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ACTIONS OF A PARTIAL D2-LIKE AGONIST DURING
LOW OR HIGH DOPAMINERGIC TONE:
A NEUROCHEMICAL STUDY USING PREWEANLING RATS

A Thesis
Presented to the
Faculty of
California State University,
San Bernardino

In Partial Fulfillment
of the Requirements for the Degree
Master of Arts
in
Psychology:
General Experimental

by
Shelly Taeko Yoshida


December 2005


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12/2/2005

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Abstract

The neurochemical effects of partial D2-like agonist (i.e., terguride) to alter striatal DOPA accumulation under high and low dopaminergic tone was examined in preweanling rats. To this end, they were injected with reserpine or GBL to create a state of low dopaminergic tone and saline was used to create a state of high dopaminergic tone.

In Experiment 1, preweanling rats were treated either repeatedly or acutely with reserpine or saline. The rats in the repeated condition received daily reserpine injections from PD 16 - PD 20, and rats in the acute condition only received reserpine treatment on PD 20. On PD 21, all rats were injected with the full D2-like antagonist haloperidol, the partial D2-like agonist terguride, the full D2-like agonist quinpirole, or saline. They were then injected with NSD 1015 and striatal DOPA accumulation was measured. As expected, the results showed that both terguride and quinpirole reduced striatal DOPA accumulation during a state of low dopaminergic tone. During a state of high dopaminergic tone, terguride had

similar effects as haloperidol, increasing in DOPA accumulation.

In Experiments 2 and 3, terguride's ability to modulate dopamine synthesis under states of low or high dopaminergic tone was assessed using impulse flow inhibitor γ -butyrolactone (GBL) or saline, respectively. Preweanling rats were injected with haloperidol, quinpirole, terguride, or saline on PD 21. After the drug injections, they were injected with GBL followed by NSD 1015. The results showed that terguride, like quinpirole, partially inhibited the GBL-induced increase in striatal DOPA accumulation. On the other hand, terguride had a haloperidol-like effect under a state of high dopaminergic tone. When considered together, the results from all three experiments indicate that terguride have agonist-like (quinpirole-like) effects under a low dopaminergic tone and antagonist-like (haloperidol-like) effects under a high dopaminergic tone during preweanling period.

ACKNOWLEDGEMENTS

I would first like to thank all of the members on my committee: Dr. Sanders McDougall, Dr. Cynthia Crawford, and Dr. Allen Butt. Their support, encouragement, and important suggestions and comments enhanced the quality of my thesis. They were very helpful and I believe I have gained tremendous experiences through writing this thesis. I thank each one of you for your time and effort. I am very fortunate to have such supportive members on my thesis committee.

Sandy, I am so thankful and happy that I had a great mentor like you. I can truly say that I would not have been where I am now without your support, patience, and above all things, belief in me. Not only have you taught me what it takes to be a scientist, but you also inspired me to pursue my career in the field of neuroscience. I am eternally grateful for everything you have done for me.

Cynthia, you have played such an important role in my life. I have always admired your work as a scientist. I cannot express how much I appreciate your guidance and introduction to the world of science. I believe you are

an outstanding teacher, mentor, and mother. I thank you from the bottom of my heart.

I would also like to thank Shelley Campbell and Nancy Stuebner for dedicating your time and effort in helping me finish this project. I could not have done this without your hard work and dedication. Although it was only for a short period of time, I greatly enjoyed working with both of you. I wish you good fortune in your future endeavors.

I want to thank Art Zavala and Dr. Bardo for your generous supply of NSD 1015. I could not have finished my experiments without your charitable donation. Thank you for your caring and kindness.

Special thanks go to Art, Jim, Carmela, Michelle, Fiona, Jodi, Sergio, and all the members in the lab. I had a great time working with all of you. Thank you and I wish you best of luck in your future.

Lastly, I would like to thank my family and friends for supporting and encouraging me in pursuing my goal to become a neuroscientist. I am very lucky and grateful to have all of you in my life. Thank you to each one of you. I could not have done this without your understanding, support, and love.

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CHAPTER ONE

OVERVIEW

General Overview

In the United States, many people are under going rehabilitation for psychostimulant (e.g., cocaine, amphetamine, and methamphetamine) addiction (National Institute on Drug Abuse, 1999). Most people seek psychostimulant drugs for their reinforcing effects. When these types of drugs are taken over a long period of time, drug abusers will go through a withdrawal phase when the drugs are not present. Common symptoms of psychostimulant withdrawal are psychomotor retardation, depression, fatigue, and decreased motivation for natural reward (e.g., food seeking behavior) (Orsini, Koob, & Pulvirenti, 2001). In animal models, withdrawal symptoms are usually measured by observing psychomotor retardation after long exposure to psychostimulant drugs (Pulvirenti & Koob, 1994).

