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Induction and expression of cocaine-induced behavioral sensitization: Modulation by a partial D_2-like agonist

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INDUCTION AND EXPRESSION OF COCAINE-INDUCED BEHAVIORAL SENSITIZATION: MODULATION BY A PARTIAL D_2-LIKE AGONIST

A Thesis

Presented to the

Faculty of

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San Bernardino

In Partial Fulfillment

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in

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ABSTRACT

Partial D2-like receptor agonists act as functional antagonists when given during periods of high dopaminergic tone (e.g., when self-administering cocaine). The ability of a partial D2-like agonist (e.g., terguride) to block the induction and expression of cocaine-induced behavioral sensitization was assessed in preweanling rats. The ability of terguride alone to produce a sensitized response was also investigated. It was hypothesized that terguride would block induction and eventual expression of cocaine-induced behavioral sensitization. It was further hypothesized that terguride alone would not produce behavioral sensitization. Subjects were 242 (n=8 per group) male and female rat pups of Sprague-Dawley descent. In Experiments 1 and 2, rats were injected with terguride (0.1-1.6 mg/kg) during the pre-exposure phase to determine if a partial D2-like agonist would block induction and eventual expression of cocaine-induced behavioral sensitization. In Experiment 3, rats were injected with terguride (0.2-0.8) on test day to determine whether expression of

cocaine-induced behavioral sensitization would be blocked by acute treatment with a partial D2-like agonist. The ability of terguride to produce behavioral sensitization in and of itself was examined in Experiment 4. In this experiment, rats were injected with terguride (0.4, 0.8, or 1.6 mg/kg) during the pre-exposure phase, and received a test day challenge injection of saline or 0.4 mg/kg terguride. Interestingly, terguride reduced the locomotor activity of cocaine-treated rats during the pretreatment phase, but the partial D2-like agonist did not block the induction of behavioral sensitization. When given on the test day, terguride decreased locomotor activity. This may indicate that a partial D2-like agonist is capable of blocking the expression of cocaine-induced behavioral sensitization, but it is more likely that terguride reduced the acute locomotor-stimulating properties of cocaine. Repeated treatment with terguride did not produce behavioral sensitization. Because partial D2-like agonists attenuate reward, it had been proposed that this class of drugs may be an effective pharmacotherapy for psychostimulant abuse. However,

the present results bring into question whether terguride will prove effective as a pharmacotherapy for psychostimulant addiction, because the sensitization component of the addiction process is apparently unaffected by partial D2-like agonist treatment.

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DEDICATION

In memory of my dad Ralph, and my son Kevin. To my mother Colleen, my husband Bill and my children; Valorie and Steve, Justin and Deanna, Donnie and Jennifer, and JoLynn. And, of course, to all my grandchildren; Justin Michael, Mason, Kenneth, Jocelyn, and Chad (and those still to come). My sisters, Colleena and Linda, have both contributed to my success by lending a sympathetic or supportive ear as needed. Without the love and support of my family and friends, all this would not have been possible.

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CHAPTER ONE

OVERVIEW

The worldwide use of the highly addictive psychostimulant drug cocaine is increasing at an alarming rate among both adults and children (National Institute of Drug Abuse, 1999). Cocaine is one of the most addictive substances known, and its use has major social and economic implications that cross cultural and societal lines (National Institute of Drug Abuse, 1999). Approximately 1 out of 10 people who use cocaine develop a severe form of addiction that involves incessant craving and chronic relapse (Di Chiara, 1995; Robinson & Berridge, 1993). Due to chemical changes in brain activity, addicted cocaine users continue taking the drug despite serious health and social consequences (National Institute of Drug Abuse, 1999; Robinson & Berridge, 1993).

Research has established that dopamine is one of the major neurotransmitters involved in the neurobiological substrates of drug addiction and relapse (for reviews, see Bozarth, 1987; Di Chiara, 1999). Dopamine synapses are a critical component of

endogenous reward systems in the brain, and are important for sex drive, mood, and locomotion (Koob, 1992a, 1992b; Wise & Bozarth, 1984). Not surprisingly, cocaine, as well as other psychostimulants, are reinforcing because they activate endogenous reward systems. Cocaine's mechanism of action is well established, as cocaine blocks the dopamine reuptake pump, resulting in large amounts of dopamine in the synaptic cleft (see Figure 1) (Reith, Sershen, & Lajtha, 1980). In this way, cocaine indirectly enhances dopamine neuronal transmission (Cooper, Bloom, & Roth, 1996; Reith et al., 1980). This increased neuronal transmission is responsible for the sense of pleasure and excitement that cocaine users report, as well as increased locomotion and stereotyped movement (Koob, 1992a, 1992b; Robinson & Berridge, 1993; Shippenberg, LeFevour, & Heidbreder, 1996).

Kebabian and Calne (1979) first described two dopamine receptors subtypes (D_1 and D_2) based on biochemical action. More recently, these receptor subtypes have been further delineated into the D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4) families of

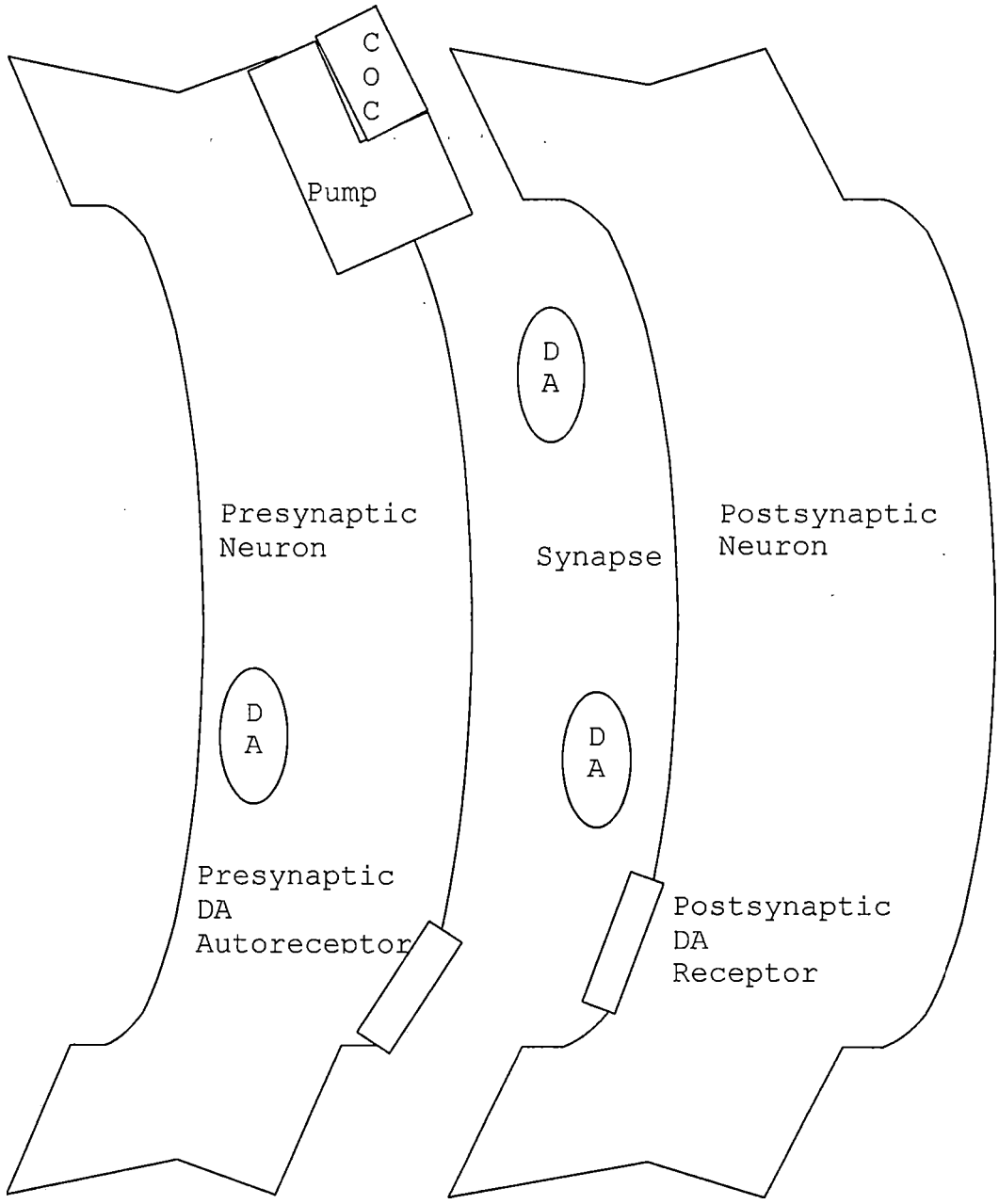

Figure 1. Action of Cocaine on Dopamine Neuron. Cocaine binds to the reuptake pump, preventing reuptake of dopamine into the cell.

receptors (Clark & White, 1987). Activation of the D_1-like receptor subtype stimulates adenylyl cyclase, whereas activation of the D_2-like receptor subtype inhibits adenylyl cyclase (Clark & White, 1987).

Besides differentially affecting adenylyl cyclase activity, D_1-like and D_2-like receptors uniquely impact behavior. For example, stimulation of the D_1-like receptor by a direct agonist drug, such as SKF 38393, increases horizontal locomotor activity, whereas stimulation of the D_2-like receptor increases stereotypy (Arnt, Hyttel, & Perregaard, 1987; Hu, Brooderson, & White, 1992; Molloy & Waddington, 1985, 1987). Evidence also shows that D_1-like and D_2-like receptors are differentially involved in mediating reward (Beninger & Miller, 1998; Koechling, Colle, & Wise, 1988). For example, reinforced responding can be blocked using a dopamine D_1-like receptor agonist (e.g., SCH 23390), whereas sulpiride, a D_2-like receptor antagonist, does not block reinforced responding (McDougall, Crawford, & Nonneman, 1992; McDougall, Nonneman, & Crawford, 1991; Nakajima, 1986; Nakajima & McKenzie, 1986). These findings provide evidence that D_1-like receptors are more intimately

involved in reward processes than are D_2-like receptors (for review, see Miller, Wickens, & Beninger, 1990).

Repeated administration of cocaine, and other psychostimulants, results in an augmented motor response known as behavioral sensitization (Kalivas & Stewart, 1991; Robinson & Becker, 1986). Sensitization is defined as a progressive increase in responding to a drug after repeated administration, whereas tolerance occurs when a drug has a lessened effect after repeated administration (Kalivas & Stewart, 1991; Robinson & Becker, 1986). Behavioral sensitization is thought to reflect processes directly related to drug craving (Brady, Lydiard, Malcolm, & Ballenger, 1991; Burger & Martin-Iverson, 1994; Post, 1975; Robinson & Berridge, 1993).

Present treatment options for cocaine addiction are inadequate, in that they fail to sufficiently decrease the intense craving and sensitized responding that are major components of chronic drug taking (Robertson, Leslie, & Bennett, 1991; Robinson & Berridge, 1993). Developing an understanding of behavioral sensitization and the synaptic changes that accompany it will be important for developing

effective treatments for addiction. Interestingly, partial D_2-like agonists, such as terguride, may have potential efficacy in the treatment of cocaine addiction (Pulvirenti & Koob, 1994). For example, it is possible that partial D_2-like agonists may block the sensitization process by binding to the receptor in place of dopamine, and thus lessen incessant craving (Bono, Balducci, Richelmi, Koob, & Pulvirenti, 1996; Izzo, Orsini, Koob, & Pulvirenti, 2001). In summary, empirical studies show that: 1) The dopamine system is involved in drug addiction; 2) Changes in brain dopamine levels may be responsible for the addiction and relapse occurring after repeated psychostimulant treatment; 3) Behavioral sensitization is an integral part of the addiction process and results in increased locomotor activity and stereotypy; and 4) Due to their pharmacological action on dopamine receptors, partial D_2-like agonists, such as terguride, may have potential efficacy for the treatment of addiction.

CHAPTER TWO

DOPAMINE RECEPTORS

Dopamine is a small catecholamine neurotransmitter synthesized from tyrosine (for review, see Cooper et al., 1996). Tyrosine is converted to L-dihydroxyphenylalanine (L-DOPA) by the enzymatic activity of tyrosine hydroxylase (TH). L-DOPA is then converted to dopamine through a rapid enzymatic process involving amino acid decarboxylase (Cooper et al., 1996). Dopamine is metabolized in the cell terminal by monoamine oxidase (MAO) and converted to dihydroxyphenylacetic acid (DOPAC). In the synaptic cleft catechol-O-methyltransferase (COMT) converts dopamine to homovanillic acid (HVA), which is then processed and excreted from the body (Cooper et al., 1996).

Dopamine specific receptors are classified into the D_1-like (D_1 and D_5) and D_2-like (D_2, D_3, and D_4) family of receptors based on their biochemical, physiological, and pharmacological actions (see Table 1) (Bouthenet, Souil, Matres, Sokoloff, Giros, & Schwartz, 1991; Clark & White, 1987).

