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# Dopamine $D_1$ Receptor Family Agonists, SK&F38393, SK&F77434, and SK&F82958, Differentially Affect Locomotor Activities in Rats

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MEYER, M. E. AND J. M. SHULTS. *Dopamine receptor agonists, SK&F38393, SK&F77434, and SK&F82958, differentially affect locomotor activities in rats.* PHARMACOL BIOCHEM BEHAV **46**(2) 269–274, 1993. – Dopamine $D_1$ receptor family agonists, 2,3,4,5,-tetrahydro-7,8-dihydroxy-1phenyl-1*H*-3-benzazepine (SK&F38393), 3-allyl-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (SK&F77434), and 3-allyl-6-chloro-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (SK&F82958), were compared for their behavioral effects on horizontal movement time, rearing time, stereotypy time, and thigmotaxis time. All agonists resulted in biphasic effects with attenuation followed by potentiation (0.01–10.0 mg/kg, SC). While SK&F38393 did not potentiate horizontal movement and rearing times, and had minor effects on thigmotaxis, SK&F77434 and SK&F82958 potentiated horizontal movement and rearing behaviors and attenuated thigmotaxis. The results were discussed in terms of the binding characteristics and current receptor theory.

Dopamine agonists SK&F38393 SK&F77434 SK&F82958 Horizontal movement Rearing Stereotypy behavior Thigmotaxis

THE existence of at least five subtypes of dopamine (DA) receptors or two main families of DA receptors is now accepted (26). The main family of $D_1$ receptors is typically associated with the stimulation of adenylate cyclase, while the $D_2$ receptor is either independent of adenylate cyclase or mediates its inhibition (11,23). The availability of DA agonists and antagonists acting primarily at the main $D_1$ and $D_2$ receptor sites stimulated research to characterize the functional effects of each receptor family. However, within the $D_1$ receptor family two subtypes have been described as $D_{1A}$ and $D_{1B}$ or $D_5$ (29) and within the $D_2$ family three subtypes have been identified as $D_{2A}$, $D_{2B}$, or $D_3$ (27) and $D_{2C}$ or $D_4$ (3). These DA subtypes are different from the main $D_1$ and $D_2$ receptors in their pharmacology and anatomic distribution.

Behavioral, biochemical, and electrophysiological studies have shown the main families of DA receptors have separate sites and each may have different and/or interactive functions (1,5,8,24,25,33). For a time, it was suggested that all DA agonist-induced behaviors were mediated by the $D_2$ receptor and that the $D_1$ receptor had no known behavioral role (4,7,8,23). However, with the development of the selective $D_1$ antagonists, SCH23390 and SK&F83566, which also bind to both the $D_{1A}$ and $D_{1B}$ receptors (29), it was apparent that systemic injections of these $D_1$ antagonists reproduced the behavioral effects of both the typical nonselective DA antagonists and the selective $D_2$ antagonists over a wide variety of behaviors (12,13,33). On the other hand, systemic injections of the $D_1$ agonist, 2,3,4,5,-tetrahydro-7,8-dihydroxy-1phenyl-1*H*-3-benzazepine (SK&F38393), which also binds with the $D_{1B}$ receptor, enhance grooming only with large dose levels of 30 mg/kg or more (3,4,15–17,28,34).

Recently, it has been reported that a number of SK&F38393 analogs appear to be behaviorally similar to nonselective DA agonists and possibly $D_2$ agonists (17–19). These investigators used a rapid time-sampling behavioral checklist procedure where a treatment-"blind" observer rated the behaviors (17). In addition, they were only interested in the total session count or the main treatment conditions. As SK&F38393 has been the primary $D_1$ agonist used, it was important to investigate the behavioral effects of SK&F38393 and a few of it analogs. In the present study, we were interested in investigating two new benzazepine analogs, 3-allyl-2,3,4,5-tetrahydro-7,8-dihydroxy-1-phenyl-1*H*-3-benzazepine (SK&F77434) and 3-allyl-6-chloro-2,3,4,5-tetrahydro-7,8-dihy-

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droxy-1-phenyl-1*H*-3-benzazepine (SK&F82958), and comparing them to SK&F38393. In addition, we were interested in their effects upon behavior in a dose × time block interaction design by using objective measures of locomotor activities.