According to Pulvirenti and Koob (1994), drug withdrawal is due to a reduction in dopamine neurotransmission, which is caused by increased sensitivity of D2-like autoreceptors. Recently, partial

D2-like agonists (e.g., aripiprazole, preclamol, terguride, SDZ 208-911, and SDZ 208-912) have received much attention as potential pharmacotherapies because of their unique property of "normalizing" dopamine neurotransmission (Pulvirenti, Balducci, Piercy, & Koob, 1998).

Specifically, partial D2-like agonists act as either agonists or antagonists depending on intrinsic dopaminergic activity (for a review, see Clark, Hjorth, & Carlsson, 1985). Thus, partial D2-like agonists act as antagonists when the dopamine system is stimulated, but act as agonists when the dopamine system is depressed. For these reasons, partial D2-like agonists should block the rewarding effects of psychostimulants while at the same time maintaining normal dopamine tone. The latter effect could potentially alleviate drug withdrawal and craving.

The antagonistic effects of partial D2-like agonists have been amply shown in animal studies. For example, cocaine or amphetamine self-administration is significantly reduced when partial D2-like agonists are given to rodents and monkeys (Callahan & Cunningham, 1993; Pulvirenti, Smith, & Koob, 1994). It has also been

demonstrated that partial D2-like agonists reduce amphetamine-induced stereotyped behavior and locomotor activity (Clark, Furmidge, Petry, Tong, Ericsson, & Johnson, 1991). Thus, partial D2-like agonists behave as dopamine antagonists when co-administered with indirect dopamine agonists such as amphetamine and cocaine (Pulvirenti & Koob, 1994).

Interestingly, partial D2-like agonists have agonistic effects when dopamine neurotransmission is depressed. For example, Orsini et al. (2001) demonstrated that terguride was able to increase saccharin-reinforced responding in dopamine-depleted rats. Normally, rats going through amphetamine withdrawal (i.e., a state of low dopaminergic tone) exhibit suppressed responding for a natural reward (e.g., saccharin). However, terguride increases responding for saccharin in a state of low dopaminergic tone, suggesting that this partial D2-like agonist was exhibiting agonistic properties. Therefore, while the majority of behavioral studies have shown that partial D2-like agonists exhibit antagonistic properties (Callahan & Cunningham, 1993; Clark et al., 1991; Pulvirenti & Koob, 1994; Pulvirenti et al., 1994),

accumulating evidence suggests that partial D2-like agonists exhibit agonistic effects on behavior in a state of low dopaminergic tone (Orsini et al., 2001).

In summary, partial D2-like agonists may serve as novel pharmacotherapies for psychostimulant addiction. To date, most studies examining partial D2-like agonists have used adult animals, while relatively few studies have examined the effects of partial D2-like agonists during early ontogeny. This thesis is designed to further investigate the properties of partial D2-like agonists in the developing brain.

CHAPTER TWO

DOPAMINE RECEPTORS

Dichotomy Based on Receptor Subtypes

There are five different types of dopamine receptors: D₁, D₂, D₃, D₄ and D₅. Due to functional and pharmacological differences, these receptor subtypes are divided into two families: D1-like and D2-like receptors. D1-like receptors consist of D₁ and D₅ receptors, while D2-like receptors include D₂, D₃, and D₄ receptors (Seeman & Van Tol, 1994; Sokoloff, Giros, Martres, Bouthenet, & Schwartz, 1990; Sunahara, Seeman, Van Tol, & Niznik, 1993).

D1-like receptors stimulate adenylyl cyclase activity (Dearry, Gingrich, Falardeau, Fremeau, Bates, & Caron, 1990; Monsma, Mahan, McVittie, Gerfen, & Sibley, 1990), while D2-like receptors inhibit adenylyl cyclase activity (Chio, Drong, Riley, Gill, Slightom, & Huff, 1994; Robinson & Caron, 1996). The mechanisms responsible for these effects are known, because stimulation of D1-like receptors activates a G_s-protein and increases adenylyl cyclase activity; whereas, stimulation of D2-like receptors activates a G_i-protein and inhibits adenylyl

cyclase activity (Cooper, Bloom, & Roth, 2003).

Alterations of adenylyl cyclase activity modulate cyclic adenosine monophosphate (cAMP) formation and protein kinase A activity (Cooper et al., 2003). Another difference between D1-like and D2-like receptors is the presence of introns. D1-like receptors do not have introns in their coding sequence, whereas D2-like receptors are interrupted by introns (Civelli, Bunzow, & Grandy, 1993; Gingrich & Caron, 1993; O'Dowd, 1993).

D1-Like Receptors

As mentioned above, D1-like receptors consist of the D₁ and D₅ subtypes. The D₁ receptor subtype is the most widespread dopamine receptor (Dearry et al., 1990), because it is found throughout various brain regions, including the striatum, nucleus accumbens, olfactory tubercles, hypothalamus, thalamus, hippocampus, and amygdala (Fremeau, Duncan, Fornaretto, Dearry, Gingrich, Breese, & Caron, 1991; Weiner, Levey, Sunahara, Niznik, O'Dowd & Brann, 1991). The D₁ receptor has been implicated in unlearned behaviors (Arnt, 1987; Clark & White, 1987), psychostimulant reward (Di Chiara, 1995), cognition (Williams & Goldman-Rakic, 1995), and incentive responding

under food deprivation (Di Chiara, Tanda, Cadoni, Acquas, Bassareo, & Carboni, 1998; Miller, Wickens, & Beninger, 1990).