Table 1. Dopamine D_1-like and D_2-like Receptor Properties

	Biochemical Response	G-Protein	Example Agonist	Example Antagonist
<u>D_1-like Receptor</u>				
D_1	↑Adenylyl Cyclase	G_s	SKF38393	SCH23390
D_5	↑Adenylyl Cyclase	G_s	6-Bromo-APB	SCH23390
				SCH39166
<u>D_2-like Receptor</u>				
D_2	↓Adenylyl Cyclase	G_i	quinpirole	sulpiride
D_3	↓Adenylyl Cyclase	G_i	7-OH-DPAT	AJ-76
			Piribedil	U99194
D_4	↓Adenylyl Cyclase	G_i	PD168077	clozapine
				L-745,870

Clark and White (1987) confirmed dopamine receptor selectivity by showing that dopamine agonists and antagonists have distinct actions on the different dopamine receptor subtypes. Dopamine receptor agonists are capable of directly stimulating the receptor, and frequently have a greater affinity for the receptor site than the endogenous

neurotransmitter. Dopamine receptor antagonists also bind to the dopamine receptor site, but do not stimulate the receptor (Cooper et al., 1996). Not surprisingly, dopamine receptor antagonists attenuate or reverse dopamine's actions (Cooper et al., 1996).

In all cases, dopamine receptors are metabotropic G-protein-coupled (guanosine triphosphate GTP-binding protein) receptors (Cooper et al., 1996). More specifically, D_2-like receptors are coupled to inhibitory G-proteins (G_i) and, when activated, depress adenylyl cyclase formation (Baldessarini & Tarazi, 1996). D_1-like receptors are coupled to stimulating G-proteins (G_s) and, when activated, facilitate adenylyl cyclase formation (Baldessarini & Tarazi, 1996). In the latter case, G_s-proteins activate effector proteins and the resulting adenylyl cyclase converts adenosine triphosphate (ATP) into cyclic adenosine monophosphate (cAMP) (Baldessarini & Tarazi, 1996; Hepler & Gilman, 1992; Hille, 1992). The resulting cAMP in the cytosol activates protein kinase A, causing changes in calcium and potassium permeability (Beninger & Miller, 1998; Hepler & Gilman, 1992; Hille, 1992).

Dopamine receptor subtypes differ in their affinity for dopamine, as well as for agonist and antagonist drugs (Cooper et al., 1996; Kebabian & Calne, 1979; Ujike, Akiyama, & Otsuki, 1990). A major difference among the D_1-like receptor subtypes is that D_5 receptors have a 10-fold higher affinity for dopamine than D_1 receptors (Cooper et al., 1996). Differences in affinity have also been observed within the D_2-like family of receptors. For example, D_3 receptors have 70 times greater affinity for dopamine than D_1 or D_2 receptors (Cooper et al., 1996). Conversely, D_2 receptors have a higher affinity for apomorphine, a prototypical dopamine agonist drug, than do D_3 or D_4 receptors (Cooper et al., 1996). Other drugs show different receptor binding profiles. For instance, clozapine (a neuroleptic) has a 10-fold greater affinity for D_4 receptors than D_2 or D_3 receptors (Gilbert, Millar, & Cooper, 1995). Thus, the various dopamine receptor subtypes not only have different affinities for dopamine, they also are differentially stimulated by dopamine agonist and antagonist drugs.

Due to the role dopamine plays in reward processes, a substantial number of studies have examined whether the dopamine neurotransmitter system is important for addiction. As indicated above, the functioning of dopamine neurons and receptors can be altered through pharmacological manipulation. Thus, therapeutic interventions may eventually be able to reverse or attenuate some of the psychostimulant-induced molecular and cellular changes responsible for addiction.

CHAPTER THREE

NEURAL SUBSTRATES OF REWARD

Dopamine neuronal pathways are critical components of the reward system. Early self-administration studies by Olds and Milner (1954), along with work by Dahlstrom and Fuxe (1964), greatly increased our knowledge regarding reward and reinforcement. They demonstrated that stimulation of the medial forebrain bundle, traveling near the lateral hypothalamus, was rewarding to a subject, while lesioning the MFB disrupted reward. Additional studies showed that stimulation of the MFB activates an endogenous dopamine reward system that projects from the midbrain to limbic structures (Bozarth, 1991). Subsequent neurochemical stimulation studies have shown that two major dopamine pathways exist in brain: the mesolimbic and nigrostriatal pathways (see Figure 2)(Koob & Bloom, 1988; Wise & Bozarth, 1987). Both the mesolimbic and nigrostriatal dopamine systems have unique roles in reward and addiction. The mesolimbic dopamine pathway is the primary site of

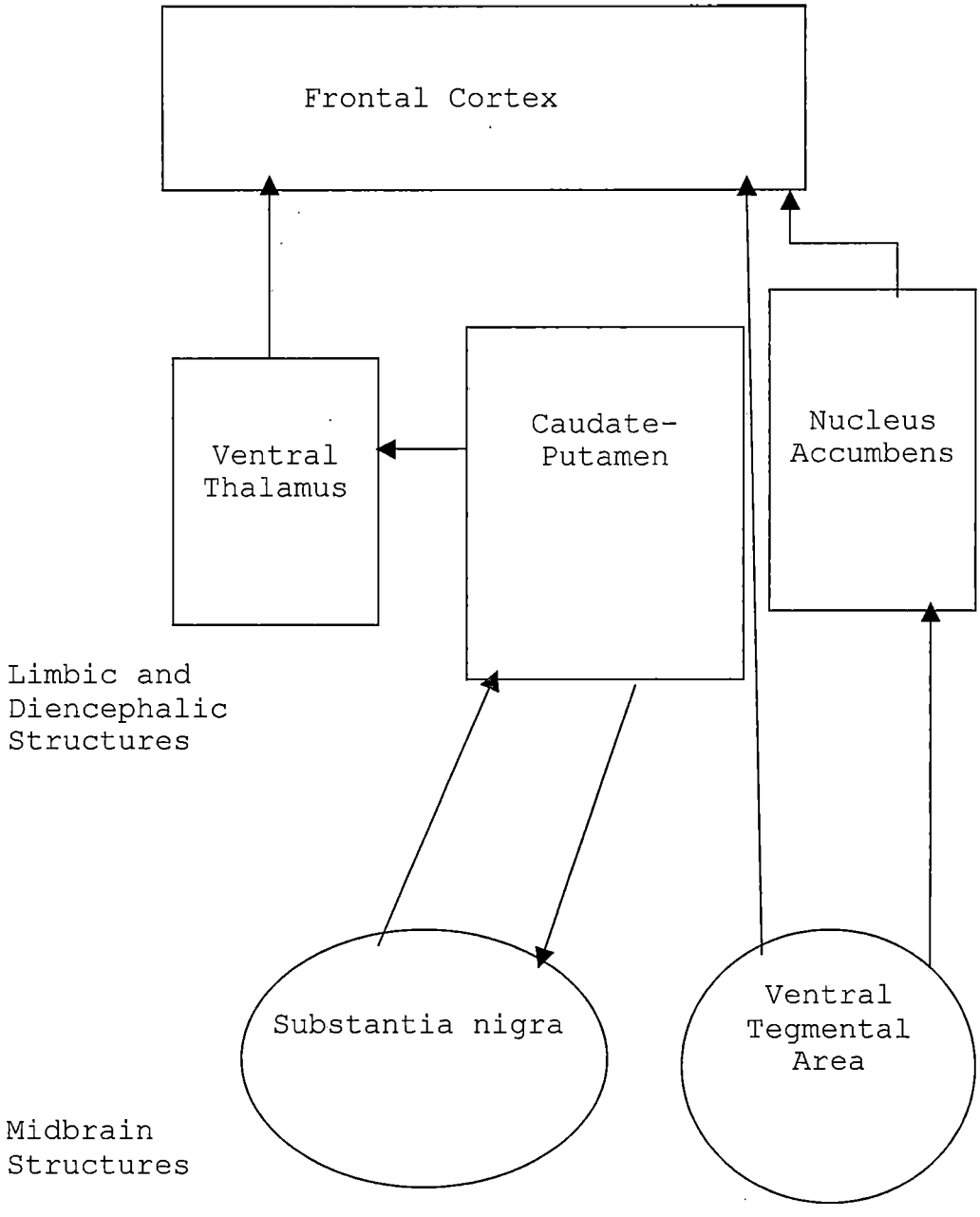

Figure 2. Brain Reward Pathways. The mesolimbic dopamine pathway originates in the ventral tegmentum and extends to the nucleus accumbens. Output fibers go to the frontal cortex. The nigrostriatal dopamine pathway projects from the caudate-putamen. Output fibers go to the frontal cortex via the ventral thalamus.

reward (Wise & Bozarth, 1984). In contrast, the increased stereotypy observed after chronic psychostimulant use appears to be due to activation of the nigrostriatal pathway (Stahl, Ferger, & Kuschinsky, 1997; Wise & Bozarth, 1984). For example, microinjecting amphetamine into the nucleus accumbens results in locomotion and reward (Wise & Bozarth, 1987), whereas, microinjecting amphetamine into the caudate-putamen results in stereotypy (Arnt, 1987). Thus, psychostimulants like cocaine enhance dopaminergic functioning in both the mesolimbic and nigrostriatal pathways resulting in reward, locomotion, and stereotypy (Wise & Bozarth, 1984).

The Mesolimbic Dopamine Pathway

Anatomy and Receptors

The mesolimbic dopamine pathway modulates and filters signals in the limbic system (Koob, 1992a, 1992b; Pierce & Kalivas, 1997). Efferent neurons from the ventral tegmental area travel thru the MFB (which is a major fiber bundle connecting the forebrain to the midbrain) to the nucleus accumbens (known as the ventral striatum) (McBride, Murphy, & Ikemoto, 1999;

Wise & Bozarth, 1984). Output fibers from the nucleus accumbens project to the prefrontal cortex (Wise & Bozarth, 1984). Various brain areas provide excitatory input into the ventral tegmental area, including the lateral hypothalamus, prefrontal cortex, and amygdala (Beninger & Hahn, 1983; Wise & Rompre, 1989; Wise, Spindler, deWit, & Gerber, 1978). The most important input into the ventral tegmental area is from the lateral hypothalamus, because it is critical for the reward associated with food, water, sex, and predation (Di Chiara, 1999; Leshner & Koob, 1999; Wise & Bozarth, 1984; Wise & Rompre, 1989).

Dopamine D_1-like and D_2-like receptors are differentially distributed across brain. Among the D_1-like receptor family, D_1 receptors are found in high numbers in the substantia nigra pars reticulata, caudate-putamen, nucleus accumbens and frontal cortex (Baldessarini & Tarazi, 1996; Boyson, McGonigle, & Molinoff, 1986; Dawson, Gehlert, McCabe, Barnett, & Wamsley, 1986; Mansour, Meador-Woodruff, Bunzow, Civelli, Akil, & Watson, 1990; Schambra, Duncan, Breese, Fornaretto, Caron, & Fremeau, 1994). D_5 receptors are localized in the cortex, hippocampus and

limbic system. Among the D_2-like receptor family, D_2 receptors are found in high numbers in the caudate-putamen, striatum, and substantia nigra, while D_3 receptors are localized in the olfactory tubercle, nucleus accumbens, striatum, substantia nigra, and hypothalamus (Boyson et al., 1986; Dawson et al., 1986; Mansour et al., 1990; Schambra et al., 1994). The final member of the D_2-like receptor family, the D_4 receptor, is found in the frontal cortex, medulla, hypothalamus, and caudate-putamen (Boyson et al., 1986; Dawson et al., 1986; Mansour et al., 1990; Schambra et al., 1994; Tarazi & Baldessarini, 2000).

Although the regional distributions of D_1-like and D_2-like receptors have been determined, the functioning of these receptors has only been partially clarified. For example, D_2-like receptors in the nigrostriatal pathway appear to be important for modulating the intensity of voluntary movement (Baldessarini & Tarazi, 1996). D_1-like receptors have a role in facilitating the commencement of D_2-like activities (Arnt & Perregaard, 1987; Clark & White, 1987). D_1-like receptors are also thought to be more critical than D_2-like receptors for reward functioning

(McDougall et al., 1991, 1992; Miller et al., 1990; Nakajima, 1986; Nakajima & McKenzie, 1986).

Evidence that Psychostimulant Drugs Affect the Mesolimbic Dopamine Pathway

In both humans and nonhuman animals, stimulation of the MFB elicits strong feelings of pleasure and reward (Bozarth, 1991; Koob, 2000; Salamone, Cousins, & Snyder, 1997). Presumably, these enhanced feelings of reward are caused by activation of the nucleus accumbens via input from the ventral tegmental area (Bozarth, 1991). The nucleus accumbens is stimulated not only by natural rewards, such as food and sex, but also by psychoactive drugs (Di Chiara, 1999; Leshner & Koob, 1999). In fact, most researchers believe that the nucleus accumbens is the locus where cocaine has its rewarding actions (Bozarth, 1991).

Substantial amounts of evidence support the idea that the mesolimbic pathway, and the nucleus accumbens in particular, is important for cocaine-induced reward. For example, administering dopamine antagonists into the nucleus accumbens blocks reward (Bozarth, 1991; Breiter, Gollub, Weisskoff, Kennedy,

Makris, Berke, Goodman, Kantor, Gastfriend, Riorden, Mathew, Rosen, & Hyman, 1997; Everitt, Parkinson, Olmstead, Arroyo, Robledo, & Robbins, 1999). Conversely, rats will readily self-administer psychostimulant drugs into the ventral tegmental area and nucleus accumbens (Schuster & Thompson, 1969). When electrical stimulation is applied to areas near the nucleus accumbens, but not in it, there is no evidence of reward (Bozarth, 1991). Lastly, lesioning the mesolimbic dopamine pathway fully attenuates self-administration of both cocaine and amphetamine (Lyness, Friedle, & Moore, 1979). Therefore, various types of studies (microinjection, electrical brain stimulation, and drug self-administration experiments) suggest that the mesolimbic pathway serves as the critical substrate for reward (McBride et al., 1999; Pierce & Kalivas, 1997).

