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# κ-Opioid receptor agonist-induced prolactin release in primates is blocked by dopamine $D_2$-like receptor agonists

Eduardo R. Butelman *, Mary-Jeanne Kreek

*Laboratory on the Biology of Addictive Diseases, The Rockefeller University (Box 171), 1230 York Avenue, New York, NY, 10021, USA*

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**Abstract**

Kappa (κ)-opioid receptor agonists may have pharmacotherapeutic potential in the management of psychostimulant abuse, due to their ability to modulate dopamine receptor systems involved in drug reinforcement. κ-Opioid receptor agonists also modulate dopamine receptor function in the hypothalamic tuberoinfundibular system, which has inhibitory control over an anterior pituitary hormone, prolactin. Prolactin levels may thus be a "biomarker" for the ability of κ-opioid receptor agonists (e.g., (+)-(5α,7α,8β)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-benzeneacetamide (U69,593)) to modulate a dopamine receptor system in vivo in primates. The effectiveness of dopamine $D_2$-like receptor agonists (quinpirole and (±)-7-hydroxy-dipropylaminotetralin (7-OH-DPAT); 0.0032–0.1 mg/kg) in preventing U69,593–induced prolactin release was studied in intact female rhesus monkeys. Quinpirole and 7-OH-DPAT inhibited U69,593-induced prolactin release ($ID_{50}$ values: 0.013 and 0.0072 mg/kg, respectively). However, the dopamine $D_1$-receptor agonist (±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazapine (SKF 82958; 1 mg/kg) did not inhibit U69,593-induced prolactin release under the same conditions. In contrast, the largest doses of quinpirole or 7-OH-DPAT presently studied (0.1 mg/kg), did not decrease sedation caused by U69,593 (0.01, 0.032 mg/kg), a prominent effect of centrally penetrating κ-opioid receptor agonists. The sedative effect of U69,593 (0.032 mg/kg) was prevented by naltrexone (0.32 mg/kg), consistent with κ-opioid receptor mediation of this effect. These studies suggest that prolactin release is a valid biomarker for the ability of κ-opioid receptor agonists to modulate dopamine $D_2$-like receptor function, and may also be used to quantify dopamine $D_2$-like receptor agonist potency in primates. © 2001 Published by Elsevier Science B.V.

*Keywords:* κ-Opioid receptor; Dopamine; Prolactin; Sedation; (*Macaca mulatta*)

## 1. Introduction

Kappa (κ)-opioid receptor ligands may have pharmacotherapeutic potential in the treatment of psychostimulant abuse, due to their ability to modulate dopamine receptor function in brain systems thought to be involved with drug reinforcement (Di Chiara and Imperato, 1988; Spanagel et al., 1990; Negus et al., 1997; Schenk et al., 1999; Kreek et al., 1999). κ-Opioid receptor ligands can also modulate dopamine receptor function in other brain areas, in particular the hypothalamic tuberoinfundibular system, which has inhibitory control over the release of the anterior pituitary hormone prolactin (Moore and Lookingland, 1995). This neuroendocrine assay is a quantifiable "biomarker" (NIH Definitions Working Group, 2000) for the pharmacological effects of peptidic and non-peptidic κ-opioid receptor agonists in human and non-human primates (Ur et al., 1997; Kreek et al., 1999; Butelman et al., 1999a,b).

Studies in rats have shown that κ-opioid receptor agonist-induced prolactin release involves changes in dopamine receptor function (Bero et al., 1987; Manzanares et al., 1991). However, given the potential differences in dopamine and κ-opioid receptor systems between rodents and primates (see Quirion and Pilapil, 1991; Weed et al., 1998 for reviews), it is of interest to study this interaction in vivo in a primate species, as this may have particular relevance as an applied model for human pharmacology.

