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HIV-1 Dynamics in Vivo: Virion Clearance Rate, Infected Cell Life-Span, and Viral Generation Time
Alan S. Perelson, Avidan U. Neumann, Martin Markowitz, John M. Leonard, David D. Ho*

A new mathematical model was used to analyze a detailed set of human immunodeficiency virus-type 1 (HIV-1) viral load data collected from five infected individuals after the administration of a potent inhibitor of HIV-1 protease. Productively infected cells were estimated to have, on average, a life-span of 2.2 days (half-life $t_{1/2} = 1.6$ days), and plasma virions were estimated to have a mean life-span of 0.3 days ($t_{1/2} = 0.24$ days). The estimated average total HIV-1 production was $10.3 \times 10^9$ virions per day, which is substantially greater than previous minimum estimates. The results also suggest that the minimum duration of the HIV-1 life cycle in vivo is 1.2 days on average, and that the average HIV-1 generation time—defined as the time from release of a virion until it infects another cell and causes the release of a new generation of viral particles—is 2.6 days. These findings on viral dynamics provide not only a kinetic picture of HIV-1 pathogenesis, but also theoretical principles to guide the development of treatment strategies.

\[ \frac{dT}{dt} = kVT - \delta T \]  
\[ \frac{dV}{dt} = NBT_* - CV \]
where $V$ is the concentration of viral particles in plasma, $\delta$ is the rate of loss of virus-producing cells, $N$ is the number of new virions produced per infected cell during its lifetime, and $c$ is the rate constant for virion clearance (8). The loss of infected cells could be the result of viral cytopathicity, immune elimination, or other processes such as apoptosis. Virion clearance could be the result of binding and entry into cells, immune elimination, or nonspecific removal by the reticuloendothelial system.

We assumed that ritonavir does not affect the survival or rate of virion production of infected cells, and that after the pharmacological delay, all newly produced virions are noninfectious. However, infectious virions produced before the drug effect are still present until they are cleared. Therefore, after treatment with ritonavir,

$$\frac{dT^*}{dt} = kV_T - \delta T^*$$

$$\frac{dV_T}{dt} = -cV_T$$

$$\frac{dV_{NI}}{dt} = N\delta T^* - cV_{NI}$$

(3)

(4)

(5)

where $V_T$ is the plasma concentration of virions in the infectious pool [produced before the drug effect; $V_T(t = 0) = V_0$], $V_{NI}$ is the concentration of virions in the noninfectious pool [produced after the drug effect; $V_{NI}(t = 0) = 0$], and $t = 0$ is the time of onset of the drug effect. In all analyses, we assumed that viral inhibition by ritonavir is 100%, although the model can be generalized for nonperfect drugs (9).

Assuming that the system is at quasi steady state before drug treatment (10) and that the uninfected cell concentration $T$ remains at approximately its steady-state value, $T_0$, for 1 week after drug administration (1, 5), we find from Eqs. 3 through 5 that the total concentration of plasma virions, $V = V_T + V_{NI}$, varies as

$$V(t) = V_0 \exp(-ct) + \frac{cV_0}{c - \delta} \left\{ \frac{c}{c - \delta} \exp(-\delta t) - \exp(-ct) - \delta t \exp(-ct) \right\}$$

(6)

which differs from the equation derived by Wei et al. (2); see (11)). Allowing $T$ to increase necessitates the use of numerical methods to predict $V(t)$ but does not substantially alter the outcomes of the analyses given below (12).

Using nonlinear regression analysis (Fig. 1), we estimated $c$ and $\delta$ for each of the patients by fitting Eq. 6 to the plasma HIV-1 RNA measurements (Table 1) (12). The theoretical curves generated from Eq. 6, using the best-fit values of $c$ and $\delta$, gave an excellent fit to the data for all patients (see Fig. 1 for examples). Clearance of free virions is the more rapid process, occurring on a time scale of hours. Values of $c$ ranged from 2.06 to 3.81 day$^{-1}$, with a mean of 3.07 ± 0.64 day$^{-1}$ (Table 1). The corresponding $t_{1/2}$ values for free virions ($t_{1/2} = \ln 2/c$) ranged from 0.18 to 0.34 days, with a mean of 0.24 ± 0.06 days (~6 hours). Confirmation of the virion clearance rate was obtained from an independent experiment that measured by quantitative cultures (13) the rate of loss of viral infectivity in plasma for patient 105 (Fig. 1B). The loss of infectious virions occurred by first-order decay, with a rate constant of 3.0 day$^{-1}$, which is within the 68% confidence interval of the estimated $c$ value for that patient (Table 1).