## METHOD

### *Animals*

Long-Evans hooded rats, weighing between 250–275 g, were obtained from Charles River. Animals were house individually, had food and water ad lib, and were maintained on a 12 L : 12 D cycle (light 0800–1600 h). Animals were tested in the light phase between 1000–1600 h. This study was carried out in compliance with the rules set forth in the NIMH Guide for the Care and Use of Laboratory Animals.

### *Drugs*

The following research drugs were used: SK&F38393 (mol wt. 291.8), SK&F77434 (mol. wt. 331.85), and SK&F82958 (mol. wt. 410.74). All drugs were dissolved in distilled water and injected SC in the nape of the neck with a volume of 1 ml/kg for each dose. The dosages used in this study were 0.00 (vehicle control), 0.1, 1.0, and 10.0 mg/kg with SK&F38393 and SK&F77434 and 0.00, 0.01, 0.1, and 1.0 mg/kg with SK&F82958. Animals were not habituated to the test apparatus but immediately after the injection procedure were individually placed in an activity chamber.

### *Apparatus and Measurement of Locomotor Activity*

Activity chambers were used to objectively measure locomotor behavior (Digiscan-16 Animal Activity Monitoring System, Omniteck Electronics, Columbus, OH). The acrylic cage within the monitor measured 41.91 × 41.91 × 30.54 cm. The monitor was equipped with 16 beams spaced 2.54 cm apart from the front to the back and 16 beams from side to side on the lower level, as well as 16 beams 2.54 cm apart from side to side on the upper level. Every 100 ms, the computer sampled the status of all the beams. The Digiscan analyzer converted the patterns of the beams broken into different patterns of locomotor activity. In this study, the following locomotor activities were automatically recorded: horizontal movement time in seconds (as long as the animal was moving movement time was incremented), rearing time in seconds (as long as the animal was rearing and activating the upper-level sensors, rearing time was incremented), stereotypy time in seconds (as long as the animal was repeatedly breaking the same beam or sets of beams, the monitor considered the animal was emitting stereotypy behavior; this measurement corresponded to grooming, head-bobbing, and weaving, chewing, etc.), and margin time in seconds (as long as the animal was within 1 cm to the walls of the cage, the margin time was incremented). The activity of animals was measured over a 2-h session where the response measures were blocked and recorded into 12 consecutive segments of 10 min each.

### *Research Design and Statistical Analyses*

The between-treatment or -dose conditions and the dose × time block interaction were of primary research interest. Therefore, a two-factor mixed-design analysis of variance (ANOVA) was used to analyze the between-treatment conditions (four dose levels), the within measures (12 consecutive 10-min time blocks), and the dose × time block interaction effect. Significant interactions for the doses × time blocks were followed up within time blocks with Dunnett's multiple-comparison tests between the vehicle control group and the treatment groups. $p$ values equal to or less than 0.05 were judged statistically significant. Each treatment group consisted of 12 animals randomly chosen. Each rat was used only once.

## RESULTS

### *Horizontal Movement Time*

*Effects of SK&F38393.* As shown in Fig. 1A, all of the dose levels of SK&F38393 significantly attenuated horizontal movement time during the 10- to 20-min time blocks. From the statistical analyses, there was a significant dose × time block interaction, $F(11, 484) = 2.76$, $p < 0.001$. The subsequent analyses revealed significant attenuation of horizontal movement time with all SK&F38393 dose levels (0.1, 1.0, and 10.0 mg/kg) in comparison to the vehicle control group at the 10- and 20-min time blocks ($ps < 0.01$). All other comparisons were not significant ($ps > 0.05$). There was a nonsignificant dose effect ($p = 0.23$).