The aim of the present studies was therefore to determine whether prolactin levels in intact rhesus monkeys may also be used as a biomarker for: (a) the ability of a κ-opioid receptor agonist ((+)-(5α,7α,8β)-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]-benzeneacetamide (U69,593)) to modulate dopamine $D_2$-like receptor systems; and (b) potency and effectiveness of dopamine $D_2$-like receptor agonists (e.g., quinpirole and (±)-7-hydroxy-dipropylaminotetralin (7-OH-DPAT)). The present

* Corresponding author. Tel.: +1-212-327-8247; fax: +1-212-327-8574.

*E-mail address:* butelme@mail.rockefeller.edu (E.R. Butelman).

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studies confirm that U69,593-induced prolactin release (but not sedation, another prominent effect of κ-opioid receptor agonists) can be potently and completely inhibited by dopamine $D_2$-like receptor agonists in non-human primates. In contrast, a dopamine $D_1$-receptor agonist ((±)-6-chloro-7,8-dihydroxy-3-allyl-1-phenyl-2,3,4,5-tetrahydro-1*H*-3-benzazapine (SKF 82958)) was unable to inhibit this neuroendocrine effect of U69,593. This suggests that the present assay may provide a valid biomarker for the ability of κ-opioid receptor agonists to modulate dopamine $D_2$-like receptor function, as well as a valuable measure of the potency of dopamine $D_2$-like receptor agonists in vivo in primates.

## 2. Methods

### *2.1. Subjects*

Captive-bred, adult intact rhesus monkeys were used. They were singly housed in a room maintained at 20–22 °C with controlled humidity, and a 12:12-h light:dark cycle (lights on at 7:30 a.m.). Monkeys used in prolactin assays were five females (studied in the follicular phase of their estrous cycle), and monkeys in the observational rating studies were two females and three males. Only females were used in the prolactin release studies, due to the greater reported sensitivity of this system in females vs. males (e.g., in humans; Kreek et al., 1999). All subjects were fed approximately 11 jumbo primate chow biscuits (PMI Feeds, Brentwood, MO) daily, supplemented by fruit and multivitamin supplements 2 times/week. Water was freely available throughout via waterspouts in the monkeys' home cages.

The present studies were approved by the Institutional Animal Care and Use Committee of Rockefeller University, in accordance with the Guidelines of the Committee on the Care and Use of Laboratory Animals of the Institute of Laboratory Animal Resources, National Health Council (Department of Health, Education and Welfare, Publication ISBN 0-309-05377-3, revised 1996).

### *2.2. Serum prolactin assay*

#### *2.2.1. Procedure*

Chair-trained monkeys were tested after extensive habituation to the experimental situation. Monkeys were chaired and brought into the experimental room between 10:00 and 10:30 a.m. on each test day. A single indwelling catheter (24-gauge; Angiocath, Becton Dickinson, Sandy, UT) was acutely placed in a superficial leg vein, and secured with elastic tape. A multi-sample injection port (Terumo, Elkton, MD) was attached to the hub of the catheter; the port and catheter were flushed (0.3 ml of 50 U/ml heparinized saline) before use, and after each blood sampling or i.v. injection. Approximately 15 min following catheter placement, two baseline blood samples were collected, 5 min apart from each other (defined as −10 and −5 min relative to the onset of dosing). At each sampling point, the initial 0.5 ml of blood drawn from the port were discarded (due to the presence of the heparinized saline "lock"); this was followed by a 2-ml blood aliquot, which was placed in a plain vacutainer. The samples were kept at room temperature until the time of spinning (3000 rpm at 4 °C) and serum separation. Serum was kept at −40 °C until the time of analysis.

These samples were analyzed in duplicate with a standard human prolactin radioimmunoassay kit (Nichols Diagnostics Institute, San Juan Capistrano, CA), following manufacturer's instructions. Calibration curves were determined for each kit with human prolactin standard (3–150 ng/ml). The reported sensitivity level of the kit was 0.14 ng/ml. The intra-assay and inter-assay coefficients of variation were 4.2% and 13.6%, respectively.