At steady state, the production rate of virus must equal its clearance rate, $cV$. Using the estimate of $c$ and the pretreatment viral concentration $V_0$, we obtained an estimate for the rate of virion production before ritonavir administration. Each patient’s plasma and extracellular fluid volumes were estimated on the basis of body weight. Total daily virion production and clearance rates ranged from 0.4 × 10$^9$ to 32.1 × 10$^9$ virions per day, with a mean of 10.3 × 10$^9$ virions per day released into the extracellular fluid (Table 1) (14). The rate of loss of virus-producing cells, as estimated from the fit of Eq. 6 to the HIV-1 RNA data, was slower than that of free virions. Values of $\delta$ ranged from 0.26 to 0.68 day$^{-1}$, with a mean of 0.49 ± 0.13 day$^{-1}$, the corresponding $t_{1/2}$ values were 1.02 to 2.67 days, with a mean of 1.55 ± 0.57 days (Table 1). A prediction of the kinetics of virus-producing cells can be obtained by solving Eq. 3 (15).

Several features of the replication cycle of HIV-1 in vivo could be discerned from our analysis. Given that $c$ and $\delta$ represent the decay rate constants for plasma virions and productively infected cells, respectively, then $1/c$ and $1/\delta$ are the corresponding average life-spans of these two compartments. Thus, the average life-span of a virion in the extracellular phase is 0.3 ± 0.1 days, whereas the average life-span of a productively infected cell is 2.2 ± 0.8 days (Table 2). The average viral generation time $\tau$ is defined as the time from the release of a virion until it infects another cell and causes the release of a new generation of viral particles; hence, $\tau$ should equal the sum of the average life-span of a free virion and the average life-span of a productively infected cell. This relation, $\tau = 1/c + 1/\delta$,

**Table 1.** Summary of HIV-1 clearance rate, infected cell loss rate, and virion production rate for the five patients. Base-line values are average of measurements taken at days -7, -4, -1, and 0; each virion contains two RNA copies. Pharmacologic delay was estimated from the first drop in plasma infectivity for patients 102, 105, and 107. Delay was estimated by best fit of viral load to Eq. 6 for patients 103 and 104. Lower and upper 68% confidence intervals were calculated by a bootstrap method (22) in which each experiment was simulated 100 times. Total virion production was calculated from plasma and extracellular fluid volumes estimated from body weights, assuming that plasma and extracellular fluid are in equilibrium.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Base-line values</th>
<th>Pharmacologic delay (hours)</th>
<th>Virion clearance</th>
<th>Confident interval</th>
<th>Infected cell loss</th>
<th>Confident interval</th>
<th>Total virion production (10$^9$/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CD4 cells (per mm$^3$)</td>
<td>Plasma virions (10$^9$ per ml)</td>
<td></td>
<td>c (day$^{-1}$)</td>
<td>Lower</td>
<td>Upper</td>
<td>$t_{1/2}$ (days)</td>
<td>$\delta$ (day$^{-1}$)</td>
</tr>
<tr>
<td>102</td>
<td>16</td>
<td>294</td>
<td>2</td>
<td>3.81</td>
<td>1.93</td>
<td>7.03</td>
<td>0.18</td>
</tr>
<tr>
<td>103</td>
<td>408</td>
<td>12</td>
<td>6</td>
<td>2.73</td>
<td>2.04</td>
<td>3.70</td>
<td>0.25</td>
</tr>
<tr>
<td>104</td>
<td>2</td>
<td>52</td>
<td>2</td>
<td>3.68</td>
<td>2.53</td>
<td>6.19</td>
<td>0.19</td>
</tr>
<tr>
<td>105</td>
<td>11</td>
<td>643</td>
<td>6</td>
<td>2.06</td>
<td>1.42</td>
<td>3.76</td>
<td>0.34</td>
</tr>
<tr>
<td>107</td>
<td>412</td>
<td>77</td>
<td>2</td>
<td>3.09</td>
<td>2.56</td>
<td>4.56</td>
<td>0.22</td>
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<tr>
<td>Mean</td>
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<td>216</td>
<td>3.6</td>
<td>3.07</td>
<td>2.10</td>
<td>5.05</td>
<td>0.24</td>
</tr>
<tr>
<td>±SD</td>
<td>196</td>
<td>235</td>
<td>2.0</td>
<td>0.64</td>
<td>0.42</td>
<td>1.34</td>
<td>0.06</td>
</tr>
</tbody>
</table>