*Effects of SK&F77434.* There was a highly significant dose × time block interaction, $F(11, 484) = 2.35$, $p <$

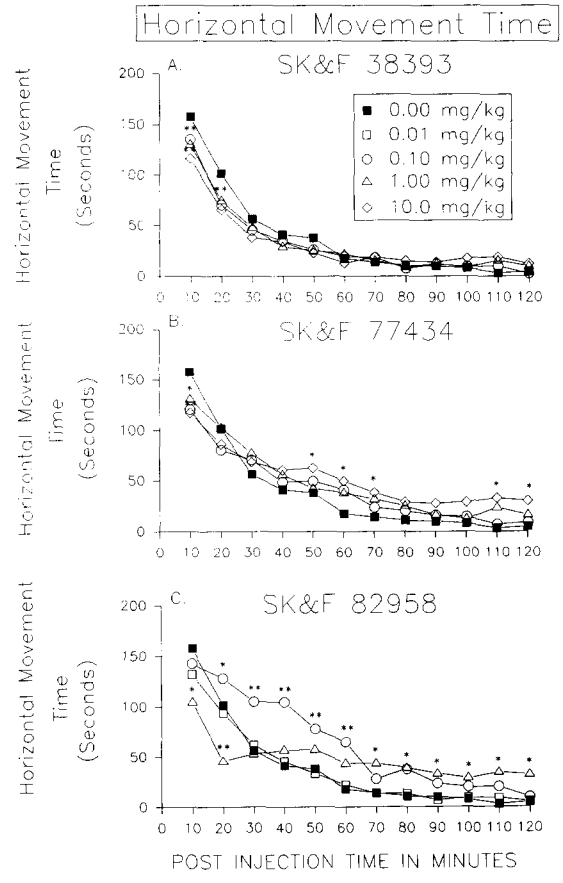


FIG. 1. Effects of various dosages of SK&F38393 (A), SK&F77434 (B), and SK&F82958 (C) on horizontal locomotor activity over 12 consecutive 10-min time blocks as measured by the horizontal movement time in seconds. The error bars have been omitted for clarity. Significant differences from the vehicle control group: $*p < 0.05$ and $**p < 0.01$.

0.001, which is shown in Fig. 1B. The subsequent analyses showed that at the 10-min time block all the SK&F77434 dose groups were significantly attenuated (*ps* < 0.05 and 0.01). However, at time blocks 50, 60, 70, 110, and 120 min the dosage of 10.0 mg/kg potentiated horizontal movement time. There was a nonsignificant dose effect ($p = 0.40$).

*Effects of SK&F82958.* There was a highly significant dose × time block interaction, $F(11, 484) = 7.53, p < 0.001$ (see Fig. 1C). The subsequent analyses resulted in an attenuation of horizontal movement time by the 1.0-mg/kg group during the time blocks of 10 and 20 min and the potentiation from time block 70 to 120 min. In addition, at time blocks 20–60 min the 0.1-mg/kg group showed significant potentiation (*ps* < 0.05 and 0.01). Unlike the other two agonists, SK&F82958 resulted in a significant dose effect with smaller dose levels, $F(3, 44) = 5.79, p = 0.002$. The subsequent analyses showed that the 1.0-mg/kg group significantly potentiated horizontal movement time ($p < 0.01$). All other comparisons were not significant.

### *Rearing Time*

*Effects of SK&F38393.* There was a significant dose × time block interaction, $F(11, 484) = 1.89, p = 0.002$. The subsequent analyses showed a significant attenuation of rearing time in the time block 10–30 min by the 10.0-mg/kg dose group (*ps* < 0.05 and 0.01). All other comparisons were not statistically significant (see Fig. 2A). Also, there was a nonsignificant dose effect.