The D₅ receptor subtype has a function that is very similar to the D₁ receptor. For example, the D₅ receptor plays an important role in reward processes and incentive motivation (for a review, see Emilien, Maloteaux, Geurts, Hoogenberg, & Cragg, 1999). D₅ receptors are predominately located in forebrain regions. More specifically, D₅ receptors are found in cerebral cortex, lateral and medial thalamus, striatum, substantia nigra, medial thalamus and hippocampus (Chio, Lajiness, & Huff, 1994; Huntley, Morrison, Prikhozhan, & Sealfon, 1992; Rappaport, Sealfon, Prikhozhan, Huntley, & Morrison, 1993).

D2-Like Receptors

D2-like receptors mediate motor movement (Arnt, 1987), reward mechanisms (Emilien et al., 1999) and they have also been implicated in schizophrenia (Arinami, Gao, Hamaguchi, & Toru, 1997) and substance abuse (Blum, Noble, Sheridan, Montgomery, Ritchie, Jagadeeswaran, Nogami, Briggs, & Cohn, 1990). For example, D2-receptor deficient mice show reduced locomotion, rearing, coordinated

The D₃ and D₄ receptor subtypes are involved in motor movement and neuropsychiatric disorders in both humans and animals (Accili, Fishburn, Drago, Steiner, Lachowicz, Park, Gauda, Lee, Cool, Sibley, Gerfen, Westphal, & Fuchs, 1996; Ekman, Nissbrandt, Heilig, Dijkstra, & Eriksson, 1998; Suzuki, Mihara, Kondo, Tanaka, Nagashima, Otani, & Kaneko, 2000; Wong, Buckle, & Van Tol, 2000). Interestingly, the D₃ receptor subtype has been implicated in the hyperactivity associated with attention-deficit hyperactivity disorder (ADHD) (Barr, Wigg, Wu, Zai, Bloom, Tannock, Roberts, Malone, Schachar, & Kennedy, 2000). In addition, many researchers believe that there is a strong relationship between the D₄ receptor and novelty seeking behavior (Benjamin, Li, Patterson, Greenberg, Murphy, & Hamer, 1996; Benjamin, Osher, Kotler, Nemanov, Belmaker, & Ebstein, 2000; Ebstein, Novick, Umansky, Priel, Osher, Blaine, Bennett, Nemanov, Katz, & Belmaker, 1996; Ebstein, Nemanov, Klotz, Gritsenko, & Belmaker, 1997; Okuyama, Ishiguro, Nankai, Shibuya, Watanabe, & Arinami, 2000; Strobel, Wehr, Michel, & Brocke, 1999; Tomitaka, Tomitaka, Otuka, Kim, Matuki, Sakamoto, & Tanaka, 1999). For example, D₄ knock-out mice show significantly less novelty seeking behavior

than controls (Dulawa, Grandy, Low, Paulus, & Geyer, 1999). The D₃ receptor subtype is found mostly in the nucleus accumbens and island of Calleja (Meador-Woodruff, Damask, & Watson, 1994), while the D₄ receptor subtype is found in the cortex, hippocampus, ventral striatum, globus pallidus, substantia nigra, thalamus, and ventral hypothalamus (for a review, see Callier, Snapyan, Le Crom, Prou, Vincent, & Vernier, 2003).

Dichotomy Based on Neuroanatomical Location

Postsynaptic Receptors

Postsynaptic receptors are typically stimulated by neurotransmitter released from nerve terminals. After dopamine binds to postsynaptic receptors, second messenger systems are either stimulated or inhibited. Second messenger activity is modulated via protein phosphorylation, which regulates many factors including: cAMP, adenylyl cyclase, voltage- and calcium-dependent channels, protein kinases, and neurotransmitter release (Cooper et al., 2003). Typically, the end result of these actions is that an excitatory or inhibitory postsynaptic potential is initiated in the dendrites.

Presynaptic Receptors: Autoreceptors

D2-like autoreceptors are located presynaptically and are sensitive to the same neurotransmitter that is released from the terminal (Cooper et al., 2003). In other words, dopamine neurons have specialized receptors, called autoreceptors that are sensitive to the neurotransmitter released by the neuron itself.

Conceptually, dopamine autoreceptors play an important role in self-regulation. Activating these autoreceptors inhibits dopamine transmission by decreasing dopamine release, firing rate, and tyrosine hydroxylase activity (Cooper et al., 2003). In general, dopamine receptor agonists decrease dopamine synthesis by stimulating autoreceptors, whereas dopamine receptor antagonists increase dopamine synthesis by blocking autoreceptors.