The Nigrostriatal Dopamine Pathway

Anatomy and Receptors

The behavioral stereotypy observed after chronic cocaine exposure is mediated by the nigrostriatal

dopamine pathway, which originates in the pars compacta of the substantia nigra and projects to the caudate-putamen (also known as the dorsal striatum) (Arnt & Perregaard, 1987; Pierce & Kalivas, 1997). Two main output pathways project from the caudate-putamen: one intrinsic and one extrinsic. The intrinsic pathway is referred to as the striatonigral tract, which extends from the caudate-putamen to the substantia nigra (Gerfen, 1984, 1992). These descending neurons express D_1 receptor mRNA and release both GABA and dynorphin from their terminal fibers (Gerfen, 1984). The extrinsic pathway projects from the caudate-putamen to the thalamus and, ultimately, to premotor areas of the frontal cortex (Gerfen, 1984).

Evidence that Psychostimulant Drugs Affect the Nigrostriatal Dopamine Pathway

Various experimental paradigms have shown that psychostimulant drugs indirectly stimulate the nigrostriatal dopamine pathway. For example, high doses of psychostimulant drugs preferentially affect the nigrostriatal dopamine pathway resulting in

stereotypy, while lower doses increase locomotor activity (Asher & Aghajanian, 1974; Kelly, Seviour, & Iversen, 1975). Using electroencephalograph (EEG) techniques, Stahl et al. (1997) also found a dose-dependent effect in which low doses of amphetamine activated D_1-like receptors in the mesolimbic pathway, while higher doses of amphetamine activated D_2-like receptors in the nigrostriatal pathway. Lastly, microinjecting amphetamine into the caudate-putamen and nucleus accumbens produce distinctly different behavioral profiles. Intense oral stereotypies develop when amphetamine is microinjected into the caudate-putamen, while microinjecting amphetamine into the nucleus accumbens results in locomotion (Dickson, Lang, Hinton, & Kelley, 1994; Staton & Solomon, 1984).

CHAPTER FOUR

BEHAVIORAL SENSITIZATION IN THE ADULT RAT

The enduring behavioral augmentation observed after chronic cocaine administration is known as behavioral sensitization (Downs & Eddy, 1932; Robinson & Becker, 1986). Behavioral sensitization is considered to be a major factor in the addiction process (Bozarth, 1987; Reith et al., 1980; Robinson & Becker, 1986; Robinson & Berridge, 1993), and is thought by some to be important for incessant drug craving and psychostimulant-induced psychoses (Brady et al., 1991; Post, 1975).

In rodents, enduring locomotor augmentation is produced by a wide variety of drugs, including methylphenidate, cocaine, and methamphetamine (Akimoto, Hamamura, & Otsuki, 1989; Crawford, Drago, Watson, & Levine, 1997; Crawford, McDougall, Meier, Collins, & Watson, 1998). In adult rats, cocaine-induced behavioral sensitization remains evident after a 3-month abstinence period, while sensitization to amphetamine and methamphetamine is evident for up to

12 months (Kalivas & Stewart, 1991; Leith & Kuczenski, 1982; Paulson, Camp, & Robinson, 1991). The strength of the sensitized response is dependent on multiple factors, including drug dose, whether the drug is administered in the home cage or a novel environment, and drug pre-exposure schedule (McDougall, Collins, Karper, Watson, & Crawford, 1999; Robinson & Berridge, 1993; Snyder, Katovic, & Spear, 1998; Weiss, Post, Pert, Woodward, & Murman, 1989; Zavala, Nazarian, Crawford, & McDougall, 2000).

The neural mechanisms underlying behavioral sensitization are only partially understood. For example, some researchers have shown that drug-induced changes in the D_1-like receptor are probably responsible for the plasticity associated with behavioral sensitization (Henry & White, 1991, 1995; Kalivas, 1995; Vezina, 1996). Other researchers have posited that D_2-like autoreceptor supersensitivity in the ventral tegmental area is responsible for the enhanced synaptic dopamine levels occurring in behavioral sensitization (Wolf, White, Nassar, Brooderson, & Khansa, 1993). With continued research it is anticipated that the precise mechanisms

mediating behavioral sensitization will become fully elucidated.

Induction and Expression of Behavioral Sensitization

Induction

Behavioral sensitization can be divided into two distinct processes referred to as induction (also known as development or initiation) and expression (Kalivas & Stewart, 1991; Leith & Kuczenski, 1982; Pierce & Kalivas, 1997; Robinson & Becker, 1986; Vanderschuren & Kalivas, 2000). Induction is the process by which a subject initially develops a sensitized response. Induction is characterized by a progressive day-dependent increase in behavioral responding that occurs after repeated administration of a psychostimulant drug. It is likely that induction is the result of long-lasting cellular changes in the neuron caused by chronic psychostimulant exposure (Pierce & Kalivas, 1997). Specifically, induction is correlated with blockade of the dopamine reuptake pump, an increase in dopamine levels in the synapse, and a decrease in D_2-like

autoreceptor sensitivity (Henry & White, 1991; Kalivas & Stewart, 1991; Pierce & Kalivas, 1997; Robinson & Becker, 1986; Vezina, 1996; Vezina & Stewart, 1989; Wolf, 1998).

Recent empirical evidence has more fully elucidated the neuronal mechanisms important for induction of behavioral sensitization. Repeated administration of amphetamine into the ventral tegmental area, but not the nucleus accumbens, causes a sensitized response after subsequent drug challenge (Kalivas & Duffy, 1990). This finding suggests that the ventral tegmental area is the primary site responsible for the induction of behavioral sensitization. Wolf, White, and Hu (1994) reported that the neurochemical changes observed in the ventral tegmental area are transient and occur soon after initial drug exposure. Changes in the nucleus accumbens are longer lasting and require substantially more drug exposures (Wolf et al., 1993, 1994). Thus, these results suggest that psychostimulant-induced changes in the ventral tegmental area are probably responsible for the induction of behavioral

sensitization, whereas changes in the nucleus accumbens are more clearly associated with expression.

Expression

Expression of behavioral sensitization occurs when a subject previously exposed to a psychostimulant shows an enhanced behavioral response after acute drug challenge (Henry & White, 1991; Pierce & Kalivas, 1997). The nucleus accumbens is important for the expression of behavioral sensitization (Pierce & Kalivas, 1997; Vanderschuren & Kalivas, 2000; Wolf, 1998). Long-term expression of behavioral sensitization is thought by some to be a result of D_1-like receptor supersensitivity in the axon terminals of the nucleus accumbens and striatum (Henry & White, 1991; Wolf, 1998). Consistent with this idea, D_1-like receptor antagonists block expression of behavioral sensitization, even though the induction of behavioral sensitization had previously occurred (Mattingly, Hart, Lim, & Perkins, 1994; White, Joshi, Koeltzow, & Hu, 1998).

Associative Learning in Behavioral Sensitization

Empirical evidence indicates that the overall strength of the sensitized response is increased when Pavlovian associations are formed between the environment and the drug (Badiani, Browman, & Robinson, 1995). In this situation, the effect drug's neurochemical actions function as the unconditioned stimulus (US), while the environment and the locomotor activity are the conditioned stimulus (CS) and unconditioned response (UR), respectively (Campbell & Raskin, 1978). For this reason, a novel environment has been shown to facilitate the development of behavioral sensitization to cocaine, amphetamine, and other psychostimulants (Badiani et al., 1995; Shippenberg et al., 1996; Tirelli & Terry, 1998). Thus, sensitized responding is more robust when cocaine challenge occurs in the same environment where the subject initially received the drug (Badiani et al., 1995; Shippenberg et al., 1996; Tirelli & Terry, 1998).

Behavioral sensitization may be an important component in drug craving. During behavioral

sensitization, the environment takes on cue salience and is able to produce craving on its own (Burger & Martin-Iverson, 1994; Post, Weiss, & Pert, 1992; Robinson & Becker, 1986; Tirelli, 2001). Consistent with this idea, rats spend more time in an environment that has been paired with a psychostimulant drug (Crombag, Badiani, Chan, Dell'Orco, Dineen, & Robinson, 2001). Interestingly, rats exhibit increased brain dopamine levels when they are placed in a previously drug-paired environment even if no new drug is administered (Crombag et al., 2001; Rebec, Grabner, Johnson, Pierce, & Bardo, 1997).

The relationship between drug and environment may be relevant to the issue of drug relapse in humans. More specifically, exposure to the drug-taking environment can result in drug relapse (Wise, 1988). This finding was first reported over 50 years ago, as Wikler (1948) noted that post-detoxification patients returning to their old environments experienced drug craving and relapse. The reinstatement of desire for a drug can occur after months, or even years, of drug abstinence (National Institute of Drug Abuse, 1999; Wise, 1988). It has even been estimated that 45% of

drug relapse may be due to associative processes involving the pairing of drug cues with environmental factors (Wise, 1988). Thus, there is substantial evidence supporting the argument that environmental cues are a critical factor in the addiction process.

CHAPTER FIVE

ONTOGENY OF BEHAVIORAL SENSITIZATION

Psychostimulant-induced behavioral sensitization shows ontogenic changes from the preweanling period to adulthood (Fujiwara, Kazahaya, Nakashima, Sato, & Otsuki, 1987; McDougall, Duke, Bolanos, & Crawford, 1994; Wood, Tirelli, Snyder, Heyser, LaRocca, & Spear, 1998; Zavala et al., 2000). Early studies using cocaine and amphetamine suggested that young animals were incapable of showing behavioral sensitization after repeated psychostimulant treatment (Barr & Wang, 1993; Fujiwara et al., 1987; Kolta, Scalzo, Ali, & Holson, 1990; Tsuchida, Ujike, Kanzaki, Fujiwara, & Akiyama, 1994). More recent studies report that behavioral sensitization to psychostimulant drugs is attainable in the young rat, although it is not as robust as in adults (Duke, O'Neal, & McDougall, 1997; McDougall et al., 1994; Tirelli & Ferrara, 1997; Wood et al., 1998; Zavala et al., 2000). A possible explanation for these age-dependent behavioral differences is that dopamine receptor systems may be

functionally immature in the young animal (Fujiwara et al., 1987; McDougall et al., 1994; Ujike, Tsuchida, Akiyama, Fujiwara, & Kuroda, 1995; Wood et al., 1998). Thus, as the dopamine system matures, sensitized responding may become more robust. Another explanation is that young and adult rats may differ in how readily they form Pavlovian associations between the environmental context and the drug (Wood et al., 1998; Zavala et al., 2000). Since Pavlovian associations are critical for the expression of behavioral sensitization, an inability to form such associations would negatively impact the robustness of the sensitized response.

A number of ontogenic constraints affect the induction and expression of behavioral sensitization, including the number of pre-exposure days and the length of the drug abstinence period. For example, as little as one drug pre-exposure is capable of inducing behavioral sensitization in adult rats, and the sensitized response may be detected for many months (Fontana, Post, Weiss, & Pert, 1993; Leith & Kuczenski, 1982; Paulson et al., 1991; Weiss et al., 1989). In order to elicit cocaine-induced behavioral

sensitization in preweanling rat pups, a longer pre-exposure phase and a shorter drug abstinence period is required (McDougall et al., 1994; Tirelli & Ferrara, 1997; Zavala et al., 2000). For example, Zavala et al. (2000) found that 10 drug pre-exposure days, rather than the usual 5 days, was necessary to produce a sensitized response that persisted across seven drug abstinence days. Further, Snyder et al. (1998) obtained a sensitized locomotor response to cocaine after a 21-day drug abstinence period, but only if an extended pre-exposure phase was used. This shows that the number of pre-exposure days, and the length of the drug abstinence period, are a critical constraint affecting the occurrence of behavioral sensitization (Zavala et al., 2000).

As mentioned above, ontogenic differences in behavioral sensitization may be due to maturational changes in the dopamine system (Fujiwara et al., 1987; McDougall et al., 1994; Ujike et al., 1995; Wood et al., 1998). For example, certain components of the dopamine system, including reuptake pumps and receptors, show substantial changes across the preweanling period (Arnauld, Arsaut, Tafani, &

Demotes-Mainard, 1995; Gelbard, Teicher, Faedda, & Baldessarini, 1989; Giorgi, De Montis, Porceddu, Mele, Calderini, Toffano, & Biggio, 1987; Pardo, Creese, Burt, & Snyder, 1977). Immaturity of the dopamine system has functional consequences, as the mesolimbic and nigrostriatal dopamine pathways appear to be hypoactive in younger animals (Arnauld et al., 1995; Pardo et al., 1977).

Another explanation for the ontogenic changes in behavioral sensitization may involve age-dependent differences in the ability to form and maintain Pavlovian associations (Zavala et al., 2000). For example, Zavala et al. (2000) found that sensitization was not dependent on associative factors when drug challenge occurred after only one abstinence day (i.e., a sensitized response was observed when the pre-exposure drug was given in the home cage rather than the test chamber). However, when a seven-day drug abstinence period was employed, rat pups only exhibited a sensitized response if drug pre-exposure and challenge occurred in the same previously novel environment (Zavala et al., 2000). When considered together, these findings show that Pavlovian factors

are particularly important for the occurrence of behavioral sensitization in preweanling rats. It is conceivable that young rats may have more difficulty forming the necessary associations between the psychostimulant drug and the environmental context, thus requiring an extended pre-exposure phase for the association to take place (Zavala et al., 2000).