Monkeys were tested in a time course design, by administering a single i.v. U69,593 injection (after baseline sample collection) through the i.v. catheter over 10 s, followed by flushing. Blood samples were then obtained at intervals (5–90 min) after administration. In dopamine receptor agonist pretreatment studies, a single dose of either quinpirole, 7-OH-DPAT or SKF 82958 was administered either 15 or 30 min before U69,593.

#### *2.2.2. Design and data presentation*

Each experiment was carried out in 4–5 females in the follicular phase (days 2–12 of each cycle of approximately 28 days). Consecutive experiments in the same subject were separated by at least 72 h. Single doses of U69,593 (0.001 and 0.01 mg/kg, i.v.) were initially studied, to replicate previous dose–effect curve experiments (Butelman et al., 1999a) and to confirm a stable baseline of U69,593-induced prolactin release. This was compared to an i.v. vehicle time course study. The dopamine receptor agonists, quinpirole (0.01–0.1 mg/kg; 15 min, s.c. pretreatment), 7-OH-DPAT (0.0032–0.1 mg/kg; 30 min s.c. pretreatment) and SKF 82958 (1 mg/kg; 30 min, s.c. pretreatment) were administered before the fully effective dose of U69,593 (0.01 mg/kg; i.v.). The peak values for U69,593 (15 min after administration) were compared in the presence and the absence of the SKF 82958 pretreatment, by means of a *t*-test. The largest doses of 7-OH-DPAT and quinpirole (0.1 mg/kg; s.c.) were also studied alone. The potency of quinpirole and 7-OH-DPAT in inhibiting peak U69,593-induced prolactin release ($ID_{50}$ ± 95% CL) were calculated by linear regression to the midpoint between the peak U69,593 effect and the maximal inhibition observed after pretreatment with these dopamine receptor agonists.

One-way repeated measures analyses of variance (ANOVAs) were calculated for the peak effect of U69,593 (0.01 mg/kg; 15 min after administration), in the presence of increasing doses of quinpirole or 7-OH-DPAT, followed

Table 1
Observational rating scale for sedation in monkeys in their home cages

| Modified sedation scale |
|---|
| 0: No observable sedation; Monkey is alert to environment[a] |
| 1: Monkey is attentive to ordinary movements of observer[b] |
| 2: Monkey responds to loud noise[c] in room |
| 3: Monkey responds only to opening of cage latch |
| 4: Monkey responds only to loud noise[c] near its ear |
| 5: Monkey responds only to touch |
| 6: Monkey does not respond to touch |

[a]Observer is stationary in corner of colony room, lack of alertness defined as apparent staring for 15 s or more.
[b]"Ordinary" movement of observer is defined as walking within the colony room.
[c]"Loud noise" stimulus is one hand clap by the observer.

by analysis for linear trend (Graphpad Prism, San Diego CA, USA). Serum prolactin values are presented graphically as mean ± S.E.M.

### 2.3. Observational rating studies (sedation rating scale)

#### 2.3.1. Procedure

Monkeys in their home cages (within the colony room) were rated on a rating scale measuring sedation. Rating was carried out by one experienced observer who was "blind" as to the injection condition for each subject in each session (e.g., drug or vehicle injections). The rating scale (Butelman et al., 1999c; based on Dykstra et al., 1987) used herein is described in Table 1. The present scale operationally quantifies sedation, based on the type of environmental stimulus that is required to elicit a response (e.g., an orienting response) from a subject. Measurement of responsiveness to environmental stimuli has been commonly used as a strategy for the quantification of sedation in humans and non-human primates (Chernik et al., 1990; Shiigi and Casey, 1999; Pollock et al., 2000). Scores on the present scale range from 0 (no apparent sedation) to 7 (complete unresponsiveness to environmental stimuli, including touch). The same five subjects were used in all the sedation experiments reported herein.