The distinction between autoreceptors and postsynaptic receptors involves more than just location and function. When compared to postsynaptic D2-like receptors, D2-like autoreceptors have a higher affinity for dopamine and certain dopamine receptor agonists (Cooper et al., 2003). Thus, D2-like autoreceptors are selectively activated after administration of a partial D2-like

agonist (Meller, Bohmaker, Namba, Friedhoff, & Goldstein,
1987).

CHAPTER THREE

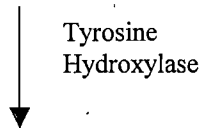
DOPAMINE METABOLISM

Dopamine Synthesis

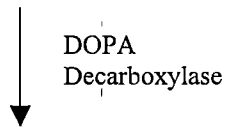
Dopamine is a catecholamine neurotransmitter found predominately in the central nervous system. Dopamine is synthesized from the amino acid precursor tyrosine, which is converted in the cytoplasm to L-3,4-dihydroxyphenylalanine (L-DOPA) by tyrosine hydroxylase. In the cytoplasm, DOPA decarboxylase transforms L-DOPA to dopamine (see Figure 1) (Cooper et al., 2003). Tyrosine hydroxylase is the rate-limiting step in this biosynthetic pathway.

The main regulatory factors modulating dopamine synthesis are the firing rate of the neurons, end-product inhibition, and autoreceptors located in the nerve-endings (Cooper et al., 2003). In general, stimulation of somatodendritic autoreceptors inhibits the firing rate of the neurons via a negative feedback mechanism (for a review, see Roth & Elsworth, 1995). On the other hand, antagonizing these autoreceptors increases the firing rate and, thus, disinhibits the release and synthesis of

Tyrosine



L-DOPA



Dopamine

Figure 1. Simplified presentation of the synthesis of dopamine metabolism. L-DOPA = L-3,4-dihydroxyphenylalanine.

neurotransmitter (Roth & Elsworth, 1995). End-product inhibition is primarily controlled by pteridine activity.

Specifically, when dopamine builds up in the cytoplasm, it decreases the release of pteridine (a co-factor for tyrosine hydroxylase). The reduced amount of pteridine decreases tyrosine hydroxylase activity and causes a corresponding decline in dopamine synthesis (Cooper et al., 2003).

Autoreceptors are present at the soma, dendrites, and nerve terminals. Stimulating autoreceptors on the nerve terminals inhibits dopamine synthesis by reducing the amount of pteridine. As mentioned above, pteridine modulates the activity of tyrosine hydroxylase. Thus, decreased pteridine causes a reduction in tyrosine hydroxylase activity and a corresponding decrease in dopamine synthesis and release. In contrast, stimulating autoreceptors on the soma and dendrites (somatodendritic autoreceptors) slows the firing rate of dopamine neurons through a negative feedback mechanism. Both somatodendritic and nerve terminal autoreceptors combine to provide feedback modulation of dopaminergic transmission (Cooper et al., 2003).

Termination of Dopamine Transmission

Dopaminergic transmission is primarily terminated by uptake of the released neurotransmitter back into the axon terminal. The dopamine transporter is responsible for this reuptake action (Cooper et al., 2003). The dopamine transporter is found only in dopamine neurons, thus it is a unique marker for dopaminergic neurons (Kuhar, 1998).

Dopamine is catabolized by the actions of two enzymes: Monoamine oxidase (MAO) and catechol-O-methyltransferase (COMT) (see Figure 2) (Cooper et al., 2003). MAO, which is found in the mitochondrial membranes of neurons and glial cells, transforms dopamine to a corresponding aldehyde (Cooper et al., 2003). More specifically, when MAO oxidizes dopamine, dihydroxyphenylacetaldehyde (DOPAL) is produced. DOPAL is subsequently metabolized by aldehyde dehydrogenase into 3,4-dihydroxyphenylacetic acid (DOPAC). DOPAC then diffuses out of the cell and is transformed into homovanillic acid (HVA) by COMT (Cooper et al., 2003).

