Published in final edited form as:

Eur J Pharmacol. 2006 December 3; 551(1-3): 54–57.

Modified ‘Joyce model’ of opioid dependence/withdrawal

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Abstract

By comprehensive and detailed measurement of the time course of withdrawal signs in rats, Joyce et al. (*J. Theo. Biol.* 240:531–537, 2006) recently provided a creative quantitative model of onset of drug-dependence based on the requirement of protein synthesis. Because the initial model fit the data imperfectly over the full time course, the authors postulated that additional features would be needed. We report excellent fit of the data ($R^2 = 0.96$) by adding: (1) a transient early phase, and (2) a delay in the buildup of protein.

Keywords

drug-dependence; model; protein synthesis

1. Introduction

Although substantial evidence suggests that protein synthesis is involved in the onset of drug-dependence, particularly to opioids (Kuhar and Joyce, 2001; 2003), there has not been a practical biologically-based mathematical model to work with until the recent publication by Joyce et al. (2006). In this seminal study, the authors implanted 296 adult male Sprague-Dawley rats with an osmotic minipump containing either morphine (~25 mg/kg daily) or 0.9% saline and then injected the rats with the opioid receptor antagonist naloxone (0.02, 0.1, or 0.5 mg/kg, s.c.) 1, 2, 4, 6, 12, 24, 48, 72, and 96 hours after pump implantation. Withdrawal was quantified using nine ‘checked’ signs (i.e., either present or absent) (diarrhea, facial fasciculations or teeth chattering, pronounced swallowing movements, profuse salivation, chromodacryorrhea, ptosis, abnormal posture, penile erection or ejaculation, irritability on handling), plus three graded signs (the number of observed escape attempts, abdominal constrictions, wet-dog shakes) and percent weight loss using a modified weighted global withdrawal score (Gellert and Holtzman, 1978). They then compared the observed results with a fit to a mathematical model based upon opioid dependence on protein synthesis. They found that the time course of observed withdrawal signs over 1 to 96 hours paralleled the known time course of protein synthesis (Kuhar and Joyce, 2001, 2003).

Unfortunately, the model fell short of fitting all of the data satisfactorily, particularly for the early time points. Based upon closer analysis, the authors speculated that there might be a transient earlier process that precedes the modeled protein synthesis. Here, we extend the ‘Joyce’ model in two ways that yield results that are more consistent with the overall data: (1) by introducing a transient early phase (this could involve a change in the level of a protein already expressed, a change in some 2nd-messenger level, or some other process), and (2) by introducing a delay in the buildup and delivery of newly synthesized protein to the target site.

2. Materials and methods

2.1. 'Joyce' model

Joyce et al. (2006) modeled the onset of drug-dependence according to a relationship that would mimic the time course of protein synthesis. Protein (P) synthesis follows zero-order kinetics (i.e., $dP/dt = r$, where r is a constant) and protein elimination follows 1st-order kinetics ($-dP/dt = kP$, where k is a constant)) (Berlin and Schimke, 1965; Schimke, 1973; Hargrove, 1993). Combining these for the simplest case, in which a change in the level of a single protein drives behavior, the proposed relationship is:

$$P_t / P_{\max} = (1 - e^{-0.693t/h}) = (1 - e^{-\beta t}), \quad (1)$$

where P_t represents the time(t)-dependent protein level, $P_{\max}$ the maximum achieved level of protein, and h the elimination half-life of the protein. The equation generalized to n sequential proteins, in which each subsequent protein or process depends on the previous one, is (Joyce et al., 2006):

$$Pn_t / Pn_{\max} = (1 - e^{-0.693t/h_1}) \times (1 - e^{-0.693t/h_2}) \dots (1 - e^{-0.693t/h_n}). \quad (2)$$

Eq. (1) is also a simplified version of Eq. (2) in which sequential proteins or processes are involved, but the half-life of one is much longer than that of the others.

Joyce and colleagues used these equations to model the extensive experimentally-derived global Gellert-Holtzman withdrawal scores (weighted adjustment of the observed checked and graded signs) for naloxone-precipitated withdrawal following 1, 2, 4, 6, 12, 24, 48, 72, and 96 hours of morphine infusion by minipump. The global withdrawal scores that they obtained for the time-dependent precipitated withdrawal for the 0.1 mg/kg dose of naloxone are shown in Table 1, along with the normalized scores (based on a maximum attainable score of 39). As seen in Fig. 1, and as reported by Joyce et al. (2006), the model only partially fits the data, even using the more complex protein-sequence models.

2.2. Modified Joyce model

Based on the authors' speculation about the incomplete fit of their data (Joyce et al., 2006), we introduce into their model a delay in the buildup of protein (to allow time for synthesis and expression at sufficient concentration) and a possibly independent earlier event (such as a 2nd messenger more proximal to the receptor). The first was modeled as a change in basal level of protein or non-protein 2nd-messenger (for simplicity, only an increase is included here). The second was modeled by introducing a delay in the time for protein synthesis to occur and for protein to accumulate to a sufficient expression level to be capable of producing the behavioral effect.