*Effects of SK&F77434.* The dose × time block interaction was highly significant, $F(11, 484) = 2.35, p < 0.001$. Both the 1.0- and 10.0-mg/kg doses significantly attenuated rearing time at the 10- and 20-min time blocks (*ps* < 0.01). On the other hand, the 0.1-mg/kg group significantly potentiated rearing time during time blocks 40–90 min and the 10.0-mg/kg group significantly potentiated rearing time from the 100- to the 120-min time block (*ps* < 0.05 and 0.01). The dose effect was also significant, $F(3, 43) = 2.83, p = 0.048$; however, only the 0.1-mg/kg group differed significantly from the vehicle control group ($p < 0.05$) (see Fig. 2B).

*Effects of SK&F82958.* As with the other agonists, SK&F82958 resulted in a highly significant dose × time block interaction, $F(11, 484) = 7.53, p < 0.001$. The subsequent analyses revealed a significant attenuation of rearing time for the 1.0-mg/kg group during time blocks 10, 20, and 30 min. On the other hand, the 0.1-mg/kg group significantly potentiated the duration of rearing time across time blocks 40–60 and 80–110 min. The 0.01-mg/kg dose potentiated rearing time at the 50-min time block (*ps* < 0.05 and 0.01). There was also a highly significant dose effect, $F(3, 44) = 10.59, p < 0.001$. The subsequent analyses showed that the dose of 0.1 mg/kg significantly potentiated rearing and the 1.0-mg/kg dose significantly attenuated this behavior (*ps* < 0.05 and 0.01).

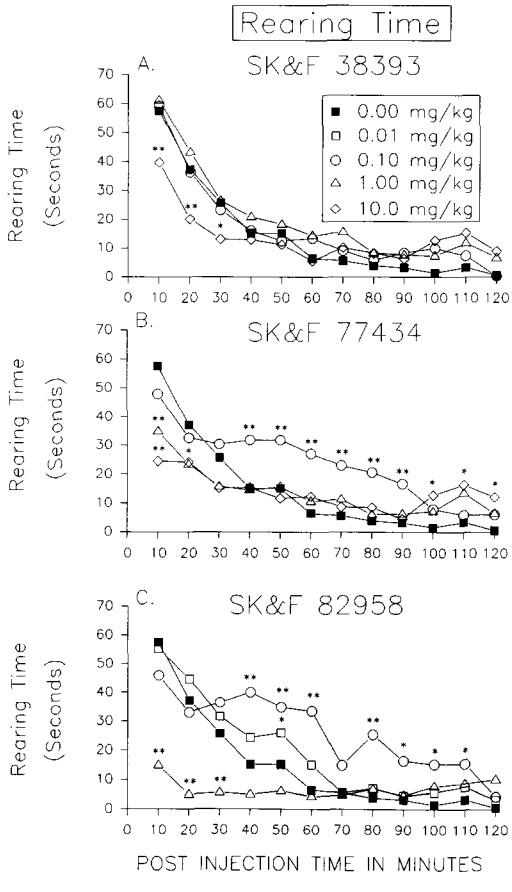


FIG. 2. Effects of various dosages of SK&F38393 (A), SK&F77434 (B), and SK&F82958 (C) upon rearing activity over 12 consecutive 10-min time blocks as measured by the rearing time in seconds. The error bars have been omitted for clarity. Significant differences from the vehicle control group: *$p < 0.05$ and **$p < 0.01$.

### *Stereotypy Time*

*Effects of SK&F38393.* Figure 3A illustrates the initial attenuation of all of the SK&F38393 dose levels within the first 10-min time block, followed by significant potentiation of stereotypy time. There was a highly significant dose × time block interaction, $F(11, 484) = 3.81, p < 0.001$. In time block 10 min, all SK&F38393 dosage groups were significantly attenuated. On the other hand, starting at time block 30 min both the 1.0- and 10.0-mg/kg dose levels significantly potentiated stereotypy time at various time blocks over the 120-min session (*ps* < 0.05 and 0.01). There was also a highly significant dose effect, $F(3, 44) = 8.72, p < 0.001$. The subsequent analyses between a dosage group and the vehicle control groups considering the overall mean effects revealed significant potentiation of stereotypy time for the 1.0- and the 10.0-mg/kg groups (*ps* < 0.05).