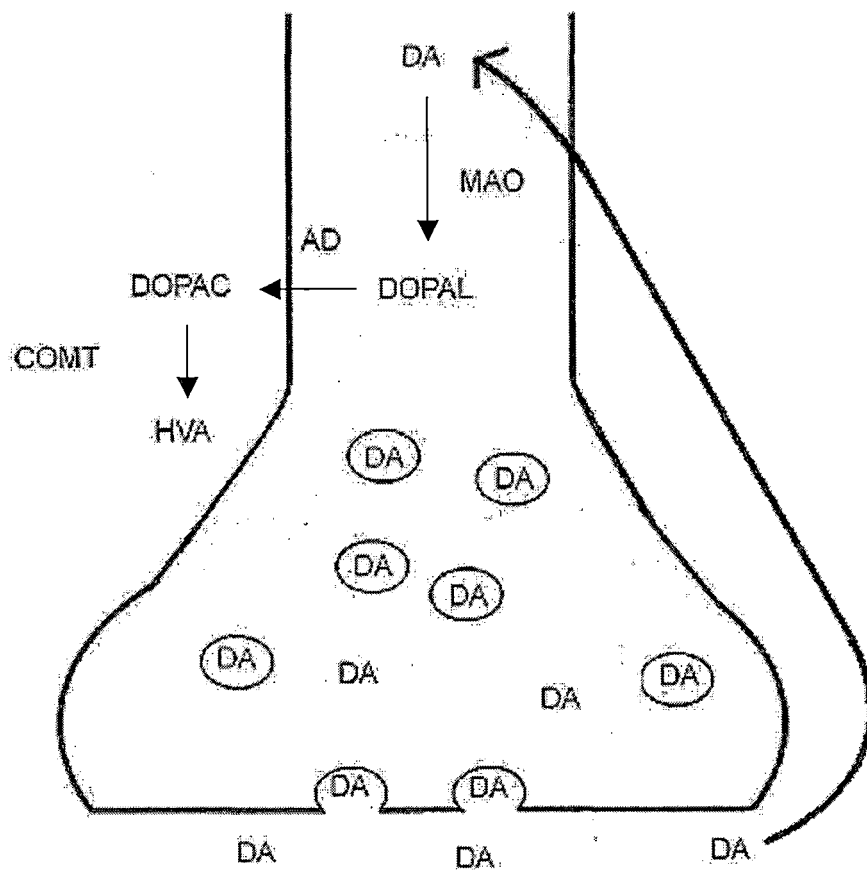


Figure 2. Metabolism of dopamine in the dopaminergic nerve terminal and synapse. MAO = monoamine oxidase, DOPAL = dihydroxyphenylacetaldehyde, AD = aldehyde dehydrogenase, DOPAC = 3,4-dihydroxyphenylacetic acid, COMT = catechol-O-methyltransferase, HVA = homovanillic acid.

CHAPTER FOUR

EFFECTS OF DOPAMINE AGONISTS AND ANTAGONISTS

Systemic Administration of Dopamine Agonists and Antagonists in Adult Rats

Non-selective dopamine receptor agonists (e.g., R(-)-propylnorapomorphine (NPA) or apomorphine) bind to pre- and postsynaptic D2-like receptors as well as postsynaptic D1-like receptors (for a review, see Arnt, 1987). When these drugs are systemically injected, adult animals exhibit dose-dependent increases in locomotor activity, rearing, grooming, sniffing, and oral behaviors (Harkin, Kelly, Frawley, O'Donnell, & Leonard, 1999; Havemann, Magnus, Moller, & Kuschinsky, 1986; Meller, Bordi & Bohmaker, 1988). Apomorphine also causes a dose-dependent increase in straub tail behavior (i.e., the tail forms an angle of at least 30°) (Zarrindast, Bayat, & Shafaghi, 1992). Depending on receptor occupancy, a continuum of behaviors can be observed. Lower doses of non-selective dopamine agonists cause non-stereotyped behaviors (e.g., grooming, locomotor activity, and rearing), while higher doses cause more intense

stereotyped behaviors (patterned locomotor activity, sniffing, and oral behaviors).

Selective stimulation of the dopamine receptor subtypes produces characteristic behavioral patterns. For example, selective stimulation of D1-like receptors with SKF 38393 causes increased grooming, non-stereotyped sniffing, rearing, and locomotor activity (Giorgi, DeMontis, Porceddu, Mele, Calderini, Toffano, & Biggio, 1987; Meller et al., 1988; Molloy & Waddington, 1984). On the other hand, more intense behaviors are observed when D2-like agonists (i.e., quinpirole and bromocriptine) are administered. Animals show increased head shakes (Gonzalez-Lima, Stiehl, & Medina, 1984), locomotor activity (Arnt & Hyttel, 1990), straub tail behavior (Zarrindast et al., 1992), sniffing, and oral behavior (Meller et al., 1988). These agonist-elicited behaviors are blocked by dopamine antagonists. For example, SKF 38393-induced grooming behavior is attenuated by SCH 23390 (a D1-like antagonist), while NPA-induced locomotor activity, rearing, and sniffing behaviors are attenuated by sulpiride (a D2-like antagonist) (Arnt, 1987; Clark & White, 1987).

Central Administration of Dopamine Agonists and
Antagonists in Adult Rats

Microinjecting selective or non-selective D1-like or D2-like agonists elicit different responses depending on brain area and dosage of injection. For example, injecting a non-selective dopamine receptor agonist (NPA) into the dorsal striatum elicits stereotyped behaviors (Bordi, Carr, & Meller, 1989). More specifically, dose-dependent increases in the intensity and duration of sniffing and oral stereotypies were observed after injecting NPA into sub-regions of the dorsal striatum. Higher doses of NPA created more intense and longer durations of these stereotypical behaviors (Bordi et al., 1989).