#### 2.3.2. Design and data presentation

Sessions were started at approximately 10 a.m. A time course design was used in all studies, similarly to the neuroendocrine experiments above. A pre-injection score was assigned to each subject before each session. Following a single injection of U69,593 (0.01 or 0.032 mg/kg, s.c.) rating occurred 5, 15, 30, 60 and 120 min after administration. In dopamine receptor agonist pretreatment studies, quinpirole or 7-OH-DPAT (0.1 mg/kg, s.c.) were administered before U69,593 (the same pretreatment times were used as in the neuroendocrine studies). Quinpirole and 7-OH-DPAT were also studied alone (0.1 mg/kg, s.c.), to detect any direct sedative effects of these compounds. Sedation scores were analyzed with non-parametric Friedman's ANOVAs followed where appropriate by post-hoc Dunn's comparisons, or with Wilcoxon's signed ranks test. Data are presented graphically as median score ($n = 5$). The 0.05 $\alpha$ level was adopted for all the studies presented herein.

### 2.4. Drugs

Quinpirole dihydrochloride, 7-OH-DPAT hydrobromide, SKF 82958 hydrobromide (Sigma-RBI, Natick, MA) and naltrexone hydrochloride (kindly supplied by NIDA Research Technology Branch, Baltimore, MD) were dissolved in sterile water. U69,593 (kindly supplied by Pharmacia&Upjohn, Kalamazoo, MI) was dissolved in sterile water with the addition of 2 drops of lactic acid. The presently reported doses are in the forms of the compound described above.

## 3. Results

### 3.1. Serum prolactin assay

The chair-trained monkeys presently used had typically low prolactin baseline levels (e.g., 5–10 ng/ml). In a control experiment ($n = 4$), prolactin baselines were 5 ng/ml or less in all subjects. Administration of vehicle solution (sterile water, 0.1 ml/kg, i.v.) did not result in any elevation of prolactin levels over 90 min (Fig. 1). The largest doses of quinpirole and 7-OH-DPAT presently studied (0.1 mg/kg, s.c.) also did not cause an increase in prolactin levels over 90 min (Fig. 1). U69,593 (0.001 or 0.01 mg/kg i.v., caused a rapid dose-dependent increase in prolactin levels starting 5 min after administration, which persisted over the 90-min test period. The peak effect of U69,593 (0.01 mg/kg, i.v.) was observed 15 min

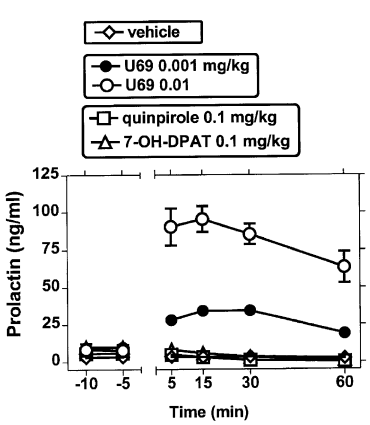


Fig. 1. Time course of the prolactin-releasing effects of i.v. vehicle or U69,593 (0.001, 0.01mg/kg), s.c. quinpirole or 7-OH-DPAT (0.1 mg/kg). Abscissa: time in min from injection (−10 and −5 indicate pre-injection control values). Ordinate: prolactin levels (ng/ml); values are mean ± S.E.M. ($n = 4$–5).

after administration (mean ± S.E.M. prolactin value = 95.4 ± 8.7 ng/ml) (Fig. 1).

Quinpirole pretreatment (0.01–0.1 mg/kg) dose-dependently prevented the prolactin increase caused by the maximally effective dose of U69,593 (0.01 mg/kg). The two largest doses of quinpirole (0.032 and 0.1 mg/kg) fully suppressed U69,593-induced prolactin release up to 60 min after administration (Fig. 2). Similarly, 7-OH-DPAT pretreatment (0.0032–0.1 mg/kg) dose-dependently prevented the prolactin release caused by U69,593 (0.01 mg/kg, i.v.) (Fig. 2).