*Effects of SK&F77434.* The dose × time block interaction was highly significant, $F(11, 484) = 3.61, p < 0.001$ (see Fig. 3B). The subsequent analyses showed that during the first 10-min time block all dose levels were significantly attenuated (*ps* < 0.05 and 0.01). At time block 30–80 min, the 0.1-mg/kg group significantly potentiated stereotypy time; at time blocks 40–120 min, the dose of 1.0 mg/kg significantly potentiated stereotypy time; and at time blocks 40, 50, and 70–120 min the 10.0-mg/kg group stereotypy time was also potentiated (*ps* < 0.05 and 0.01). However, the overall dose effect was not significant.

*Effects of SK&F82958.* The dose × time block interaction was highly significant, $F(11, 484) = 7.05, p < 0.001$ (see Fig. 3C). The further analyses resulted in a significant attenuation of stereotypy time in the 0.01-mg/kg group at the first 10-min time block and potentiation at the time block 30 min. The 0.1-mg/kg group significantly potentiated stereotypy time

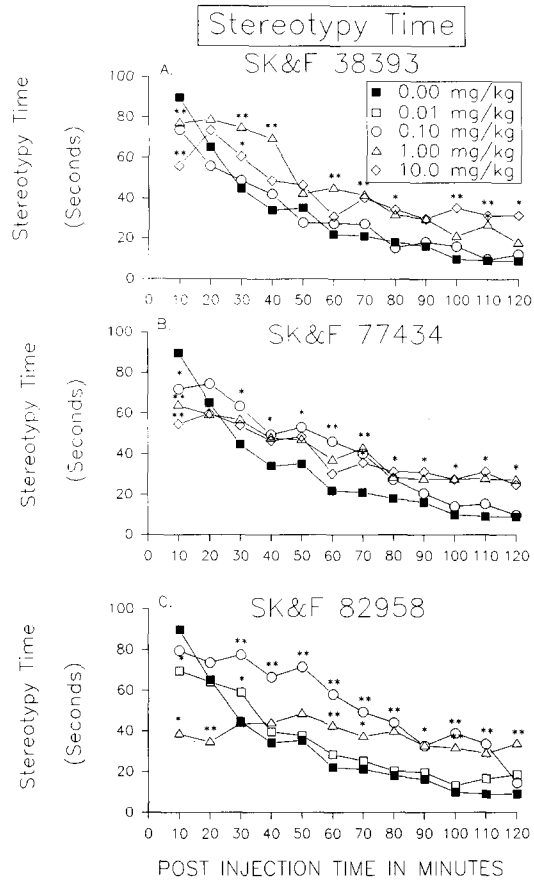


FIG. 3. Effects of various dosages of SK&F38393 (A), SK&F77434 (B), and SK&F82958 (C) upon stereotypy behavior over 12 consecutive 10-min time blocks as measured by stereotypy time in seconds. The error bars have been omitted for clarity. Significant differences from the vehicle control group: $*p < 0.05$ and $**p < 0.01$.

starting at time block 30 min through 120 min. At time blocks 10 and 20 min, the 1.0-mg/kg group showed significant attenuation but significant potentiation at time blocks 60, 70, 90, 100, and 120 min ($ps < 0.05$ and 0.01). There was a significant dose effect, $F(3, 44) = 6.31$, $p = 0.001$. The subsequent analyses showed that only the 0.1-mg/kg group differed significantly from the vehicle control group ($p < 0.01$).

### *Margin Time*

*Effects of SK&F38393.* The significant dose × time block interactions are shown in Fig. 4A. The statistical analyses revealed a significant interaction effect, $F(11, 484) = 1.55$, $p = 0.028$. The subsequent analyses resulted in a significant potentiation of margin time for the 0.1-mg/kg group at time blocks 10 and 20 min and a significant attenuation of margin time with the 10.0-mg/kg group at time blocks 40, 60, and 70 min ($ps < 0.05$). All other comparisons were not significant. There was a significant dose effect, $F(3, 44) = 3,47$, $p = 0.023$. The subsequent analyses resulted in a significant attenuation of the 10.0-mg/kg group in margin time ($p < 0.05$).