On the other hand, biphasic drug effects are observed when the selective D2-like agonist quinpirole is injected into the dorsal striatum. For example, rats showed increased locomotor activity when a high dose of quinpirole was bilaterally injected into the dorsal striatum; however, rats showed decreased locomotor activity when a low dose of quinpirole was microinjected into the same region (Van Hartesveldt, Cottrell, Potter, & Meyer, 1992). In a similar experiment, microinjecting

quinpirole into the dorsal striatum caused a dose-dependent decrease in locomotor and rearing behavior (Canales & Iversen, 1998; Swanson, Heath, Stratford, & Kelley, 1997), while causing an increase in stereotyped behavior (Canales & Iversen, 1998). In addition, microinjecting quinpirole into the dorsal striatum increased yawning (Canales & Iversen, 1998).

Surprisingly, very different effects were found when centrally administering the D1-like agonist SKF 38393 into the dorsal striatum. Specifically, when SKF 38393 was microinjected into the dorsal striatum, there were no observable changes in behavior (i.e., locomotor activity and stereotypy). However, after 3-4 hr, rats exhibited a decrease in "still" behavior, as well as an increase in oral behavior (Delfs & Kelley, 1990).

Injecting non-selective and selective agonists into the ventral striatum (i.e., nucleus accumbens) caused a different pattern of results. When the non-selective dopamine agonist, apomorphine, was injected into the ventral striatum, it caused a dose-dependent reduction in locomotor activity. More specifically, when a low dose of apomorphine (1 - 1000 ng) was microinjected into the

ventral striatum, there was no change in locomotor activity; however, a higher dose of apomorphine (10 µg) caused a significant decrease in locomotor activity (Barik & de Beaurepaire, 1996). Likewise, when quinpirole was microinjected into the ventral striatum, a reduction of both locomotor activity and rearing was observed, however stereotyped behaviors became more prominent (Canales & Iversen, 1998).

Different patterns of effects are observed when selective D1-like agonists are microinjected into the ventral striatum. Direct D1-like agonists (SKF 38393 or SKF 82958) cause significant dose-dependent increases in locomotor activity and rearing (Swanson et al., 1997).

Systemic Administration of Dopamine Agonists and Antagonists in Prewanling Rats

When non-selective dopamine receptor agonists (e.g., NPA or apomorphine) are systemically given to young rats they exhibit very similar behavioral effects as adults, including increased grooming, locomotor activity, sniffing, and intense stereotypies (McDougall & Bolanos, 1994; Mestlin & McDougall, 1992; Shalaby & Spear, 1980). More specifically, apomorphine increased locomotor activity at

all ages tested (PD 7, PD 14, PD 21, PD 28, and PD 35), but stereotyped sniffing was not observed until PD 21 (Shalaby & Spear, 1980). Similar effects were found using NPA, as this non-selective dopamine receptor agonist increased locomotor activity at PD 17 and stereotyped sniffing at both PD 11 and PD 17 (McDougall & Bolanos, 1994).

When selective dopamine D1-like or D2-like agonists are given, young rats again show behavioral patterns similar to adults (McDougall, Arnold, & Nonneman, 1990). For example, 11- and 17-day-old rats showed increased locomotor activity and grooming after being treated with SKF 38393 (a D1-like agonist) (McDougall et al., 1990). In addition, the D2-like agonist quinpirole increased locomotor activity in preweanling rats, an effect that was antagonized by either SCH 23390 (a D1-like antagonist) or sulpiride (a D2-like antagonist).

Interestingly, some dose-dependent effects are observed across early ontogeny. For example, quinpirole caused a dose-dependent increase in locomotor activity from PD 10 to PD 20; however, quinpirole-induced locomotion subsequently declined at PD 30 and PD 60 (Van

Hartesveldt, Meyer, & Potter, 1994). In addition, SKF 38393-induced grooming and quinpirole-induced vertical movement was observed at PD 21, but not at PD 3 or at PD 10 (Moody & Spear, 1992). In summary, there are some drug-induced ontogenetic effects, but research typically shows that dopamine agonists and antagonists cause qualitatively similar effects across the life-span.

CHAPTER FIVE
EFFECTS OF PARTIAL DOPAMINE D2-LIKE AGONISTS
ON UNLEARNED BEHAVIOR

Systemic and Central Administration of Partial D2-Like
Agonists in Adult Rats

Partial D2-like agonists have both agonistic and antagonistic effects on behavior (Spealman, 1995); however, the preponderance of studies indicates that partial D2-like agonists have antagonistic effects (Kikuchi, Tottori, Uwahodo, Hirose, Miwa, Oshiro, & Morita, 1995; for a review, see Pulvirenti & Koob, 1994). For example, partial D2-like agonists (e.g., SDZ 208-911, SDZ 208-912, OPC-14597, (-)-3-PPP, and terguride) reduce amphetamine- or apomorphine-induced locomotion and stereotyped behavior (Clark et al., 1991; Kikuchi et al., 1995). Further, apomorphine-induced hyperlocomotion, cataplexy, and stereotyped behavior were blocked by the partial D2-like agonist terguride (Kohler & Herbster, 1987). Consistent with its actions as an antagonist drug, microinjecting the partial D2-like agonist (-)-3-PPP into the ventral striatum, but not the dorsal striatum, decreased

exploratory behavior in adult rats (Svensson & Ahlenius, 1983).

