induces a relatively slow and small increase in extracellular dopamine, namely no more than 50% of baseline levels (13). In this regard, it is of interest that striatal dopamine D$_{2/3}$ receptor imaging is a well-validated method to assess striatal dopamine release (6). Applying this method shows that a 4- to 5-fold increase (400%–500%) of extracellular dopamine is required to produce a decrease of only 10% in striatal dopamine D$_{2/3}$ receptor binding (14). Similarly, effects of dopamine on the DAT expression are reported only after administration of high doses of dopamine. Richards and Zahniser showed significant decreases in DAT cell surface expression of 49% in the dorsal striatum and 22% in the nucleus accumbens after a 1-h preincubation period with 100 µM dopamine (12). However, in monkeys, the baseline striatal extracellular dopamine concentration is around 5–6 nM (14). So, if the increase induced by acute administration of a 1 mg/kg dose of haloperidol is indeed not more than 50%, the increase of dopamine may be only 2–3 nM. If one assumes that there is a linear relationship between DAT downregulation and dopamine concentration, it is not likely that such a small increase in dopamine concentrations may lead to large changes in DAT levels. In line with this possibility, we did not observe even a trend for a change in DAT binding in the dorsal striatum, an area that may be more prone to downregulation of DAT than the ventral striatum (12). In addition, Hadlock et al. showed that sole administration of the dopamine D$_2$ antagonist eticlopride (0.5 mg/kg intraperitoneally) also did not influence DAT expression in rats (15). Finally, the binding of $^{123}$I-FP-CIT to DAT is nearly irreversible (16), strongly implying a very small dissociation constant, which in turn means that dopamine would have to be present at huge concentrations to displace it. All in all, although it is well accepted that DAT substrates, including high dopamine concentrations, may influence DAT binding in vivo, our present data do not support the possibility that acute administration of a single 1 mg/kg dose of haloperidol induces enough dopamine release to influence $^{123}$I-FP-CIT binding in rats.

Nikolaus et al. argued that the haloperidol-induced dopamine release may compete with $^{123}$I-FP-CIT binding (7). After dopamine is released, it is rapidly taken up as a substrate via DAT (17). The rate of dopamine uptake is described by the Michaelis–Menten equation $\frac{d[\text{dopamine}]}{dt} = -V_{\text{max}}[K_{\text{m}}[\text{dopamine}]+1]$ (18). In this equation, $K_m$ is the Michaelis–Menten constant for uptake, $V_{\text{max}}$ the uptake rate, and $d[\text{dopamine}]/dt$ the rate of disappearance of dopamine. When the dopamine concentration is sufficiently high, this uptake can be saturated. However, when there are low increases in the concentration of extracellular dopamine, the DAT uptake is unsaturated, and dopamine disappears by a first-order process with a rate constant of $V_{\text{max}}/K_m$ (18). Consequently, it is questionable whether acute dopamine release induced by a single 1 mg/kg dose of haloperidol can compete with DAT binding.

We tried to imitate several relevant parts of the study by Nikolaus et al. (7) as much as possible. Haloperidol and saline were administered intraperitoneally 1 h before injection of the radiotracer in Wistar rats, and at the same dose. Also, the same anesthetics were used, and DAT binding was assessed 2 h after injection, a time point at which a pseudoequilibrium is reached in rats (10). We also used the same DAT radiotracer. One difference
is that we used saline in the control group instead of ethanol. However, Nikolaus et al. used haloperidol from Sigma-Aldrich. In this formulation, ethanol is not used as a solvent, and we therefore used saline to pretreat the animals in the control group. We do not believe that this difference can explain the conflicting results. An explanation of why we could not replicate a significant effect of haloperidol on striatal 123I-FP-CIT binding in rats might be as follows. In the Nikolaus study, SPECT was performed on the Tier-SPECT. However, accurate delineation of striatal DAT binding is more difficult than with storage phosphor imaging, and it may be even harder to delineate nonspecific binding in the cerebellum. In their study, the SPECT assessments were not validated with ex vivo measurements. We used a technique (8) in which dorsal striatal, nucleus accumbens, and cerebellar binding can be delineated easily (Fig. 1), resulting in high binding ratios with a small SD within groups.

A limitation of our study was the relatively small groups that were studied. However, the difference between groups did not show even a trend toward statistical significance (the striatal binding ratios were even 1% higher in the haloperidol-treated rats than in the saline-treated rats; Fig. 2). Also, a positive control group was lacking; however, in a previous study we showed that the DAT blocker methylphenidate was able to decrease the 123I-FP-CIT binding in rats using storage phosphor imaging (8). Finally, only a single dose of haloperidol was tested. Higher doses of haloperidol (e.g., 5 mg/kg) may be able to influence DAT binding, at least in rats (19). However, the results of such high doses are of less importance when one is considering whether it’s worth evaluating if a single dose of haloperidol is able to induce enough dopamine release in humans.

CONCLUSION

Changes in synaptic dopamine due to acute haloperidol administration were not detectable using the SPECT tracer 123I-FP-CIT. It is therefore unlikely that 123I-FP-CIT SPECT in combination with acute administration of haloperidol in a tolerable dose can be used to detect changes in synaptic dopamine release in vivo in humans.

DISCLOSURE

The costs of publication of this article were defrayed in part by the payment of page charges. Therefore, and solely to indicate this fact, this article is hereby marked “advertisement” in accordance with 18 USC section 1734. Jan Booij is a consultant at GE Healthcare. No other potential conflict of interest relevant to this article was reported.

REFERENCES


EFFECTS OF HALOPERIDOL ON DAT • Booij et al. 3