*Effects of SK&F77434.* There was a highly significant dose × time block interaction of margin time, $F(11, 484) = 5.03$, $p < 0.001$. This interaction is shown in Fig. 4B. The subsequent analyses showed significant attenuation of margin time for the 1.0-mg/kg group starting at time block 30–80 min. The 10.0-mg/kg group also showed significant attenuation at 30- through 120-min time blocks ($ps < 0.05$ and 0.01). With SK&F77434, there was also a highly significant dose effect, $F(3, 44) = 28.01$, $p < 0.001$. The subsequent analyses between the vehicle control group and the SK&F77434 dose means revealed that both the 1.0- and 10.0-mg/kg groups were significantly attenuated in their mean margin times ($ps < 0.01$).

*Effects of SK&F82958.* There was a highly significant dose × time block interaction, $F(11, 484) = 10.66$, $p < 0.001$ (see Fig. 4C). The subsequent analyses of margin time revealed significant attenuation at time blocks 30 and 40 min for the 0.1-mg/kg group and between 30 through 120 min for the 1.0-mg/kg group ($ps < 0.05$ and 0.01). There was also a significant dose effect, $F(3, 44) = 33.39$, $p < 0.001$. Further analyses revealed that only the 1.0-mg/kg group showed significant attenuation of margin time ($p < 0.01$).

## DISCUSSION

The results of the present experiment confirm, in part, previous research showing that systemically administered

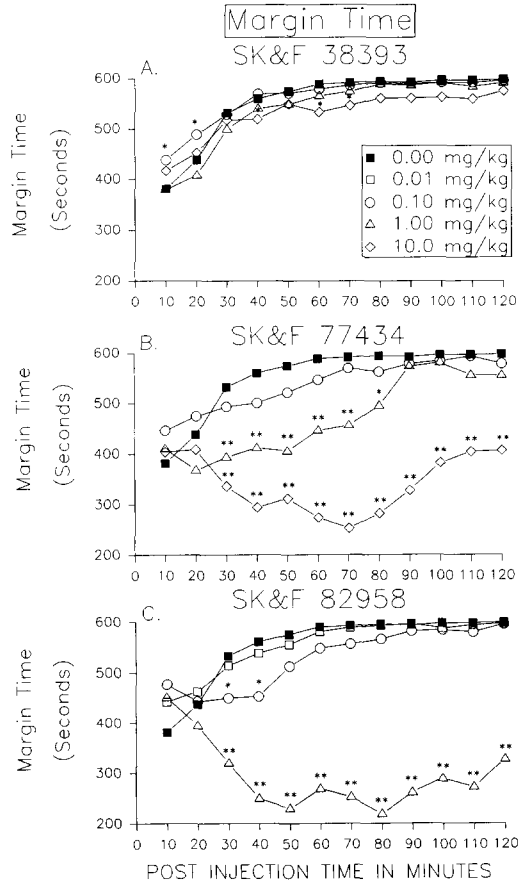


FIG. 4. Effects of various dosages of SK&F38393 (A), SK&F77434 (B), and SK&F82958 (C) upon thigmotaxis over 10 consecutive 12-min time blocks as measured by margin time in seconds. The error bars have been omitted for clarity. Significant differences from the vehicle control group: $*p < 0.05$ and $**p < 0.01$.

SK&F38393, SK&F77434, and SK&F82958 induced stereotypy behaviors (17). One major methodological difference was that in the present study animals were not habituated to the test apparatus and were introduced to it immediately after receiving a drug dose whereas other studies were conducted with rats that had been habituated. However, the present experiment revealed four features that differ from the previous studies.