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= 1/c + 1/β, can be shown formally (Table 2). The average value of \( τ \) for the patients was 2.6 ± 0.9 days (Table 2).

By a heuristic procedure, we found minimal estimates for the average duration of the HIV-1 life cycle and of its intracellular or eclipse phase (from virion binding to the release of the first progeny). The duration of the HIV-1 life cycle, \( S \), is defined as the time from the release of a virion until the release of its first progeny virus; we estimated \( S \) by the lag in the decay of HIV-1 RNA in plasma (Fig. 1) after the pharmacologic delay (Table 1) is subtracted. The shoulder in the RNA decay curve is explained by the fact that virions produced before the pharmacologic effect of ritonavir are still infectious and capable of producing, for a single cycle, viral particles that would be detected by the RNA assay. Thus, the drop in RNA concentration should begin when target cells interact with drug-affected virions and do not produce new virions. These “missing virions” would first have been produced at a time equal to the minimum time for infection plus the minimum time for production of new progeny. The estimated values for \( S \) were quite consistent for the five patients, with a mean duration of 1.2 ± 0.1 days (Table 2). In steady state, \( 1/c = 1/\left(NT_{\text{vir}} \cdot \beta \right) \) is the average time for infection (Table 2, legend); if this average time is assumed to be greater than the minimal time for infection, then a minimal estimate of the average duration of the intracellular phase of the HIV-1 life cycle is given by \( S = (1/c) = 0.9 \text{ days} \) (16).

Previous studies that used potent antiretroviral agents to perturb the quasi steady state in vivo provided a crude estimate of the \( t_{1/2} \) of viral decay in which the life-span of productively infected cells could not be separated from that of plasma virions (1, 2). Our results show that the average life-span of a productively infected cell (presumably an activated CD4 lymphocyte) is 2.2 days; thus, such cells are lost with an average \( t_{1/2} \) of ~1.6 days (Fig. 2). The life-spans of productively infected cells were not markedly different among the five patients (Table 2), even though individuals with low CD4 lymphocyte counts generally have decreased numbers of virus-specific, major histocompatibility complex class I-restricted cytotoxic T lymphocytes (17).

The average life-span of a virion in blood was calculated to be 0.3 days. Therefore, a population of plasma virions is cleared with a \( t_{1/2} \) of 0.24 days; that is, on average, half of the population of plasma virions turns over approximately every 6 hours (Fig. 2). Because our analysis assumed that the antiviral effect of ritonavir was complete and that target cells did not recover during treatment, our estimates of the virion clearance rate and infected cell loss rate are minimal estimates (12, 16). Consequently, the true virion \( t_{1/2} \) may be shorter than 6 hours. For example, Nathanson and Harrington (18) found that monkeys clear the Langat virus from their circulation on a time scale of ~30 min. Thus, the total number of virions produced and released into the extracellular fluid is at least 103 × 10⁶ particles per day (14); this rate is about 15 times our previous minimum estimate (1). At least 99% of this large pool of virus is produced by recently infected cells (1, 2) (Fig. 2). At quasi steady state, the virion clearance rate \( cV \) equals the virion production rate \( NB\beta \). Because \( c \) has similar values for all patients studied (Table 1), the degree of plasma viremia is a reflection of the total virion production, which in turn is proportional to the number of productively infected cells \( \Delta T \) and their viral burst size \( N \).

The average generation time of HIV-1 was determined to be 2.6 days, which suggests that ~140 viral replication cycles occur each year, about half the number estimated by Coffin (19).

It is now apparent that the repetitive replication of HIV-1 (left side of Fig. 2) accounts for ~99% of the plasma viruses in infected individuals (1, 2, 19), as well as for the high destruction rate of CD4 lymphocytes. The demonstration of the highly dynamic nature of this cyclic process provides several theoretical principles to guide the development of treatment strategies:

1) An effective antiviral agent should detectably lower the viral load in plasma after only a few days of treatment.