A dose–effect curve for the effects of quinpirole and 7-OH-DPAT in inhibiting the peak effects of U69,593 is plotted in Fig. 3. From these data, a repeated measures, one-way ANOVA for quinpirole dose was significant ($F[3,3] = 35.5$, $P < 0.0001$; also linear trend, $P < 0.05$). Likewise, a repeated measures one-way ANOVA for 7-OH-DPAT dose was significant ($F[3,2] = 8.6$, $P < 0.02$; also linear trend, $P < 0.003$; one subject was dropped from the analysis due to one missing data point). The potency ($ID_{50}$ value) of quinpirole and 7-OH-DPAT in preventing U69,593-induced prolactin release was calculated. This revealed that 7-OH-DPAT was slightly but not significantly more potent than quinpirole in this neuroendocrine endpoint (Table 2; Fig. 3).

The high-efficacy dopamine $D_1$-receptor agonist SKF 82958 (1 mg/kg, s.c.) was administered as a 30-min pretreatment to U69,593 (0.01 mg/kg, i.v.). The dose and pretreatment time of SKF 82958 were chosen from available data on active doses in primates (Tidey and Bergman, 1998; Caine et al., 2000). Under these conditions, SKF 82958 alone (20 min after administration) did not affect prolactin levels, relative to pre-injection baseline (baseline mean ± S.E.M. = 9.4 ± 2.6 ng/ml; SKF 82958 alone

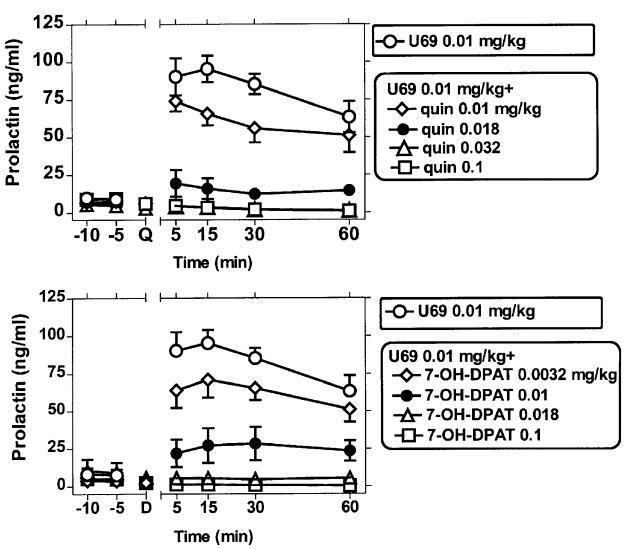


Fig. 2. Inhibition of the prolactin-releasing effect of U69,593 (0.01 mg/kg) by quinpirole or 7-OH-DPAT pretreatment (upper and lower panels, respectively). See Fig. 1 for other details.

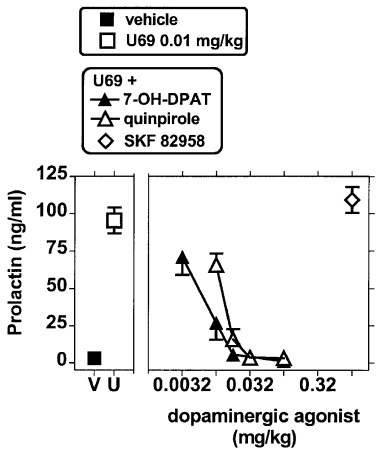


Fig. 3. Dose–effect curves for the inhibition of the prolactin-releasing effect of U69,593 by quinpirole, 7-OH-DPAT or SKF 82958. Data are presented from the time of peak effect for U69,593 (i.e., 15 min after administration). Abscissa: dopamine receptor agonist dose (mg/kg). See Fig. 1 for other details.

mean ± S.E.M. = 7.5 ± 1.6 ng/ml). This SKF 82958 pretreatment also did not affect U69,593-induced prolactin release at any time (i.e., 5–60 min after U69,593). Peak U69,593-induced prolactin release after SKF 82958 was 109 ng/ml (S.E.M. = 8.7; Fig. 3). This was not different from the peak effect of U69,593 alone ($t[7] = 1.1$; ns).