First, the behavioral effect was biphasic with respect to both dose and time. What was striking was the fact that SK&F38393, SK&F77434, and SK&F82958 resulted in an initial attenuation followed by later potentiation of stereotypy time. In addition, this biphasic effect with SK&F77434 and SK&F82958 generalized to other measures of locomotor activities (horizontal movement time, rearing time, and thigmotaxis time or wall-hugging behavior). This biphasic effect was similar to those drugs, such as LY 171555 and N-0434, that bind primarily with the family of $D_2$ receptors (9,14,30). SK&F38393 and SK&F77434, while associated primarily with $D_1$ binding, have been shown to have some affinity to the $D_2$ receptor family (17–19). The classic explanation for the biphasic effect of the $D_2$ receptor ligands has centered on the autoreceptors associated with the $D_2$ receptor (6,35). This explanation may have been acceptable except for the fact that this biphasic effect was also elicited with SK&F82958, which is a full agonist for the $D_1$ receptors (17–19).

Much of the prior research focused on the induction of various categories of stereotypy behaviors, such as grooming and various syndromes of perioral dyskinesia (2,10,17,20,21, 32). Rather than using a time-sampling behavioral checklist rating procedure by an observer, in the present study activity chambers were used to objectively measure locomotor behavior including stereotypy behavior. One limitation of this automatic computer system was that it did not break stereotypy behavior into various other categories such as grooming, chewing, and gnawing and may be more comparable to the overall stereotypy rating scale. However, as a method this automatic system has been reported to be highly correlated with observer ratings (22). In this present experiment, SK&F38393 induced stereotypy behavior as a function of dose × time interaction at dose levels of 1.0 and 10.0 mg/kg, which were far smaller than those needed to typically induce grooming (30 mg/kg or more). On the other hand, SK&F82958 elicited stereotypy at dose levels as small as 0.1 mg/kg.

The second difference from the prior literature was the dose effect of SK&F38393, SK&F77434, and SK&F82958 upon locomotor activities. SK&F38393 was not associated with the induction of horizontal movement or rearing behaviors. However, SK&F77434 and SK&F82958 elicited horizontal movement and rearing as a function of a dose × time interaction. These findings were similar to other reports for only the statistical main effects.

Third, as measured by margin time thigmotaxis or wall-seeking behavior was differentially influenced by SK&F38393, SK&F77434, and SK&F82958. SK&F38393 had minor potentiation effect on thigmotaxis, whereas SK&F77434 and SK&F82958 induced an attenuation function in a dose × time interaction. This attenuation function of thigmotaxis was similar to that reported with both the antagonists of the $D_1$ family of receptors (13) and the agonists of the $D_2$ family of receptors (14,30). While differential change in thigmotaxis has been suggested as an indicator for emotionality in rodents, other paradigms must be used to verify this conclusion.

Fourth, it should be noted that SK&F38393 is a partial agonist at the classic $D_1$ receptor and that the intrinsic activity of SK&F77434 is similar to SK&F38393; on the other hand, SK&F82958 is a full agonist (18,19). In the present study, the dose levels used with SK&F82958 were lower than SK&F38393 and SK&F77434 to elicit strong locomotor activation, as measured by horizontal movement time, rearing time, and stereotypy time. This fuller stimulation of the $D_1$ family of receptors by SK&F82958 resulted in behavioral changes somewhat more similar to those seen by $D_2$ and mixed DA agonists.

As SK&F38393 binds to both the $D_{1A}$ and $D_{1B}$ receptor subtypes, it is assumed that the SK&F38393 analogs may also bind to these same subtypes. The present data do not differentiate behaviorally between these two DA subtypes. On the other hand, SK&F82958 is a full $D_1$ agonist (17–19). Thus, these data do not answer the theory that the main $D_1$ and $D_2$ receptors functionally interact and that the induction of locomotor activity requires the mutual interaction of both families of $D_1$ and $D_2$. However, the data clearly showed that even with small dose levels SK&F82958 induces stereotypy behavior, elicits horizontal movement and rearing, and affects thigmotaxis.

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