In summary, empirical evidence shows that: 1) The sensitization process is dependent on changes across ontogeny; 2) Young rats can exhibit behavioral sensitization to psychostimulant drugs, although the sensitization is not as robust as that observed in adult rats; 3) The number of pre-exposure days and the length of the drug abstinence period are important ontogenic constraints affecting the occurrence of behavioral sensitization; 4) Ontogenic differences in behavioral sensitization may be due to (a) maturational changes in the dopamine system or (b) age-dependent differences in the ability to form Pavlovian associations between the drug and environmental context.

CHAPTER SIX

PHARMACOLOGICAL ACTION OF PARTIAL D_2-LIKE RECEPTOR AGONISTS

Although psychostimulant addiction is a major problem in society, no effective pharmacotherapies have yet been developed to treat this problem (National Institute of Drug Abuse, 1999). Dopamine receptor antagonists are effective at blocking reward, but complete blockade of dopamine receptors produces anhedonia and motor side effects (e.g., tardive dyskinesia and tremors) (for reviews, see Baldessarini, 1996; Miller et al., 1990). Partial D_2-like receptor agonists have been suggested as a potential pharmacotherapy that may be effective in reducing the rewarding value of psychostimulant drugs, without having the same aversive properties as dopamine receptor antagonists.

Partial D_2-like receptor agonists have both agonist and antagonist actions on G-protein-coupled dopamine receptor sites (Hoyer & Boddeke, 1993). In situations where dopaminergic functioning is

depressed, partial D_2-like agonists act in an agonistic manner, thus stimulating the dopamine system. In situations where dopaminergic functioning is enhanced, partial D_2-like agonists act in an antagonistic manner, thus depressing the dopamine system (Clark, Furmidge, Petry, Tong, Ericcson, & Johnson, 1991). Because partial D_2-like agonists bind to dopamine receptor sites with high affinity and low intrinsic activity, this class of drugs has the ability to block the effects of psychostimulant drugs without depressing baseline levels of dopaminergic activity (Hoyer & Boddeke, 1993).

Pre- and postsynaptic D_2-like receptors are differentially affected by partial D_2-like receptor agonists. For example, D_2 autoreceptors are 5-10 times more sensitive to partial agonist activity than D_2-like postsynaptic receptors (Clark & White, 1987). Although exhibiting low intrinsic affinity for D_2-like postsynaptic receptors, partial D_2-like agonists typically have antagonistic actions at these receptor sites (Arnt et al., 1987; et al., 1991; Clark, Salah, & Galloway, 1991). In the nucleus accumbens, cocaine enhances dopaminergic activity by indirectly

stimulating postsynaptic D_2-like receptors. Thus, functioning of the mesolimbic pathway could potentially be restored to normal levels if cocaine's actions were attenuated by a partial D_2-like agonist (Izzo et al., 2001; Robertson et al., 1991).

Terguride, an analog of lisuride is a partial D_2-like dopamine receptor agonist that has pharmacological properties suggesting potential efficacy in the treatment of addiction (Brücke, Bankiewicz, Harvey-White, & Kopin, 1988; Carratu, DeSerio, Mitolo-Chieppa, & Federico, 1991; Ekman & Eriksson, 1992; Koller & Herbster, 1987; Lange, Löschmann, Wachtel, Horowski, Jähnig, Jenner, & Marsden, 1992; Piercy, Hoffman, Vogelsang, & Travis, 1987). D_2-like agonists, such as terguride, may be able to modulate multiple aspects of psychostimulant addiction. For example, terguride decreases both cocaine self-administration (Clark, Furmidge, et al., 1991; Clark, Salah, et al., 1991; Pulvirenti, Balducci, Piercy, & Koob, 1998; Spealman, 1995) and alcohol consumption in rats (Bono et al., 1996). This seems to indicate that terguride has a modulating effect on craving, perhaps by normalizing dopaminergic

functioning in the nucleus accumbens. Terguride also blocks cocaine-induced locomotor activity, suggesting that this partial D_2-like agonist is capable of attenuating other reward-related behavioral effects (Clark, Furmidge, et al., 1991). Lastly, terguride alone is not rewarding (Callahan & Cunningham, 1993; Pierce & Kalivas, 1997), nor does it possess the discriminative stimulus properties of other psychostimulants (Akai, Ozawa, Yamaguchi, Mizuta, & Kuno, 1995; Akai, Yamaguchi, Mizuta, & Kuno, 1993; Callahan & Cunningham, 1993; Pierce & Kalivas, 1997). The latter point is important, because drugs that act as discriminative stimuli can produce cue-induced craving (Akai et al., 1995; Callahan & Cunningham, 1993; Pierce & Kalivas, 1997).

In summary, the potential efficacy of partial D_2-like receptor agonists, such as terguride, may lie in their ability to modulate critical processes involving psychostimulant addiction (i.e., reward and incessant craving) (Bono et al., 1996; Brucke et al., 1988; Izzo et al., 2001; Pulvirenti & Koob, 1994; Ranaldi, Wang, & Woolverton, 2001; White et al., 1998). As shown in the above studies, substantial evidence suggests that

terguride may have therapeutic benefits for psychostimulant addiction.

CHAPTER SEVEN

PURPOSE

In general, the contents of the previous chapters can be summarized as follows: 1) Endogenous activation of dopamine receptors in the mesolimbic pathway is rewarding; 2) Cocaine exogenously activates the mesolimbic pathway, not only causing reward, but also producing long-term changes in neurotransmitter functioning; 3) Behavioral sensitization is believed to be a critical component of the addiction process; 4) Psychostimulant-induced behavioral sensitization shows ontogenic changes (i.e., the sensitized responding of preweanling rats is not as robust as that shown by adults); 5) If the dopamine system is maximally activated, partial D_2-like agonists have the ability to depress dopaminergic functioning towards basal levels. It has already been established that partial D_2-like agonists can reduce the rewarding effects of cocaine and other psychostimulants (Bono et al., 1996; Izzo et al., 2001; Pulvirenti et al., 1998). It is unclear, however, whether partial D_2-like agonists can block the induction and expression of

behavioral sensitization. If partial D_2-like agonists are capable of blocking behavioral sensitization, it would provide additional evidence that this class of drugs might have therapeutic efficacy for the treatment of psychostimulant addiction.

Based on previous findings, it was hypothesized that a partial D_2-like agonist (i.e., terguride) would block both the induction and expression of behavioral sensitization in preweanling rats. It was further hypothesized that terguride would not produce behavioral sensitization by itself. To test these hypotheses I conducted four experiments. In Experiments 1 and 2, I investigated whether terguride would block induction of cocaine-induced behavioral sensitization in preweanling rats. In Experiment 3, I examined whether a test day injection of terguride would block expression of cocaine-induced behavioral sensitization. In Experiment 4, the focus was to determine whether terguride itself can produce behavioral sensitization. If terguride produces behavioral sensitization, it would suggest that this partial D_2-like agonist has abuse potential in its own right.

CHAPTER EIGHT

GENERAL METHODS

Subjects

Subjects were 242 (n = 8 per group) male and female rat pups of Sprague-Dawley descent (Charles River, Wilmington, MA), born and raised at California State University, San Bernardino. Litters were culled to ten pups by 3 days of age and kept with the dam throughout behavioral testing. Assignment of males and females to groups was random, with only one rat per litter in each particular group. Rats were housed in the colony room on a 12:12 hr light-dark cycle. Temperature was maintained at 22-24°C. Behavioral testing was done during the light cycle, at approximately the same time each day. Subjects were treated according to the American Psychological Association "Ethical Principles" (1992), and the Principles of Laboratory Animal Care (National Institute of Health Publication # 85-23).

Apparatus

Coulbourn Tru-Scan (Coulbourn Instruments, Allentown, PA) activity monitoring chambers (25.5 × 25.5 × 41 cm) were used to measure distance traveled (i.e., horizontal locomotor activity). The Coulbourn chambers have clear Plexiglas walls, open tops, and smooth plastic floors. Each chamber has 16 photocells and detectors in an X-Y photobeam arrangement. To avoid olfactory contamination the Plexiglas walls were wiped with 30% alcohol between subjects. The floor trays were cleaned with a commercially available bactericide between testing sessions.

Drugs

Terguride (transdihydrolisuride) (Sigma, St Louis, Mo) was dissolved in a drop of glacial acetic acid and then mixed in saline. Cocaine (Sigma) was dissolved in saline. All injections were given intraperitoneally (i.p.) at a volume of 5 ml/kg.

Statistical Analysis

Behavioral data were analyzed using repeated measures analyses of variance (ANOVA). Distance

traveled was the dependent variable in all experiments. In each of these analyses, litter effects were controlled by using within-litter statistical procedures (Zorrilla, 1997). Additional analysis of behavioral data was made using Tukey tests. Alpha level criterion of .05 was used for all ANOVA's and Tukey tests.

CHAPTER NINE

EXPERIMENT ONE

The purpose of this experiment was to assess whether low doses of terguride (0.1-0.4 mg/kg) are capable of blocking the induction of behavioral sensitization to cocaine.

Procedure

Pre-Exposure Phase (Days 1-7)

The pre-exposure phase started at postnatal PD 15 and continued to PD 21. On seven consecutive days (i.e., PD 15-21), pups were injected with saline or terguride (0.1, 0.2, or 0.4 mg/kg). Pups were then returned to the dam in their home cage. After 30 min, pups were taken to the experimental room and placed in individual chambers for a 5-min habituation period. At the end of habituation, pups initially injected with saline were injected with either cocaine (30 mg/kg) or saline. In contrast, pups initially injected with terguride were injected with cocaine (30 mg/kg). After the 30-min observation session, pups were returned to the dam in their home cage. In summary, five groups of rats received the following

5-min time blocks) repeated measures ANOVA. Post hoc analysis of behavioral data was made using Tukey tests.

CHAPTER TEN

EXPERIMENT TWO

The purpose of this experiment was to assess whether higher doses of terguride (0.4-1.6 mg/kg) are able to block the induction of behavioral sensitization to cocaine.

Procedure

Pre-Exposure Phase (Days 1-7)

The pre-exposure phase started at PD 15 and continued to PD 21. On seven consecutive days (i.e., PD 15-21), pups were injected with saline or terguride (0.4, 0.8, or 1.6 mg/kg). Pups were then returned to the dam in their home cage. After 30 min, pups were taken to the experimental room and placed in individual chambers for a 5-min habituation period. At the end of habituation, half of the pups were injected with cocaine (30 mg/kg) and the other half received saline. After the 30-min observation session, pups were returned to their home cage. In summary, eight groups of rats received the following sequence of drugs on each day of the pre-exposure phase: Sal-Sal, Terg(0.4)-Sal, Terg(0.8)-Sal,

Terg(1.6)-Sal, Sal-Coc, Terg(0.4)-Coc, Terg(0.8)-Coc, and Terg(1.6)-Coc. As mentioned above, the initial injection of saline or terguride occurred 30 min prior to the cocaine injection.

Test Day (Day 9)

After a 24 h drug abstinence period, sensitization was assessed on a single test day. On the test day (PD 23), pups were injected with saline and returned to the dam for 30 min. Pups were then taken to the experimental room and placed in a chamber for a 5-min habituation period. After habituation, all pups were given a single challenge injection of cocaine (15 mg/kg). After the 30-min testing period, pups were returned to their home cage.

Statistical Analysis

Horizontal locomotor activity during the pre-exposure phase was analyzed using a 4 × 2 × 7 (Pre-Exposure Drug × Stimulant Condition × Pre-Exposure Day) repeated measures ANOVA; whereas, horizontal locomotor activity from test day was analyzed using a 4 × 2 × 6 (Pre-Exposure Drug × Stimulant Condition × 5-min time

blocks) repeated measures ANOVA. Post hoc analysis of behavioral data was made using Tukey tests.

CHAPTER ELEVEN

EXPERIMENT THREE

The purpose of this experiment was to assess whether terguride is capable of blocking the expression of behavioral sensitization to cocaine.

Procedure

Pre-Exposure Phase (Days 1-7)

The pre-exposure phase started at PD 15 and continued to PD 21. On seven consecutive days (i.e., PD 15-21), pups were taken to the experimental room and placed into the individual chambers for a 5-min habituation period. At the end of habituation, half of the pups were injected with cocaine (30 mg/kg) and the other half with saline. After the 30-min observation session, pups were returned to their home cage.

Test Day (Day 9)

After a 24 h drug abstinence period, sensitization was assessed on a single test day. On the test day (PD 23), pups were injected with saline or terguride (0.2, 0.4, or 0.8 mg/kg) and returned to

their home cage for 30 min. After 30 min, pups were taken to the testing room and placed in a chamber for a 5-min habituation period. At the end of habituation, pups were injected with a challenge dose of cocaine (15 mg/kg). After the 30-min testing period, pups were returned to their home cage. As mentioned above, the initial dose of saline or terguride occurred 30 min prior to the cocaine injection.