### 3.2. Sedation rating

Untreated subjects displayed no signs of sedation in the present studies (i.e., scores of 0 were observed throughout). Similarly, vehicle administration (under blind rating conditions) did not result in positive scores on the scale over a 120-min test period. U69,593 (0.01 and 0.032 mg/kg, s.c.) dose-dependently increases sedation (peak median effects were observed at 15 and 30 min after administration) (Fig. 4). Friedman's ANOVAs for U69,593 (0.01 or 0.032 mg/kg) vs. vehicle ($n = 5$) were significant at 15, 30 and 60 min after administration (respective $F$-statistics were: 9.3, 9.6 and 9.5; all $P < 0.05$). Post-hoc Dunn's comparisons revealed that at 15, 30 and 60 min after administration, the largest dose of U69,593 (0.032 mg/kg) caused a

Table 2
Potency of dopamine $D_2$-like receptor agonists in inhibiting the peak prolactin-releasing effect of U69,593 (0.01 mg/kg; 15 min after administration)

| | $ID_{50}$[a] | 95% CL |
|---|---|---|
| Quinpirole | 0.013 | 0.011–0.016 |
| 7-OH-DPAT | 0.0072 | 0.0026–0.02 |

[a] $ID_{50}$ values were calculated by linear regression to the midpoint between the maximal effect of U69,593 and the maximal inhibition observed after pretreatment with dopamine receptor agonists (i.e., a midpoint value of 49.2 ng/ml).

significant effect compared to vehicle (all $P < 0.05$). Therefore, under the present blind rating conditions, U69,593 caused a dose-dependent sedative effect.

To confirm whether the sedative effects of U69,593 were mediated by opioid receptors, we studied the sedative effect of U69,593 (0.032 mg/kg) after vehicle or naltrexone (0.32 mg/kg, s.c.) pretreatment. Naltrexone alone did not have any sedative effect 20 min after administration. However, naltrexone (0.32 mg/kg) fully blocked the sedative effect of U69,593 (0.032 mg/kg) throughout the 120 min session. For example, Friedman's ANOVA was significant ($F = 22.8$; $n = 5$; six time groups; $P < 0.05$) for vehicle pretreatment followed by U69,593 (0.032 mg/kg). By contrast, following naltrexone pretreatment, U69,593 (0.032 mg/kg) did not cause changes in sedation scores, relative to baseline ($F = 8.0$; $P > 0.05$). At a time of peak effect for U69,593 (i.e., 15 min after administration), sedation scores were lower after naltrexone pretreatment than after vehicle pretreatment (Wilcoxon signed ranks test; $W = 15$; $P < 0.05$).

The largest quinpirole or 7-OH-DPAT doses used above (0.1 mg/kg, s.c.) did not by themselves cause sedation over a 120-min session, when rated blind against vehicle administration (not shown). Furthermore, quinpirole or 7-OH-DPAT (0.1 mg/kg) pretreatment to U69,593 (0.01 and 0.032 mg/kg) did not affect sedation scores caused by U69,593, when rated against vehicle pretreatment (Fig. 5). At a time of peak effect (i.e., 15 min after U69,593) sedation scores did not differ after vehicle vs. quinpirole (0.1 mg/kg) pretreatment (Wilcoxon signed ranks test; [0.01 mg/kg U69,593, $W = 6$; ns] [0.032 mg/kg U69,593, $W = 6$; ns]). Likewise, peak U69,593-induced sedation scores did not differ after vehicle vs. 7-OH-DPAT pretreatment [0.01 mg/kg U69,593, $W = 7$; ns] [0.032 mg/kg U69,593, $W = 3$; ns]).