3. Results

Keeping as close as possible to the intent of the Joyce model and the origin and form of their equations (see section 2.1. above), we introduce an early-phase perturbation of basal level of 2nd messenger that follows zero-order kinetics (i.e., is of the form $dM/dt = r$, where r is a constant) and a return to baseline that follows 1st-order kinetics (i.e., is of the form $-dM/dt = kM$, where k is a constant). This is the same kinetics proposed by Joyce et al. (2006), we merely generalize it to the early phase. This leads to an equation similar in form to that of Eq. (1), namely,

$$M_t / M_{\max} = (1 - e^{-0.693 t / h_m}), \quad (3)$$

where M and m (messenger) are used to designate the new mechanistic step. Our second modification, i.e., introduction of a delay for the time that it takes for protein synthesis to occur and for the attainment of adequate concentration buildup at the relevant target site, is easily incorporated by replacing t with $t + \delta$ in Eq. (1). Applying these two changes, our modifications lead to an equation of general form (in which W represents combined effect on withdrawal):

$$W_t / W_{50} = (1 - e^{-\alpha t}) + (1 - e^{-\beta(t+\delta)}), \quad (4)$$

where α is the time constant related to the half-life ($0.693/h_1$) of the early phase, β is the time constant related to the half-life of the protein responsible for the late phase, δ is the delay between initiation of protein synthesis and protein expression, and W_{50} is the half-maximal effect. In the case of more than one component of either process, α , β , or δ are lumped quantities or represent the rate-determining step. Eq. (4) can be presented in simplified or alternative forms, but is left in this form to mirror the original formulation and the physiological processes modeled.

Modeling the data of Table 1 with Eq. (4) allows fitting both the rapid initial rise and the slower latter phase. Nonlinear regression analysis (Tallarida, 2000) produced α , β , and δ values (best-fit estimates, $R^2 = 0.96$) as follows: $\alpha = 5.4$, $\beta = 0.14$, and $\delta = 0.77$. The application of Eq. (3) to the data of Table 1 using these best-fit estimates is shown in Fig. 2.

4. Discussion

A large number of studies (cited in Joyce et al., 2006) implicate protein synthesis in the development of physical dependence to opioids and other abused drugs. mRNA and protein levels change following opioid administration (Nestler and Aghajanian, 1997; Berke and Hyman, 2000; Kuhar et al., 2001; Jacobs et al., 2002) and mRNA synthesis and proteins appear to be required for opioid reward, tolerance, and physical dependence (Cohen et al., 1965; Loh et al., 1969; Cox and Osman, 1970; Cox, 1973; Contarino et al., 2002; Nitsche et al., 2002; Terman et al., 2004). However, to date there has not been a data set sufficiently comprehensive and detailed for modeling. Joyce et al. (2006) supply such a data set. In addition, they provide a mathematical model (Eqs. (1) and (2)) that is consonant with the proposed biological mechanism. Our modifications (Eq. 4) provide an improved fit of the data set without compromising the intent of the original model. Namely, that the model be based on mechanistic principles, rather than just curve-fitting technique, and that protein synthesis be a central component. Eq. (4) retains the protein synthesis component (the second summand) and adds a, possibly independent, earlier component (the first summand). The close fit of the observed data supports the approach and mechanistic postulates of Joyce et al. (2006).

The best-fit estimates of α , β , and δ obtained in the present study correspond to an elimination half-life of the early phase of about 77 min (0.128 scaled time) and a delay and elimination half-life of the latter phase of approximately 8 and 48 h, respectively. These values are physiologically realistic and support the hypothesis of Joyce et al. (2006) of two processes: acute and chronic dependence. The elimination half-life of the protein component is much longer than in the 'Joyce' results and is intriguing. Such a long half-life might provide a physiological basis for alteration of the 'hedonic set-point' proposed to be involved in long-lasting phenomena of chronic drug use such as craving and relapse (Koob and Le Moal, 1997; Self and Nestler, 1998) and might suggest novel targets for pharmacologic intervention.

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Fig. 1.

Normalized total global naloxone(0.1 mg/kg, s.c.)-precipitated withdrawal scores (individual points on graph) in rats after various times (normalized) of continuous infusion of morphine (from Table 2 of Joyce et al., 2006) and a representative family of curves for various time constants (β) of protein elimination half-life in the 'Joyce' model (Eq. (1)).

Fig. 2. Nonlinear regression fit of the same data as in Fig. 1 to Eq. (4). The best-fit estimates are $\alpha = 5.4$, $\beta = 0.14$, and $\delta = 0.77$.

Table 1

Global (Gellert and Holtzman, 1978) (means $\pm$ SEM) and normalized ($\div 39$) withdrawal signs precipitated by naloxone (0.1 mg/kg, s.c.) in rats implanted with minipumps containing morphine for 1 to 96 h (global score data from Joyce et al., 2006).

Infusion (h)	G-H score (global)	G-H score (normalized)
1	9.5 $\pm$ 1.21	24
2	14.1 $\pm$ 0.953	36
4	22.1 $\pm$ 1.53	57
6	25.4 $\pm$ 1.16	65
12	26.4 $\pm$ 1.18	68
24	22.7 $\pm$ 1.02	58
48	32.3 $\pm$ 1.31	83
72	32.1 $\pm$ 1.67	82
96	34.4 $\pm$ 1.64	88