Statistical Analysis

Horizontal locomotor activity from the pre-exposure phase was analyzed using a 2 × 7 (Stimulant Condition × Pre-Exposure Day) repeated measures ANOVA; whereas, horizontal locomotor activity from test day was analyzed using a 2 × 4 × 9 (Stimulant Condition × Test Day Drug × 5-min time blocks) repeated measures ANOVA. Post hoc analysis of behavioral data was made using Tukey tests.

CHAPTER TWELVE

EXPERIMENT FOUR

The purpose of this experiment was to assess whether terguride is capable of producing behavioral sensitization.

Procedure

Pre-Exposure Phase (Days 1-7)

The pre-exposure phase started at and continued to PD 21. On seven consecutive days (i.e., PD 15-21), pups were taken to the experimental room and placed into individual chambers for a 5-min habituation period. At the end of habituation, all pups were injected with saline or terguride (0.4, 0.8, or 1.6 mg/kg). After the 60-min observation session, pups were returned to their home cage.

Test Day (Day 9)

After a 24 h abstinence period, sensitization was assessed on a single test day. On the test day (PD 23), pups were taken to the testing room and placed in a chamber for a 5-min habituation period. After habituation, pups were given a challenge injection of either saline or terguride (0.4 mg/kg). After the 60-

min testing period, pups were returned to their home cage.

Statistical Analysis

Horizontal locomotor activity during the pre-exposure phase was analyzed using a 4 × 7 (Drug Condition × Pre-Exposure Day) repeated measures ANOVA; whereas, horizontal locomotor activity from test day was analyzed using a 4 × 12 (Drug Condition × Test Day Drug × 5-min time blocks) repeated measures ANOVA. Post hoc analysis of behavioral data was made using Tukey tests.

CHAPTER THIRTEEN

RESULTS

Experiment One

Pre-Exposure Phase

Overall, rats showed a day-dependent increase in distance traveled (i.e., horizontal locomotor activity) across the pre-exposure phase [Pre-Exposure Day main effect, $F(6,54) = 27.36$, $p < .05$] (see Figure 3). This effect varied according to drug group, as rats receiving cocaine (filled symbols) exhibited greater horizontal locomotor activity than saline controls (open symbols) [Stimulant Condition main effect, $F(4,36) = 12.53$, $p < .05$]. Tukey tests revealed that only rats in the 0.0 mg/kg Terg/Coc groups had greater horizontal locomotor activity than saline controls on PD 16; whereas, on PD 17, rats in the 0.0 mg/kg Terg/Coc and 0.2 mg/kg Terg/Coc groups exhibited more locomotor activity than rats in the 0.0 mg/kg Terg/Sal group [Stimulant Condition × Pre-Exposure Day interaction, $F(24,216) = 4.43$, $p < .05$]. By PD 18, only rats in the 0.4 mg/kg Terg/Coc group did not exhibit more distance traveled than saline

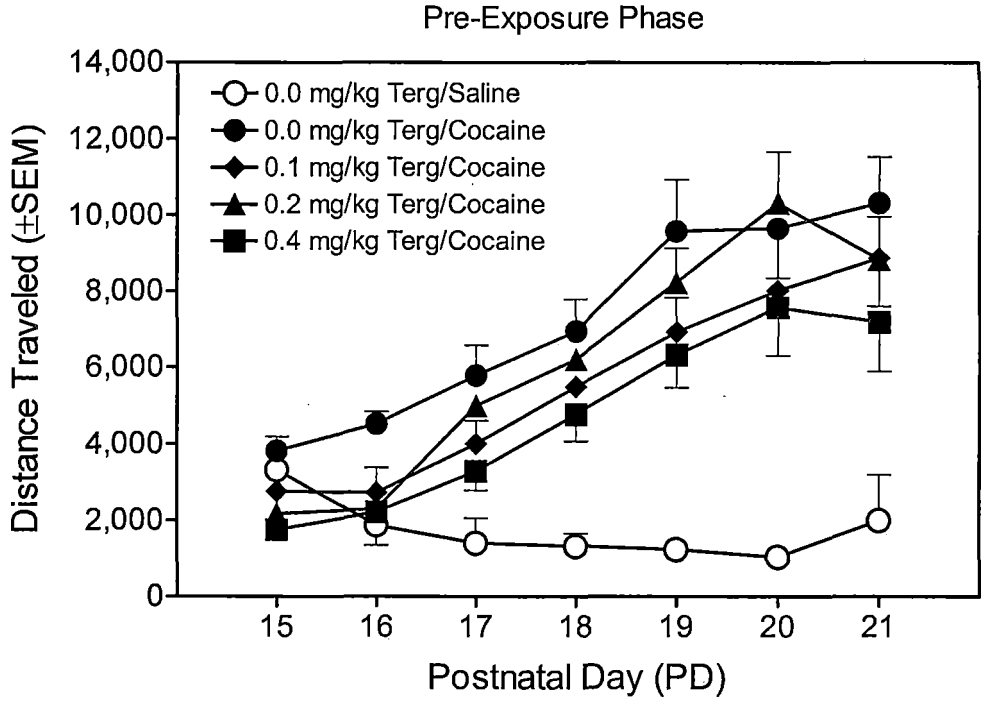

Figure 3. Mean (± SEM) distance traveled (i.e., locomotor activity) of rats (n = 8 per group) given daily injections of terguride (0.0, 0.1, 0.2, or 0.4 mg/kg, i.p.) followed, 35 min later, by an injection of saline (open circles) or 30 mg/kg cocaine (filled symbols). Behavioral testing lasted 30 min.

controls. On the final three days of the pre-exposure phase (i.e., on PD 19-21), all of the groups treated with cocaine had greater horizontal locomotor activity than saline controls.

A separate ANOVA was conducted to determine whether the various cocaine groups differed among themselves. This analysis showed that rats receiving both terguride and cocaine had significantly less horizontal locomotor activity than rats receiving cocaine alone [Stimulant Condition main effect, $F(3,27) = 3.48$, $p < .05$] (see Figure 4). Tukey tests revealed a significant decrease in cocaine-induced locomotor activity in all Terg/Coc Groups (0.1-0.4 mg/kg). The ability of terguride to reduce cocaine-induced locomotor activity did not vary according to pre-exposure day. Therefore, these results indicate that low doses of terguride partially attenuate the locomotor activating effects of cocaine.

Test Day

Overall, cocaine induced a sensitized locomotor response, since rats in the 0.0 mg/kg Terg/Coc group (filled circles) had greater horizontal locomotor

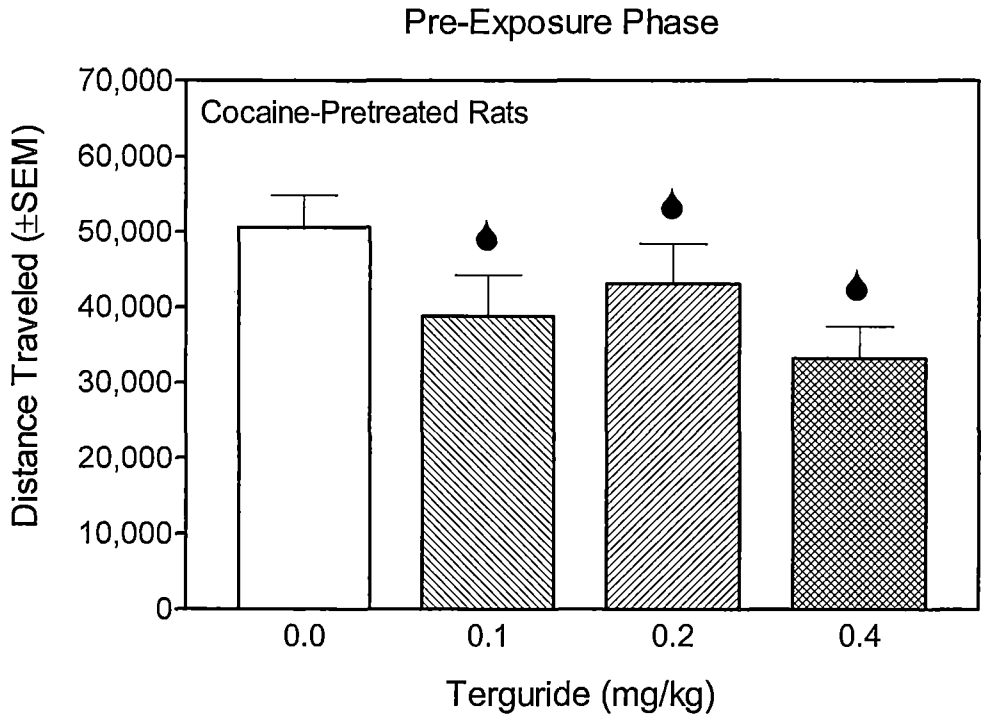

Figure 4. Mean (± SEM) distance traveled (i.e., locomotor activity) of rats (n = 8 per group) given daily injections of terguride (0.0, 0.1, 0.2, or 0.4 mg/kg, i.p.) followed, 35 min later, by an injection of 30 mg/kg cocaine (these are the same rats as described in Fig. 3). Data are collapsed across the pre-exposure phase. *Significantly different from rats receiving 0.0 mg/kg terguride.

activity than the rats in the 0.0 mg/kg Terg/Sal group (open circles) on time blocks 1, 2, and 5 [Stimulant Condition × Time interaction, $F(5,45) = 6.55$ $p < .05$] (see Figure 5). An ANOVA including all five treatment groups showed that horizontal locomotor activity varied across the testing session, with rats in the cocaine groups (filled symbols) exhibiting more test day locomotion than rats treated with saline during the pre-exposure phase (open circles) [Stimulant Condition × Time interaction, $F(20,180) = 2.45$, $p < .05$]. Importantly, however, terguride (0.1-0.4 mg/kg) did not reduce the horizontal locomotor activity of cocaine-pretreated rats (compare the filled symbols). Thus, there is no evidence that low doses of terguride (0.1-0.4 mg/kg) administered during the pre-exposure phase block the induction or eventual expression, of cocaine-induced locomotor sensitization.

Experiment Two

Pre-Exposure Phase

Overall, cocaine-treated rats had greater horizontal locomotor activity than saline-treated rats [Stimulant Condition main effect, $F(1,7) = 86.49$, $p <$

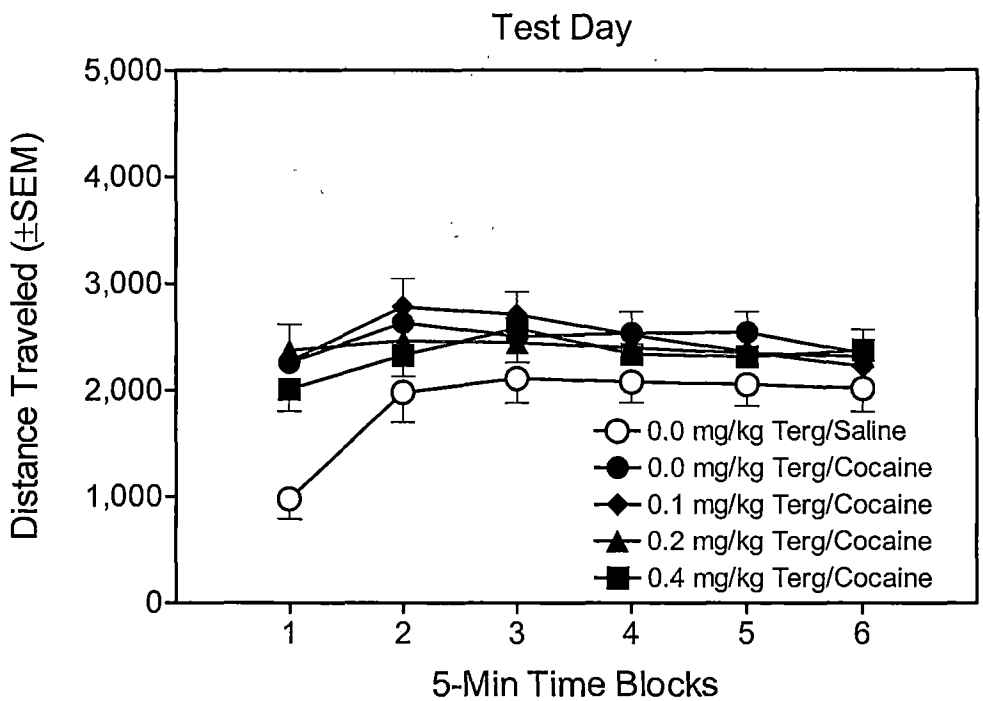

Figure 5. Mean (± SEM) distance traveled (i.e., locomotor activity) of rats (*n* = 8 per group) receiving a challenge injection of 15 mg/kg cocaine after one drug abstinence day (i.e., PD 23). During the pre-exposure phase, rats had received daily injections of terguride (0.0, 0.1, 0.2, or 0.4 mg/kg, i.p.) followed, 35 min later, by an injection of saline (open circles) or 30 mg/kg cocaine (these are the same rats as described in Figs. 3 & 4). Behavioral testing lasted 30 min.