Partial D2-like agonists seldom exhibit agonistic effects when tested on behavioral paradigms. However, one example of an agonistic effect is provided by Arnt and Perregaard (1987), because co-administration of B-HR 920 (a partial D2-like agonist) and SKF 38393 (a direct D1-like agonist) induced contralateral turning in hemitransected-rats. A few other examples of agonistic-like effects are available, as the stimulus effects of cocaine were increased by administering SDZ 208-911 to monkeys (Spealman, 1995). In addition, Orsini et al. (2001) demonstrated the agonistic effects of terguride by measuring saccharin-reinforced responding in dopamine-depleted rats. Normally, rats exhibit suppressed responding for a natural reward (e.g., saccharin) when they are in a state of low dopaminergic tone; however, terguride exhibited agonistic properties by reversing this effect. In conclusion, partial D2-like agonists exhibit both agonistic and antagonistic properties in adult rats. Partial D2-like agonists typically act as antagonists in

behavioral models but, in a few circumstances, partial D2-like agonists have been shown to act like agonists.

Systemic Administration of Partial D2-Like Agonists in Preweanling Rats

Partial D2-like agonists have both agonistic and antagonistic behavioral effects in adult animals; however, it is not known whether a similar pattern of effects is evident in younger animals. In studies conducted by McDougall and colleagues (2005), antagonistic effects of partial D2-like agonist were found. More specifically, terguride was able to block NPA-, amphetamine-, and cocaine-induced locomotor activity (McDougall, Hernandez, Reichel, & Farley, 2005; Sibole, Matea, Krall, & McDougall, 2003). Interestingly, terguride also reduced locomotor activity under the saline condition as well. This indicates that terguride acts as an antagonist under conditions of normal and enhanced dopaminergic tone in preweanling animals.

As with terguride, the partial D2-like agonist (-)-3-PPP induces antagonistic effects in preweanling rats. More specifically, young rats (PD 11 and PD 20) exhibited increased locomotor activity when injected with the full

D2-like agonist (+)-3-PPP, but no effect was found when they were injected with the partial D2-like agonist (-)-3-PPP (Arnt, 1983). In addition, when (-)-3-PPP was given to rats at PD 11, PD 20, or PD 30, it antagonized amphetamine-induced hyperactivity, however this effect was not observed after treatment with (+)-3-PPP (Arnt, 1983).

Interestingly, the preponderance of studies have shown that partial D2-like agonists have pronounced antagonistic effects during the preweanling period (Arnt, 1983; McDougall et al., 2005; Sibole et al., 2003); however, evidence of agonistic properties has not been found. McDougall et al. (2005) used either an escalating regimen of amphetamine or AMPT (a tyrosine hydroxylase inhibitor) to induce states of low dopaminergic tone in preweanling rats. Rats were then given an injection of saline, terguride, or NPA. The full D2-like agonist NPA enhanced locomotor activity in states of low dopaminergic tone, whereas terguride did not stimulate locomotor activity. These behavioral results suggest that partial D2-like agonists do not exhibit agonistic properties during the preweanling period.

While a few studies have shown that partial D2-like agonists act like agonists in adult rats, comparable studies have not shown agonistic actions in young animals under a state of low dopaminergic tone. There are a number of possible explanations for this apparent ontogenetic difference. First, during amphetamine withdrawal (a state of low dopaminergic tone), terguride may not have induced agonistic effects because of a substantial receptor reserve. More specifically, reducing dopaminergic tone is believed to "create a receptor reserve where none had existed before" (Meller et al., 1987), and it should cause partial D2-like agonists to exhibit agonistic effects. However, it is possible that preweanling rats have a very large receptor reserve, thus even under a state of low dopaminergic tone terguride was not able to produce agonist-like effects (McDougall et al., 2005).

Second, terguride may not act like an agonist under a state of low dopaminergic tone due to a presumed immaturity of D2-like receptors. According to Carlsson (1983), the conformation of a receptor changes depending on intrinsic activity (see also Clark et al., 1985;

Drukarch & Stoof, 1990). Theoretically, partial D2-like agonists should act as agonists under low dopaminergic tone (i.e., low intrinsic activity), because of conformational changes in the D2-like receptor. It is possible that during the preweanling period these conformational changes may not occur in the same manner in adulthood.

Lastly, terguride may not have elicited agonistic effects under a state of low dopaminergic tone because of paradigmatic considerations. Specifically, in the McDougall et al. (2005) study, a state of low dopaminergic tone was presumably induced by AMPT or an escalating regimen of amphetamine. It is possible that neither of these manipulations was sufficient to induce a state of low dopaminergic tone in preweanling rats. Therefore, it remains possible that partial D2-like agonists will exhibit agonistic properties in preweanling rats if manipulations cause a more intense or prolonged reduction in dopamine levels. In light of these considerations, the use of non-behavioral paradigms (i.e., measuring autoreceptor mediated changes in dopamine synthesis) may

be necessary to determine whether partial D2-like agonists exhibit agonistic properties during the preweanling period.