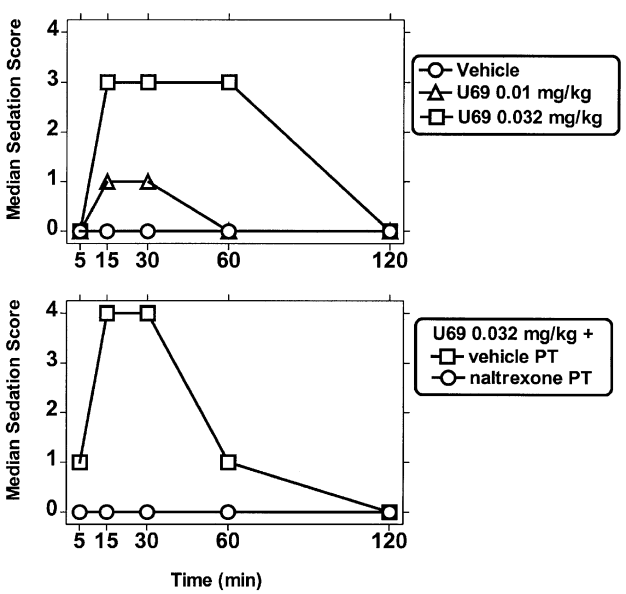


Fig. 4. Time course of the sedative effect of U69,593 (vehicle, 0.01, 0.032 mg/kg, s.c.; upper panel), and antagonism of U69,593 (0.032 mg/kg) by pretreatment with naltrexone (0.32 mg/kg, s.c.; lower panel). Abscissae: time in min from U69,593 injection. Ordinates: median sedation score ($n = 5$).

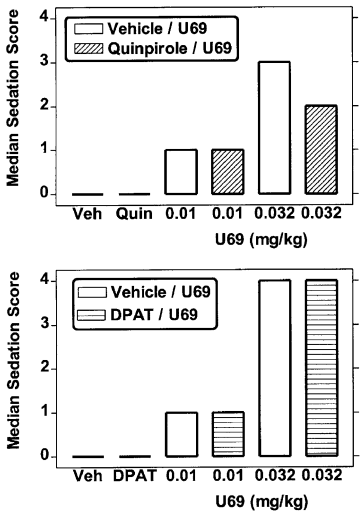


Fig. 5. Effect of quinpirole or 7-OH-DPAT (0.1 mg/kg, s.c.; upper and lower panels, respectively) on the sedative effect of U69,593 (0.01 or 0.032 mg/kg, s.c.). Bars above "V", "Quin" and "DPAT" represent scores after vehicle, quinpirole or 7-OH-DPAT alone. Open bars represent the effect of U69,593 after vehicle pretreatment, and hatched bars represent the effect of U69,593 after quinpirole or 7-OH-DPAT pretreatment. Other details as in Fig. 4.

## 4. Discussion

In the present studies, dopamine $D_2$-like receptor agonists dose-dependently and fully prevented prolactin release by the κ-opioid receptor agonist U69,593 in intact female rhesus monkeys, studied in the follicular phase of their estrous cycle. This is consistent with the notion that κ-opioid receptor agonist-induced prolactin release is due to a modulation of a dopamine receptor system in vivo in primates (Moore and Lookingland, 1995). The presently used U69,593 dose (0.01 mg/kg, i.v.) is the smallest dose to cause maximal prolactin release under these conditions (present studies; Butelman et al., 1999a).

This neuroendocrine effect of the dopamine $D_2$-like receptor agonists, quinpirole and 7-OH-DPAT, was dose-dependent and allowed the calculation of potency of these compounds ($ID_{50}$ values). From a comparison of present $ID_{50}$ values for quinpirole and 7-OH-DPAT with potency data from other in vivo assays in rhesus monkeys, this neuroendocrine assay design may provide a sensitive endpoint to study dopamine $D_2$-like receptor agonist function (e.g., Kleven and Koek, 1996; Lamas et al., 1996; Caine et al., 2000).