.05] (see Figure 6). Horizontal locomotor activity of rats increased in a day- dependent manner over the pre-exposure phase [Pre-Exposure Day main effect, $F(6,42) = 14.78$, $p < .05$] (see Figure 6); however, this effect varied according to both pre-exposure drug and stimulant condition [Pre-Exposure Drug × Stimulant Condition × Pre-Exposure Day interaction, $F(18,126) = 3.40$, $p < .05$]. Horizontal locomotor activity of saline-treated rats was reduced by terguride (see upper graph, Figure 6), as Tukey tests showed that rats in the 0.0 mg/kg Terg/Sal group (open circles) exhibited more horizontal locomotor activity on PD 15 and PD 17 than rats in the 0.4-1.6 mg/kg Terg/Sal groups (other open symbols). On PD 18, rats in the 0.0 mg/kg Terg/Sal group had more horizontal locomotor activity than rats in the 0.8 mg/kg and 1.6 mg/kg Terg/Sal groups.

A different pattern of results was observed with cocaine-treated rats (see lower graph, Figure 6). Across the pre-exposure phase rats in the 0.0 mg/kg Terg/Coc group (filled circle) had more horizontal locomotor activity than all other Terg/Coc groups

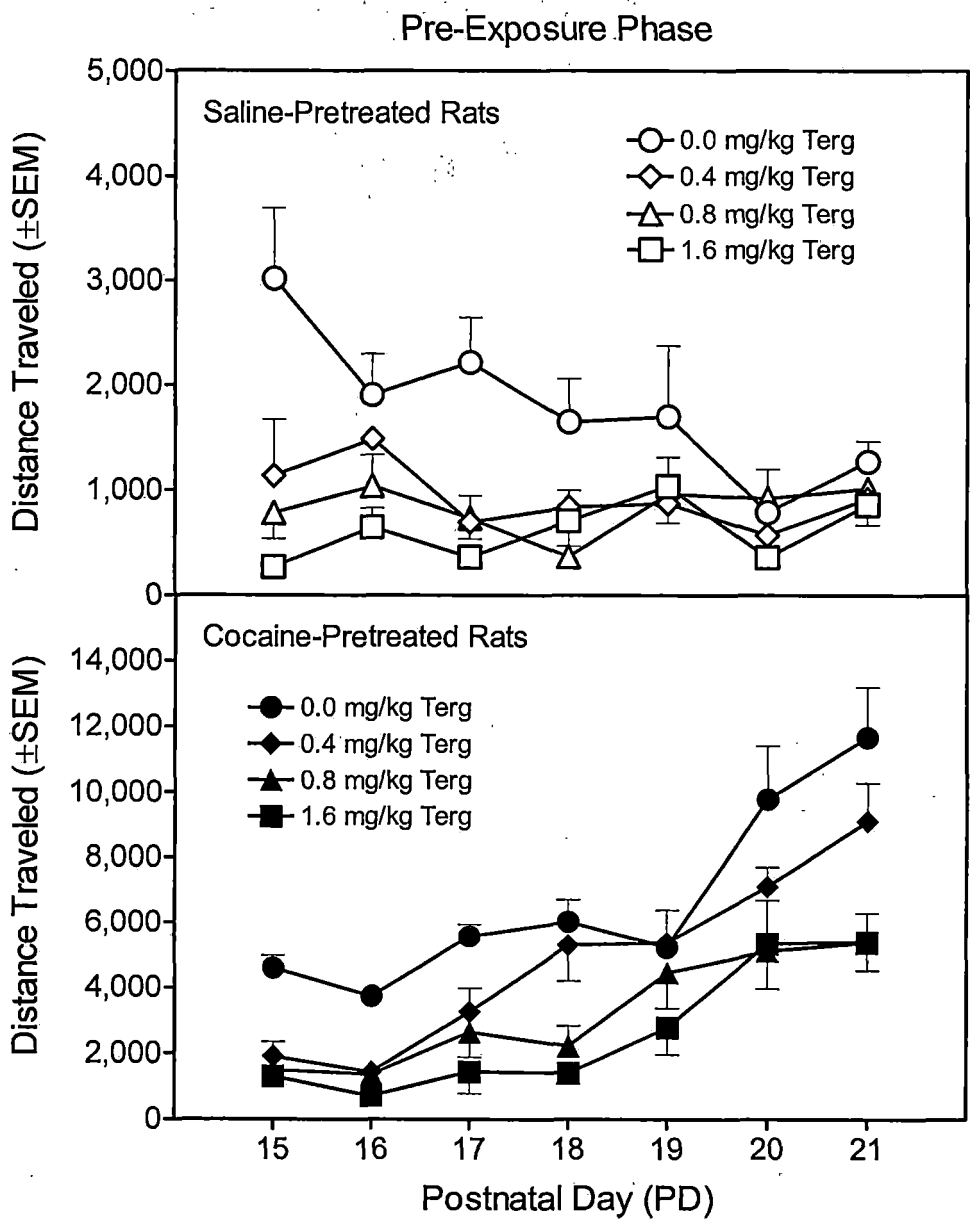

Figure 6. Mean (± SEM) distance traveled (i.e., locomotor activity) of rats (n = 8 per group) given daily injections of terguride (0.4, 0.8, or 1.6 mg/kg, i.p.) followed, 35 min later, by an injection of saline (open symbols) or 30 mg/kg cocaine (filled symbols). Behavioral testing lasted 30 min.

(other filled symbols). The only exception was on PD 19, when no group differences were apparent. Generally, rats pretreated with the various doses of terguride (0.4-1.6 mg/kg) behaved similarly, but on PD 18, rats in the 0.4 mg/kg Terg/Coc group had greater locomotor activity than rats in the 0.8 mg/kg and 1.6 mg/kg Terg/Coc groups.

Test Day

Overall, cocaine induced a sensitized locomotor response, as rats pre-exposed to cocaine had greater horizontal locomotor activity than saline pre-exposed rats on time blocks 1-5 [Stimulant Condition × Time interaction, $F(15,105) = 6.14$, $p < .05$] (see Figure 7). Administering terguride during the pre-exposure phase did not affect subsequent responding on the test day. Specifically, terguride did not reduce the cocaine-induced horizontal locomotor activity of either the saline pre-exposed rats (see upper graph, Figure 7), or the cocaine pre-exposed rats (see lower graph, Figure 7).

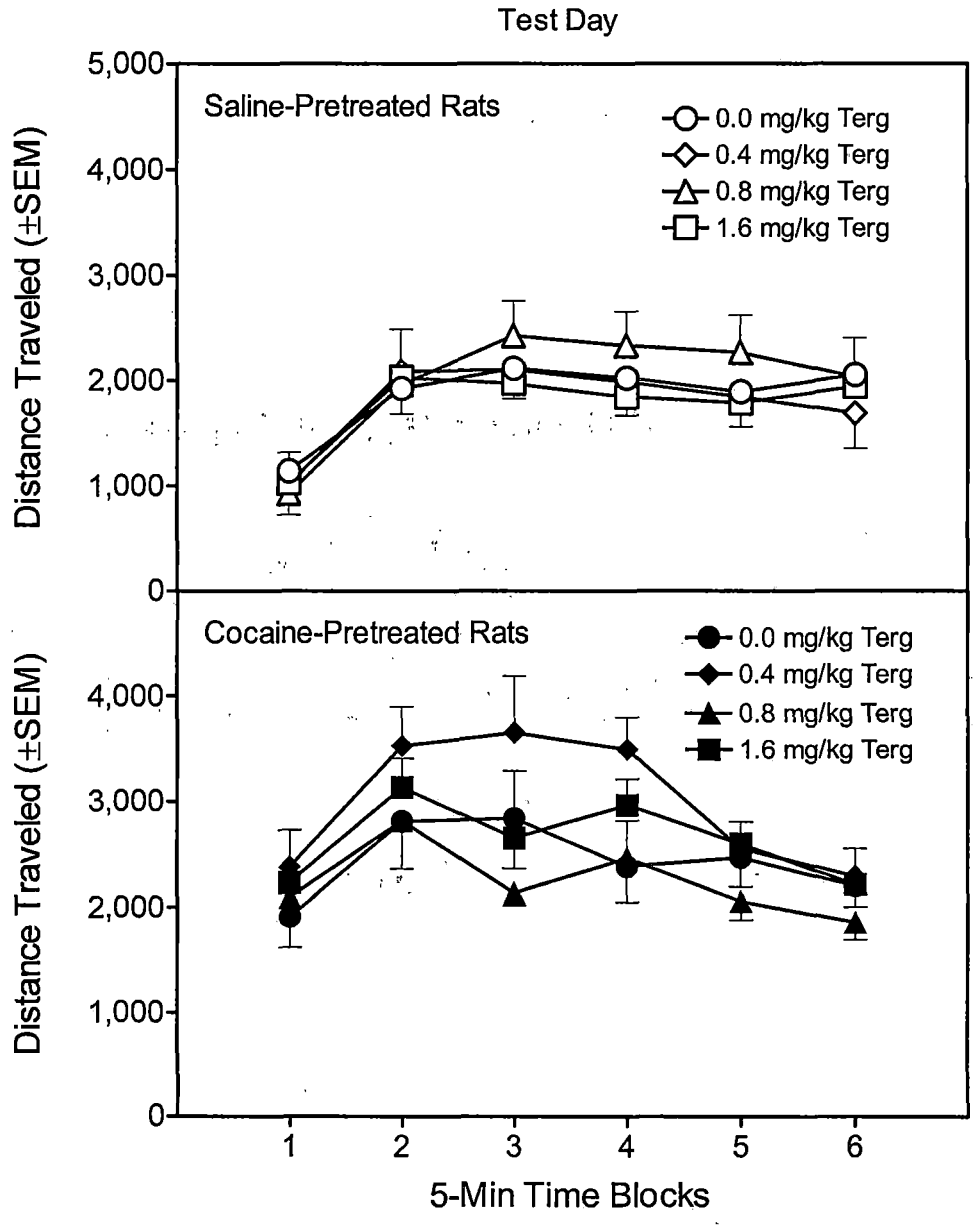

Figure 7. Mean (± SEM) distance traveled of rats (*n* = 8 per group) receiving a challenge injection of 15 mg/kg cocaine after one drug abstinence day (i.e., PD 23). During the pre-exposure phase, rats had received daily injections of terguride (0.0, 0.4, 0.8, or 1.6 mg/kg, i.p.) followed, 35 min later, by an injection of saline (open symbols) or 30 mg/kg cocaine (filled symbols (these are the same rats as described in Fig. 6). Behavioral testing lasted 30 min.

Experiment Three

Pre-Exposure Phase

Overall, rats treated with cocaine (filled circles) exhibited greater distance traveled (i.e., horizontal locomotor activity) than rats treated with saline (open circles) [Stimulant Condition main effect, $F(1,7) = 195.89$, $p < .05$] (see Figure 8). This effect varied according to pre-exposure day, as cocaine-treated rats exhibited a day-dependent increase in horizontal locomotor activity across the pre-exposure phase [Pre-Exposure Day main effect, $F(6,42) = 8.27$, $p < .05$; Stimulant Condition × Pre-Exposure Day interaction, $F(6,42) = 20.93$, $p < .05$] (see Figure 8).

Test Day

As expected, a separate ANOVA comparing the saline- and cocaine-pretreated rats showed that repeated treatment with cocaine produced behavioral sensitization (see Figure 9). An overall ANOVA comparing all groups showed that horizontal locomotor activity of the saline- and cocaine-pretreated rats differed [Stimulant Condition main effect, $F(1,7) =$

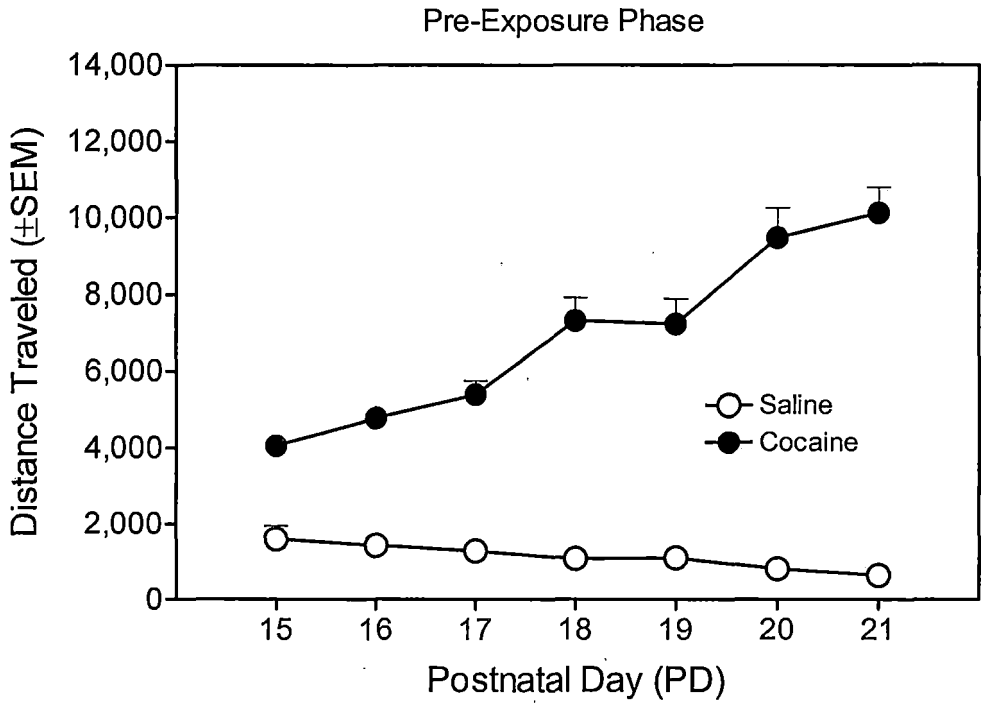

Figure 8. Mean (± SEM) distance traveled (i.e., locomotor activity) of rats (n = 32 per group) receiving daily injections of saline (open symbols) or 30 mg/kg cocaine (filled symbols). Behavioral testing lasted 30 min.