2) On the basis of previous estimates of the viral dynamics (1, 2) and data on the mutation rate of HIV-1 (3.4 × 10⁻⁵ per base pair per replication cycle) (20) and the genome size (10⁶ base pairs), Coffin has cogently argued that, on average, every mutation at every position in the genome would occur numerous times each day (19). The larger turnover rate of HIV-1 described in our study makes this type of consideration even more applicable. Therefore, the failure of the current generation of antiviral agents,
when used as monotherapy, is the inevitable consequence of the dynamics of HIV-1 replication. Effective treatment must, instead, force the virus to mutate simultaneously at multiple positions in one viral genome by means of a combination of multiple, potent antiretroviral agents. Moreover, because the process of producing mutant viruses is repeated for \( \sim 140 \) generations each year, early and aggressive therapeutic intervention is necessary if a marked clinical impact is to be achieved (21).

From our study and previous reports (1, 2, 5), it is now clear that the "raging fire" of active HIV-1 replication (left side of Fig. 2) could be put out by potent antiretroviral agents in 2 to 3 weeks. However, the dynamics of other viral compartments must also be understood. Although they contribute \( \leq 1\% \) of the plasma virus, each viral compartment (right side of Fig. 2) could serve as the "ember" to reignite a high rate of viral replication when the therapeutic intervention is withdrawn. In particular, we must determine the decay rate of long-lived, virus-producing populations of cells such as tissue macrophages, as well as the activation rate of cells latently carrying infectious proviruses. This information, somewhat, will enable the design of a treatment regimen to block de novo HIV-1 replication for a time sufficient to permit each viral compartment to "burn out."

Table 2. Summary of virion life-span (1/c) and infected cell life-span (1/\( \alpha \)), duration of the viral life cycle (S) and of the intracellular phase \( [S - (1/c)] \), and average viral generation time (\( \tau \)) for the five patients. The values for S and for the minimal estimate of \( S - (1/c) \) were obtained by a heuristic procedure and should be viewed as rough estimates (S was estimated by the length of the shoulder on graphs of RNA copies versus time, as in Fig. 1). Confidence intervals for \( \tau \) were obtained by a bootstrap method on a model with \( \tau \) and \( 1/\alpha \) as parameters. SDs reflect the differences between patients and not the accuracy of the estimates. The rate of a large population of virions was followed to estimate the in vivo value of \( \tau \). For a system in quasi steady state, the average generation time can be defined as the time required for \( V_o \) particles to produce the same number of virions in the next generation. After a protease inhibitor is administered, all newly produced virions are assumed to be noninfectious. To keep track of the number of noninfectious particles, we assumed for the purposes of this calculation that noninfectious particles are not cleared and act as a perfect marker, recording the production of virions after one round of infection. Thus, from Eq. 5, \( dV_o/dt = NBT^* \). We also assumed that before the drug is given, there are no infected cells (\( [T]^0 = 0 \)), so that only new infections are tracked. Under these circumstances, \( \tau \) is the average time needed for \( V_o \) virions to produce \( V_o \) noninfectious virions after nontarget administration. After treatment, no further infectious particles are produced and hence the number of infectious particles \( V_i \) declines exponentially (that is, \( V_i(t) = V_o \exp(-ct) \), where \( t = 0 \) is the time at which the drug takes effect after pharmacokinetic delays). The existing infectious particles infect cells, and the number of infected cells \( T \) varies as given by the solution of Eq. 3, with the initial condition \( T^0 = 0 \). At any given time \( t \), the mean number of virions produced from the initial \( V_o \) virions is \( V_o \exp(-ct) \). Hence, the (cumulative) probability that a virion is produced by time \( t \). The probability density of a virus being produced at time \( t \) is \( d\tau(t) = dV_o/dt \), and thus the average virion production time \( \tau_j = \int_{V_o}^{[V_o]} \exp(-ct) \). The integration yields \( \tau = \tau^1 + \int_{1/c}^{S - (1/c)} \tau(t) dt \). Substituting the solution of Eq. 3 for \( T^* \) and integrating yields \( \tau = (1/\alpha) + (1/c) \).