The high-efficacy dopamine $D_1$-receptor agonist SKF 82958 was inactive in this neuroendocrine assay, under the

present conditions. The SKF 82958 dose used in the present studies (1 mg/kg) was active in other in vivo assays in rhesus monkeys (e.g., cocaine and food-reinforced responding; Caine et al., 2000). Overall, this suggests that dopamine $D_2$-like (i.e., $D_2$ or $D_3$) but not dopamine $D_1$-receptor agonists can prevent κ-opioid receptor agonist-induced prolactin release in primates.

Other lines of evidence would suggest that dopamine $D_2$ and not $D_3$ receptors are involved in the present neuroendocrine effect of quinpirole and 7-OH-DPAT (which have affinity and efficacy at both dopamine $D_2$ and $D_3$ receptors; Sautel et al., 1995; Coldwell et al., 1999). For example, administration of relatively selective dopamine $D_2$ and $D_3$ agonists in rodents is consistent with mediation of an inhibition of prolactin release by $D_2$ receptors (Kurashima et al., 1996; Durham et al., 1997). Furthermore, administration of selective dopamine $D_3$-receptor antagonists in rodents does not result in hyperprolactinemia, as contrasted with that observed with antagonists possessing affinity at both dopamine $D_2$ and $D_3$ receptors (Audinot et al., 1998). Also, dopamine $D_2$-receptor deficient mice exhibit hyperprolactinemia (Kelly et al., 1997). Inhibition of κ-opioid receptor agonist-induced prolactin release may therefore be a useful in vivo assay to study dopamine $D_2$-receptor-mediated effects of agonists which possess efficacy at more than one dopamine $D_2$-like receptor subtype (Sautel et al., 1995; Moore and Lookingland, 1995; Coldwell et al., 1999; Perachon et al., 1999).

Sedation is a prominent effect of centrally penetrating κ-opioid receptor agonists in humans, nonhuman primates and rodents (Dykstra et al., 1987; Rimoy et al., 1994; Giardina et al., 1995), and has been a limiting factor in the clinical application of these compounds. In contrast with the effectiveness of quinpirole and 7-OH-DPAT in preventing U69,593-induced prolactin release, these dopamine $D_2$-like receptor agonists were ineffective in preventing U69,593-induced sedation. The dose of quinpirole or 7-OH-DPAT presently used (0.1 mg/kg) was at least 7-fold larger than the $ID_{50}$ values for suppression of prolactin release. This dose of quinpirole and 7-OH-DPAT also has other behavioral effects in primates, therefore these compounds lack of effectiveness in preventing sedation is unlikely to be due to insufficient dosing (Kleven and Koek, 1996; Sinnott et al., 1999; Caine et al., 2000). Furthermore, the sedative effect of U69,593 was completely blocked by naltrexone, consistent with mediation of this effect by κ-opioid receptors (e.g., Ko et al., 1998). Therefore, it appears that sedative effects of U69,593 are not secondary to a modulation of dopamine $D_2$-like receptor systems in rhesus monkeys, and that dopamine $D_2$-like receptor agonists could not be used to prevent sedation induced by κ-opioid receptor agonists.

Overall, the present studies confirm that κ-opioid receptor agonist-induced prolactin release in intact rhesus monkeys is due to a modulation of dopamine $D_2$-like receptor systems. This supports the use of this neuroendocrine biomarker for the ability of κ-opioid receptor agonists to modulate dopamine $D_2$-like receptor systems in vivo. This may be of particular value, given the pharmacotherapeutic potential of κ-opioid receptor ligands for the management of psychostimulant abuse. Furthermore, this neuroendocrine biomarker may also provide a quantitative and noninvasive measure of dopamine $D_2$-like receptor agonist pharmacology in vivo in primates.

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