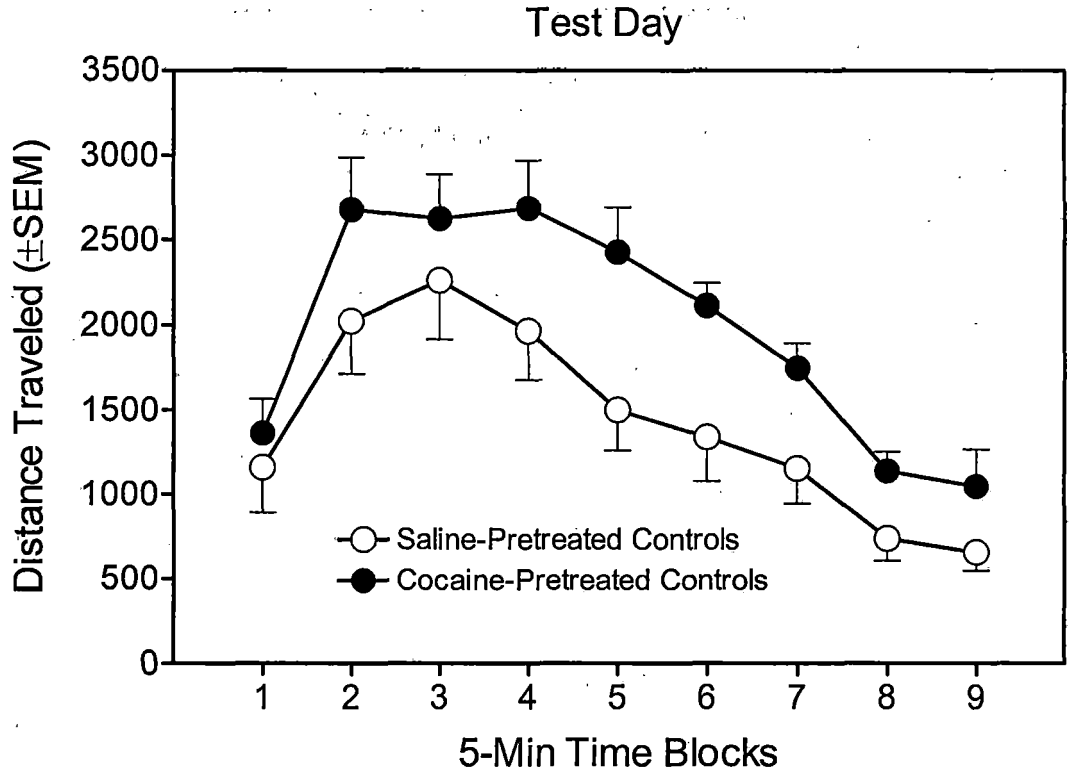

Figure 9. Mean (± SEM) distance traveled of rats (n = 8 per group) receiving a challenge injection of 15 mg/kg cocaine on the test day. Rats had received a test day injection of 0.0 mg/kg terguride 35 min prior to cocaine treatment. During the pre-exposure phase, rats had received daily injections of saline (open circles) or 30 mg/kg cocaine (filled circles). Behavioral testing lasted 45 min.

17.80; Stimulant Condition × Time interaction, $F(8,56) = 2.64$, $p < .05$] (see Figure 10). Among the saline-pretreated groups (see upper graph, Figure 10), rats receiving both cocaine and 0.0 mg/kg terguride (open circles) had greater horizontal locomotor activity than those receiving cocaine and 0.2-0.8 mg/kg terguride (other open symbols) [Test Day Drug main effect, $F(3,21) = 5.03$, $p < .05$]. The differences between the 0.0 mg/kg terguride group and the 0.2-0.8 mg/kg groups reached statistical significance on time blocks 1-3 [Test Day Drug × Time interaction, $F(24,168) = 5.96$, $p < .05$]. Thus, terguride significantly reduced the cocaine-induced locomotor activity of rats that had been previously treated with saline during the pre-exposure phase.

A similar pattern of results was observed in the cocaine-pretreated rats (see lower graph, Figure 10). On time blocks 2 and 3, cocaine-treated rats in the 0.0 mg/kg Terg/Coc group (filled circles) exhibited more locomotor activity than rats the 0.4 mg/kg and 0.8 mg/kg Terg/Coc groups (filled triangle and filled square, respectively). During time block 4, the 0.0

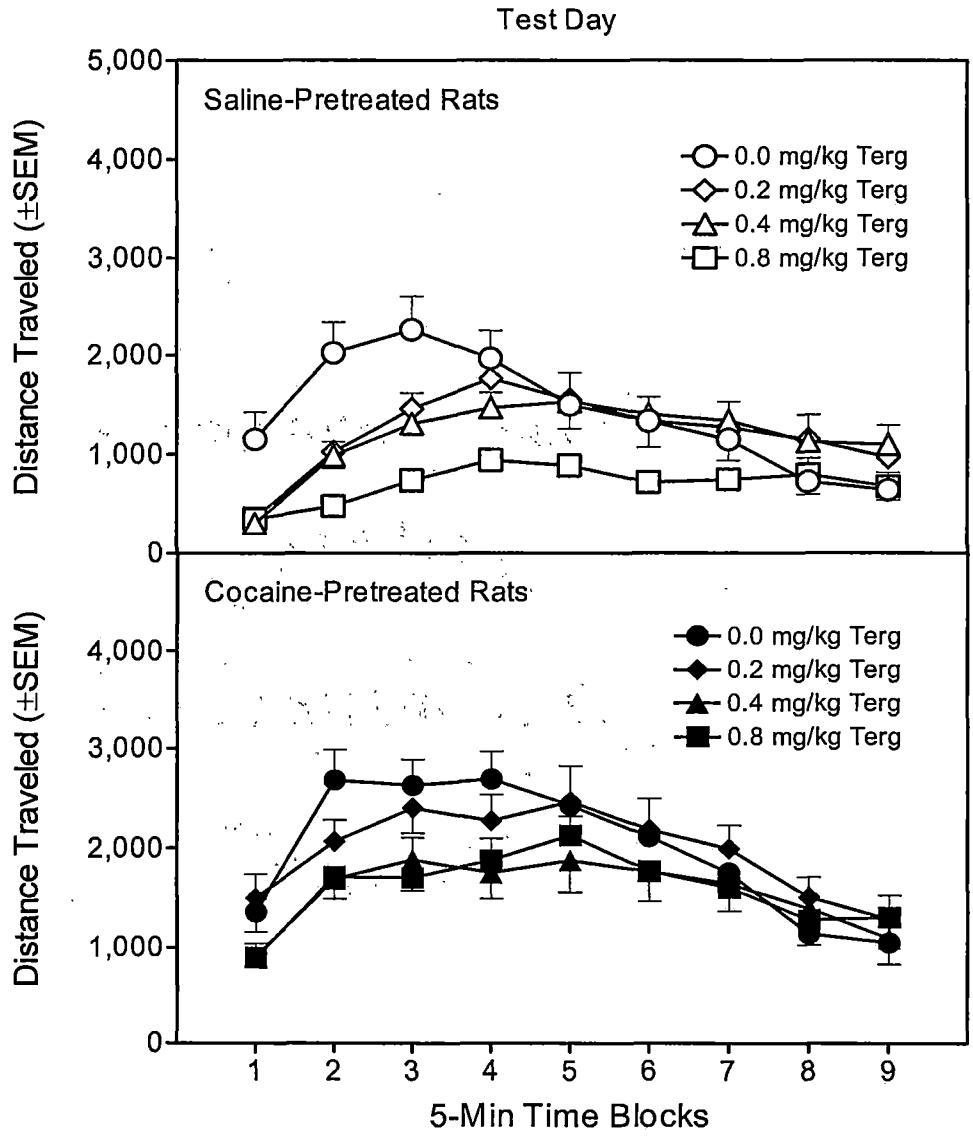

Figure 10. Mean (± SEM) distance traveled of rats (*n* = 8 per group) receiving a challenge injection of 15 mg/kg cocaine on the test day. Rats had received a test day injection of terguride (0.0, 0.2, 0.4, or 0.8 mg/kg, i.p.) 35 min prior to cocaine treatment. During the pre-exposure phase, rats had received daily injections of saline (open symbols) or 30 mg/kg cocaine (filled symbols) (these are the same rats as described in Fig. 8). Behavioral testing lasted 45 min.

mg/kg Terg/Coc group (filled circle) had significantly more horizontal locomotor activity than the 0.4 mg/kg Terg/Coc group (filled triangle).

A separate ANOVA was conducted to determine whether the cocaine-pretreated control group (i.e., the cocaine group receiving 0.0 mg/kg terguride) showed a sensitized locomotor response. Cocaine-pretreated rats given cocaine and 0.0 mg/kg terguride on the test day (filled circles, lower graph, Figure 10) exhibited significantly more locomotor activity than saline-pretreated rats given cocaine and 0.0 mg/kg terguride (open circles, upper graph, Figure 10) [Stimulant Condition main effect, $F(1,7) = 6.90$, $p < .05$]. Thus, cocaine did produce locomotor sensitization in the control subjects.

Experiment Four

Pre-Exposure Phase

Overall, rats treated with terguride had less locomotor activity during the pre-exposure phase than rats treated with saline [Drug Condition main effect, $F(6,42) = 3.21$, $p < .05$]. This effect varied according to test day, as the saline group (filled

circle) had significantly more horizontal locomotor activity than the terguride groups (other filled symbols) on PD 15 and PD 16 [Drug Condition x Pre-Exposure Day interaction, $F(18,126) = 2.10$, $p < .05$] (see Figure 11). No group differences were observed on PD 17-21.

Test Day

Overall, locomotor activity of the cocaine-treated rats declined rapidly over the first four time blocks, at which time it stabilized [Time main effect, $F(11,77) = 36.50$, $p < .05$] (see Figure 12). Terguride pre-exposure did not affect the test day locomotor activity of the rats. Thus, terguride alone is not capable of inducing sensitized responding in young rats.

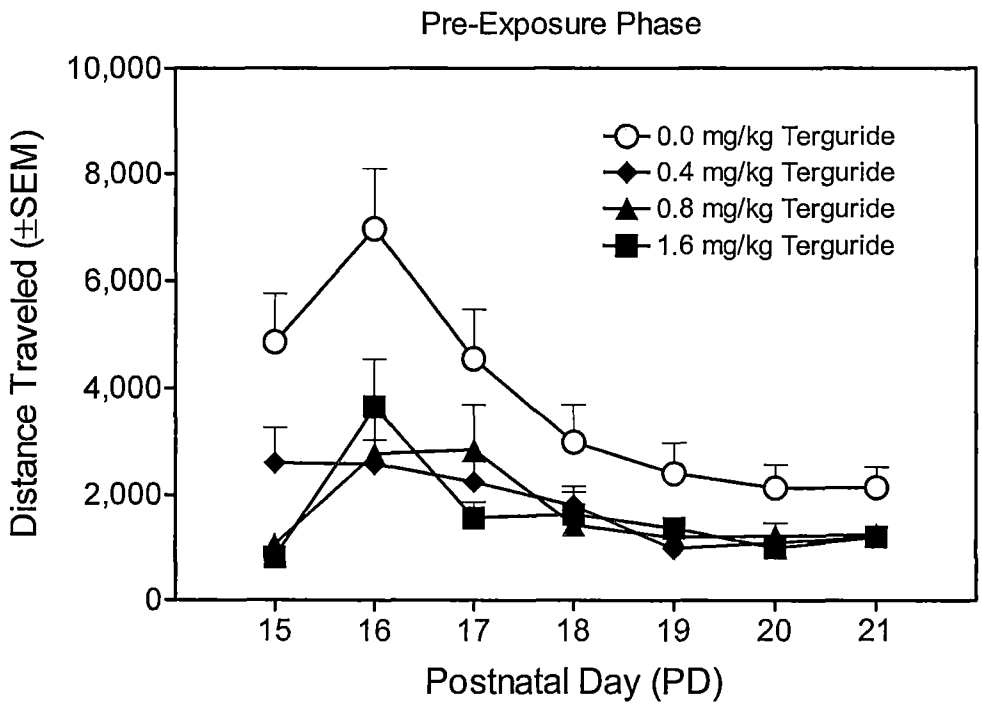

Figure 11. Mean (± SEM) distance traveled (i.e., locomotor activity) of rats (n = 10 per group) receiving daily injections of terguride (0.4, 0.8, or 1.6 mg/kg, i.p.). Behavioral testing lasted 60 min.