<table>
<thead>
<tr>
<th>Patient</th>
<th>1/c (days)</th>
<th>1/( \alpha ) (days)</th>
<th>S (days)</th>
<th>S - (1/c) (days)</th>
<th>( \tau ) (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>102</td>
<td>0.3</td>
<td>3.6</td>
<td>1.2</td>
<td>0.9</td>
<td>4.1</td>
</tr>
<tr>
<td>100</td>
<td>0.4</td>
<td>1.5</td>
<td>1.2</td>
<td>0.6</td>
<td>1.8</td>
</tr>
<tr>
<td>104</td>
<td>0.3</td>
<td>2.0</td>
<td>1.2</td>
<td>0.9</td>
<td>2.3</td>
</tr>
<tr>
<td>105</td>
<td>0.5</td>
<td>1.9</td>
<td>1.3</td>
<td>0.8</td>
<td>2.4</td>
</tr>
<tr>
<td>107</td>
<td>0.3</td>
<td>2.0</td>
<td>1.2</td>
<td>0.9</td>
<td>2.3</td>
</tr>
<tr>
<td>Mean</td>
<td>0.3</td>
<td>2.2</td>
<td>1.2</td>
<td>0.9</td>
<td>2.6</td>
</tr>
<tr>
<td>±SD</td>
<td>0.1</td>
<td>0.8</td>
<td>0.1</td>
<td>0.1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

Fig. 2. Schematic summary of the dynamics of HIV-1 infection in vivo. Shown in the center is the cell-free virion population that is sampled when the viral load in plasma is measured.
drug is not completely effective, cell life-spans may be somewhat less than we estimate. If the target cells are allowed to increase by the maximum factor observed in the five patients (that is, fivefold), we find that the derived values of c and 8 are minimal estimates. Thus, for example, for data generated with $n_1 = 1$, with c = 3.00 and $8 = 0.500$, we find that our fitting procedure yields estimates of c = 2.76 and $8 = 0.499$.


14. Virions that are not released into the extracellular fluid are not included in this estimate. Thus, the total production in the body is even larger.

15. The solution to Eq. 3 is

$$T(t) = \frac{\gamma}{\delta_c - \delta} \left[ e^{\delta_c t} - e^{\delta t} \right]$$

If cellular RNA data were obtained, this equation could be fitted to those data, and the parameter estimates for c and $\delta$ could be verified for consistency with the viral kinetics.

16. In principle, more accurate estimates of the duration of the latent or eclipse phase of the viral life cycle can be obtained with a model that explicitly includes a delay from the time of infection until the time of viral release. For example, Eq. 2 can be replaced by

$$dV/dt = k \int_0^t (t - \tau) \delta V d\tau - cV \quad (8)$$

where $\delta V(t)$ is the probability that a cell infected at time $t$ produces virus at time $t$. Explicit solutions to our model, with $\delta V(t)$ given by a gamma distribution, will be published elsewhere (A. S. Perelson et al., in preparation). Alternatively, if virally producing cells $T_0$ rather than infected cells $T$ are to be tracked, Eq. 1 can be replaced by

$$dT_0/dt = k \int_0^t (t - \tau) \delta V d\tau - \delta T_0 \quad (9)$$

Models of this type can also be solved explicitly when $\delta V(t)$ is given by a gamma function. M. Nowak and A. Herz (personal communication) have solved this model for the case where $\delta V(t)$ is a delta function, in which case the delay simply adds to the pharmacologic delay and Eq. 6 is regained after this combined delay.

Analysis of current data by nonlinear least squares estimation has so far not allowed accurate qualitative estimation of c, $\delta$, and the intracellular delay. However, the qualitative effect of including the delay in the model is to increase the estimate of c, which is consistent with our claim that the values of c in Table 1 are minimal estimates. Higher values of c (hence lower values of 1/c) would lead to increased estimates of the intracellular delay ($\delta$ - 1/c). Thus our estimate of the duration of the intracellular phase, as derived above and given in Table 2, is still a minimal estimate.