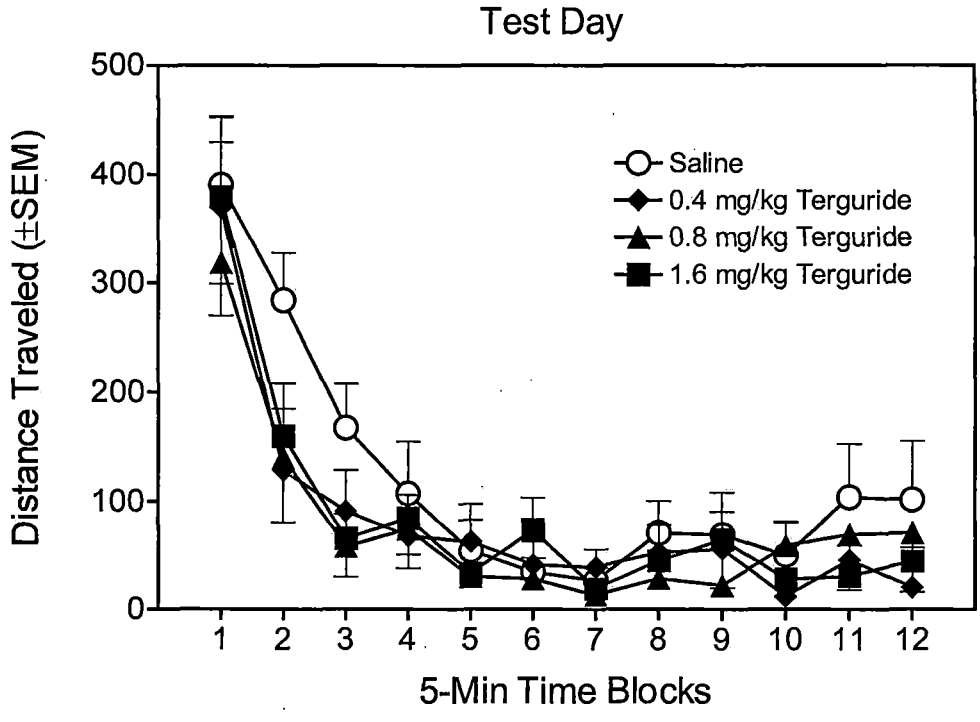

Figure 12. Mean (± SEM) distance traveled (i.e., locomotor activity) of rats (n = 10 per group) receiving a challenge injection of saline (open symbols) or 0.4 mg/kg terguride (filled symbols) after one drug abstinence day (i.e., PD 23). During the pre-exposure phase, rats had received daily injections of terguride (0.0, 0.4, 0.8, or 1.6 mg/kg, i.p.) (these are the same rats as described in Fig. 11). Behavioral testing lasted 60 min.

CHAPTER FOURTEEN

DISCUSSION

The purpose of the present study was to investigate whether a partial D_2-like dopamine agonist (i.e., terguride) would block the induction or expression of cocaine-induced behavioral sensitization in preweanling rats. The ability of terguride to induce behavioral sensitization was also examined, as partial D_2-like agonists have agonistic actions in cases of low dopaminergic tone (Clark, Furmidge et al., 1991). It was originally hypothesized that terguride would be effective in blocking both the induction and expression of cocaine-induced behavioral sensitization. It was also hypothesized that terguride alone would be unable to induce behavioral sensitization.

Results showed that a partial D_2-like agonist was unable to block the induction or ultimate expression of cocaine-induced locomotor sensitization in preweanling rats. Terguride partially attenuated cocaine-induced locomotion during the pre-exposure phase, however no dose completely eliminated locomotor

activity. The induction of behavioral sensitization was not blocked by terguride, as pups were able to express a sensitized locomotor response when cocaine was administered on the test day. Due to the large dose range employed in this study (0.1-1.6 mg/kg), it is unlikely that an insufficient dose of terguride was used. Thus, these results indicate that a partial D_2-like agonist is unable to block the sensitization component of the addiction process, even though it does decrease the acute locomotor activating effects of cocaine.

When terguride was administered on test day (Experiment 3), pups showed a dose-dependent decrease in cocaine-induced locomotor activity. This was true of both saline- and cocaine-pretreated rats. Thus, it is possible that terguride blocked the expression of behavioral sensitization to cocaine. Alternatively, it is possible that terguride caused a general reduction in locomotor activity that was not related to sensitization.

The ability of terguride to induce behavioral sensitization was examined in Experiment 4. Results showed that terguride (0.4-1.6 mg/kg) did not cause a

day-dependent increase in locomotor activity, nor did a test day challenge injection of terguride (0.4 mg/kg) cause a sensitized locomotor response. Thus, repeated administration of terguride did not induce behavioral sensitization in preweanling rats. Because behavioral sensitization is a component of the addiction processes (Di Chiara, 1995; Robinson, & Berridge, 1993), these results suggest that terguride lacks abuse potential. This conclusion is consistent with studies showing that terguride does not maintain self-administration in rats or rhesus monkeys (Pulvirenti et al., 1998; Ranaldi et al., 2001).

In conclusion, partial D_2-like receptor agonists have both agonistic and antagonistic actions on G-protein-coupled dopamine receptor sites (Hoyer & Boddeke, 1993). In situations where dopaminergic functioning is depressed, partial D_2-like agonists stimulate the dopamine system; whereas, in situations where dopaminergic functioning is enhanced, partial D_2-like agonists depress the dopamine system (Clark, Furmidge et al., 1991). Because of these pharmacological characteristics, it was not surprising that terguride partially attenuated the cocaine-

induced locomotor activity of young rats. However, it was surprising that terguride was unable to block the induction of behavioral sensitization, especially since partial D_2-like agonists have previously been shown to reduce the rewarding effects of cocaine and other psychostimulants (see Bono et al., 1996; Izzo et al., 2001; Pulvirenti et al., 1998). At present, it remains unclear why neither the induction nor expression of behavioral sensitization was blocked by terguride administration, or why the cellular changes believed to underlie behavioral sensitization were apparently unaffected by this partial D_2-like agonist. There are several possibilities that may account for these findings, including: the relative importance of D_2-like receptor stimulation for behavioral sensitization, ontogenic differences in dopaminergic substrates, and neuroplasticity.

Importance of D_2-like Dopamine Receptor Stimulation for Cocaine-Induced Behavioral Sensitization

A possible reason for terguride's lack of effect is that D_2-like dopamine receptor stimulation may not

be necessary for cocaine-induced behavioral sensitization. If true, neither a partial D_2-like agonist, nor a full D_2-like receptor antagonist, should block the induction of cocaine-induced behavioral sensitization. Although this is the first study to examine the effects of a partial D_2-like agonist on cocaine sensitization, many researchers have administered D_2-like receptor antagonist drugs prior to pre-exposure or challenge injections of cocaine. Surprisingly, these studies provide conflicting results, as selective D_2-like receptor antagonists have alternately been reported to block the induction of cocaine-induced sensitization (Mattingly, Rowlett, Ellison, & Rase, 1996; Tella, 1994; Weiss et al., 1989), or leave sensitization unaffected (Kuribara & Uchihashi, 1993; Mattingly et al., 1994; White et al., 1998). If, as the latter studies suggest, D_2-like receptor stimulation is unimportant for behavioral sensitization, then it is not surprising that terguride did not block the induction of cocaine-induced sensitization. If, on the other hand, D_2-like receptor stimulation is necessary for cocaine-induced behavioral sensitization, then terguride's inability

to fully attenuate the locomotor activating effects of cocaine may have permitted the induction process to occur. Unfortunately, the present study is unable to distinguish between these possibilities.

Ontogenic Differences

Another possible reason why terguride did not block the induction of cocaine sensitization involves the age of animals used. More specifically, there may be ontological differences in how rats respond to partial D_2-like agonists such as terguride. Across the postnatal period dopamine systems undergo substantial maturational changes (Gelbard et al., 1989; Jung & Bennett, 1996). For example, D_1-like (Gelbard et al., 1989; Giorgi et al., 1987) and D_2-like (Murrin & Zeng, 1986; Schambra et al., 1994) binding sites increase in number across the postnatal period. During the same developmental period there is an increase in dopamine levels (Coyle & Campochiaro, 1976; Giorgi et al., 1987), as well as in increase in the number of dopamine transporters (Bonnet & Costentin, 1989; Rao, Molinoff, & Joyce, 1991). In terms of function, D_1-like receptors are coupled to adenylyl cyclase by PD 1

(Broaddus & Bennett, 1990; De Vries, Mulder, & Schoffelmeer, 1992) and G-proteins by PD 5 (Jung & Bennett, 1996); whereas, D_2-like receptors are coupled to adenylyl cyclase by PD 7 (Broaddus & Bennett, 1990; De Vries et al., 1992) and G-proteins by PD 1 (Sales, Martes, Bouthernet, & Schwartz, 1991). Notably, an adult-like interaction between dopamine D_1- and D_2-like receptors is evident by PD 11 (McDougall, Arnold, & Nonneman, 1990).

In terms of psychopharmacological actions, dopamine-mediated behaviors are present in early ontogeny. For example, administering a full dopamine receptor agonist (e.g., apomorphine and quinpirole) as early as PD 4 increases the locomotor activity of rat pups (Camp & Rudy, 1987; Moody & Spear, 1992). Further, administering a direct D_2-like dopamine receptor antagonist (e.g., sulpiride), reduces the locomotor activity of young (McDougall et al., 1990), as well as adult rats (Neiswander, O'Dell, & Redmond, 1995). Dopamine systems mediating reward also become functionally mature early in ontogeny, since cocaine and amphetamine potentiate intracranial self-administration by PD 3 (Barr & Lithgow, 1986), and

cocaine supports conditioned place preferences by PD 10 (Pruitt, Bolanos, & McDougall, 1995). Therefore, available evidence suggests that while dopamine systems are maturing across the postnatal period, they are capable of mediating behavior in an adult-like manner. For this reason, it seems that immaturity of the dopamine system is an unlikely explanation for why terguride did not block the induction of cocaine-induced behavioral sensitization.

Neuroplasticity

Another explanation for terguride's lack of effect involves the neuroplasticity characteristic of younger animals. Developmental neuroplasticity allows for reorganization of neurons in a manner that is not observed in adult animals, and may serve to make brain less vulnerable to endogenous (e.g., developmental defect) or exogenous (e.g., drug-induced) damage (Weiss et al., 1989). Receptor formation and replacement occurs at a higher rate in the striatum of younger animals, and synaptic formations are more easily corrupted or changed than in the adult (Fassano & Brambilla, 2002).

Empirical evidence has shown that neuroplasticity is evident across ontogeny in both non-human animals and humans. For example, young kittens that are monocularly or binocularly deprived of vision show evidence of robust plasticity in brain areas mediating vision (Hubel & Wiesel, 1967, 1970). After monocular deprivation, there is an increase in cortical cells involving the sighted eye, along with increased lateral geniculate nucleus (LGN) terminals in striatal cells normally utilized by neurons from the non-sighted eye (Hubel & Wiesel, 1967, 1970). This finding provides evidence that environmental influences induce neuroplasticity during early ontogeny. Environmental deprivation can also result in a neuroplastic response (Greenough & Chang, 1989). Rats raised in an isolated environment show 20-25% fewer synaptic connections than rats raised in an enriched environment (Oppenheim, 1985). In humans, brain damaged children have been shown to recover from brain damage that would induce aphasia in adults (Alajouanine & L'Hermittee, 1965). This type of recovery of function occurs most robustly before 5 years of age, and seldom occurs after 8 years of age

(Kolb & Whishaw, 1989). This time frame of enhanced neuroplasticity (0-5 years in humans and 0-30 days in rats) is coincident with the time that brain undergoes substantial neuronal maturation, refinement, and development (Fassano & Brambilla, 2002).

Based on the general evidence cited above, it is possible that there are neuroplastic changes in the neural circuitry of young rats that permit the induction of behavioral sensitization despite the administration of a partial D_2-like agonist drug. More specifically, terguride may be unable to block the induction of behavioral sensitization because other neural circuits are capable of compensating for the D_2-like receptor blockade. Consistent with the explanation, mice genetically engineered to lack the D_1 receptor (i.e., the receptor is missing since initial fertilization) show amphetamine-induced behavioral sensitization (Crawford et al., 1997; Karper, De La Rosa, Newman, Krall, Nazarian, McDougall, & Crawford, 2002). This indicates that neural processes systems underlying behavioral sensitization are capable of showing a robust compensatory response.

Lastly, one of the most consistent findings in this study was that terguride attenuated the cocaine-induced horizontal locomotor activity of rat pups. Wise and Bozarth (1987) have posited that the addictive potential of a drug is related to its ability to induce locomotion. If true, attenuation of psychostimulant-induced locomotor activity may indicate that the rewarding effect of the psychostimulant is diminished. Thus, terguride's ability to reduce cocaine-induced locomotor activity may indicate that this partial D_2-like agonist is capable of disrupting other aspects of the addiction process. It is possible, therefore, that terguride may be efficacious for treating psychostimulant addiction by impacting process (i.e., not involving behavioral sensitization) that contributes to reward or reinforcement.

Summary

Terguride did not block the induction of behavioral sensitization in young rats. These findings are not in accordance with past self-administration studies showing that terguride is

capable of blocking the reward process. Possible reasons for terguride's lack of effect include: the relative importance of D_2-like receptor stimulation for behavioral sensitization, ontogenic differences in dopaminergic substrates, and neuroplasticity. The present results bring into question whether terguride will prove useful as a pharmacotherapy for psychostimulant addiction. On the one hand, terguride appears promising because it blocks the self-administration of psychostimulants, however it does not block the induction of cocaine-induced behavioral sensitization in young animals. Importantly, the drug self-administration and behavioral sensitization paradigms model different aspects of the addiction process, so it is likely that a pharmacotherapy involving terguride may still be of benefit for the treatment of psychostimulant addiction. Finally, It is possible that terguride may be able to modulate ancillary processes of addiction that contribute to reward and reinforcement.

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