23. We thank the patients for participation; A. Hurley, Y. Cao, and scientists at Chiron for assistance; B. Goldstein for the use of his nonlinear least squares fitting package; and G. Belt, T. Kepler, C. Macken, E. Schwartz, and B. Sulzer for helpful discussions and calculations. Portions of this work were performed under the auspices of the U.S. Department of Energy. Supported by Abbott Laboratories, grants from NIH (AI44825 and RO100553) and from the New York University Center for AIDS Research (AI27742) and General Clinical Research Center (MC1 RR00096), the Aaron Diamond Foundation, the Joseph and Jeanine M. Sullivan Foundation, and the Los Alamos National Laboratory Directed Research and Development program.

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Opposite Modulation of Cocaine-Seeking Behavior by D1- and D2-Like Dopamine Receptor Agonists

David W. Self,* William J. Barnhart, David A. Lehman, Eric J. Nestler

Activation of the mesolimbic dopamine system is known to trigger relapse in animal models of cocaine-seeking behavior. We found that this "priming" effect was selectively induced by D2-like, and not by D1-like, dopamine receptor agonists in rats. Moreover, D1-like receptor agonists prevented cocaine-seeking behavior induced by cocaine itself, whereas D2-like receptor agonists enhanced this behavior. These results demonstrate an important dissociation between D1- and D2-like receptor processes in cocaine-seeking behavior and support further evaluation of D1-like receptor agonists as a possible pharmacotherapy for cocaine addiction.

Relapse of cocaine use in cocaine-dependent people is often precipitated by episodes of intense drug craving even after prolonged abstinence. Cocaine craving, has been described subjectively as resembling the positive or "high"-like qualities of the drug itself (1). In this sense, cocaine craving may differ from cravings for opiates or ethanol, which are sometimes described as a desire to alleviate the negative, withdrawal-associated symptoms of dependence (2). Both cocaine craving in humans and relapse in animal models of cocaine-seeking behavior are triggered by environmental stimuli associated with the drug experience (2, 3) and by low doses of cocaine itself (3, 4).

The priming effects of such cues in animal models of cocaine-seeking behavior can be mimicked by activation of the mesolimbic dopamine system (5), which is a major neural substrate of cocaine reinforcement (6). Dopamine acts at two general classes of dopamine receptors, termed D1-like and D2-like, that are distinguishable by their structural homology (7), opposite modulation of adenylyl cyclase activity (8), and differential localization within the brain (9).

We tested the ability of full D1- or D2-like dopamine receptor agonists to induce relapse in an animal model of cocaine-seeking behavior. Male Sprague-Dawley rats were trained to press a lever to self-administer intravenous cocaine (10, 11). A daily 4-hour reinsertment procedure was followed in which rats self-administered cocaine for 2 hours, after which saline was substituted for the cocaine during the final 2 hours. During the time that saline was substituted, the rats' "nonreinforced" lever-press responses progressively diminished, a behavioral phenomenon known as extinction.

Response after had diminished (11), the rats were given intraperitoneal priming injections of either the D2-like selective receptor agonist 7-hydroxy-6,11-dihydroprop-2-aminotetralin (7-OH-DPAT) (12) or quinpirole (13), or the D1-like selective receptor agonist SKF 82958 (14). Although these dopamine agonists can selectively discriminate the D1- from the D2-like class of receptors, they do not adequately distinguish the various subtypes within each class in vivo. The priming ability of these dopamine receptor agonists was assessed by their ability to reinitiate nonreinforced lever pressing for saline infusions at the lever that previously delivered cocaine infusions (drug-paired lever) during the cocaine phase of the test session (Fig. 1).

The D2-like agonist 7-OH-DPAT induced large dose-related increases in nonreinforced responding at the drug-paired lever as compared with very low levels of responding induced both by the drug vehicle and at an inactive lever (Figs. 1 and 2A). Quinpirole also induced selective responding at the drug-paired lever and with higher potency but with less efficacy and dose-dependency than responding induced by 7-OH-DPAT. These differences cannot be explained by the relative selectivity or affinity of the two agonists at D1 or D2 receptor subtypes (12) and therefore probably reflect different pharmacokinetic properties of the drugs. The possibility of a generalized rate-increasing effect of the D2-like agonists is eliminated by the lack of significant responding at the inactive lever and by previous studies in which D2-like agonists produced decreases rather than increases in responding when animals were treated during cocaine self-administration tests (15, 16). Thus, we conclude that the D2-like agonists initiate neural processes that trigger relapse in an animal model of cocaine-seeking behavior.

In contrast to the D2-like agonists, the