CHAPTER SIX

DOPAMINE SYNTHESIS

Effects of Full Dopamine D2-Like Drugs on Dopaminergic Synthesis

Dopamine synthesis is frequently defined as the accumulation of L-DOPA after treatment with the aromatic amino acid decarboxylase inhibitor, 3-hydroxybenzylhydrazine hydrochloride (NSD 1015) (Cooper et al., 2003). One of the primary ways to determine the agonistic and antagonistic effects of dopaminergic drugs is to assess drug-induced changes in dopamine synthesis. For example, when the D2-like agonist, N-0437, is given to NSD 1015-treated rats, DOPA accumulation declines. Similarly, dorsal striatal DOPA accumulation is reduced when NSD 1015-treated rats are injected with amphetamine, NPA, or apomorphine (Argiolas, Melis, Fadda, Serra, & Gessa, 1982). Conversely, the D2-like antagonist haloperidol causes a dose-dependent increase in DOPA accumulation in NSD 1015-treated rats (Svensson, Eriksson, & Carlsson, 1993).

It is also of interest to determine the effects of dopamine agonists and antagonists during a state of low

dopaminergic tone. To that end, reserpine, which is a dopamine depleting agent (Ahlenius, Hillegaard, & Wijkstrom, 1991; Argiolas et al., 1982; Guldberg & Broch, 1971; Roth & Stone, 1968), is frequently used to create a state of low dopaminergic tone (Svensson, Ekman, Piercey, Hoffman, Lum, & Carlsson, 1991). After acute administration of reserpine, the D2-like agonist quinpirole causes a dose-dependent decrease in dorsal striatal DOPA accumulation, whereas haloperidol or sulpiride (D2-like antagonists) increase DOPA accumulation (Ahlenius et al., 1991; Argiolas et al., 1982; Svensson et al., 1991). This phenomenon is regulated by dopamine autoreceptors in the dorsal striatum (Murrin & Roth, 1987).

Autoreceptor-mediated effects can also be examined by measuring DOPA accumulation after treatment with the impulse inhibitor γ -butyrolactone (GBL) (Bannon, Michaud, & Roth, 1981; Kehr, 1984). Not surprisingly, GBL dramatically increases DOPA accumulation in the dorsal striatum (Bannon et al., 1981; Kehr, 1984). Apomorphine reverses this GBL-induced increase in DOPA accumulation, whereas haloperidol accelerates dopamine synthesis in the striatum (Bannon et al., 1981). Thus, full agonists and

antagonists differentially affect GBL-induced DOPA accumulation.

Effects of Partial Dopamine D2-Like Agonists on Dopaminergic Synthesis

Partial D2-like agonists bind to autoreceptors, but their intrinsic activity is less than full agonists (Lahti, Mutin, Cochrane, Tepper, Dijkstra, Wikstrom, & Tamminga, 1996; Lahti, Weiler, Corey, Lahti, Carlsson, & Tamminga, 1997). In a state of high dopaminergic tone, partial D2-like agonists typically act like antagonist drugs. For example, the partial D2-like agonist (-)-3-PPP causes a dose-dependent decline in DOPA accumulation in NSD 1015-treated rats; however, a dose-dependent increase in DOPA accumulation was observed after administration of the full agonist (+)-3-PPP (Clark, Salah, & Galloway, 1991). Similarly, SDZ 208-911 and terguride dose-dependently reduced striatal DOPA accumulation (after treatment with NSD 1015) by 80%, whereas SDZ 208-912 only produced a 32% reduction (Svensson et al., 1991). SDZ 208-911 and terguride partially reversed (by approximately 50%) the GBL-induced increase in striatal DOPA accumulation, but SDZ 208-912, which is a weaker partial agonist, was

inactive under the same conditions. In summary, evidence suggests that partial D2-like agonists function like antagonists during states of high dopaminergic tone.

Pretreatment with the dopamine depleting agent reserpine creates a state of low dopaminergic tone: a situation where partial D2-like agonists function like agonist drugs. For example, terguride and SDZ 208-911, like quinpirole, reduce DOPA accumulation (after injection of NSD 1015) in the dorsal striatum by approximately 80% (Svensson et al., 1991). D2-like antagonists, on the other hand, increase striatal DOPA accumulation in reserpinized rats (Argiolas et al., 1982).

The impulse inhibitor GBL also induces a functional state of low dopaminergic tone. Not surprisingly, GBL-induced DOPA accumulation is inhibited by both full (e.g., quinpirole) and partial (e.g., terguride, SDZ 208-911, OPC-14597, and OPC-4392) D2-like agonists (Ahlenius et al., 1991; Clark, Hjorth, & Carlsson, 1984; Kikuchi et al. 1995; Svensson et al., 1991). These effects of partial D2-like agonists are subsequently blocked by the D2-like antagonist haloperidol (Svensson, 1991).

CHAPTER SEVEN

SUMMARY AND HYPOTHESES

General Summary and Hypotheses

Partial D2-like agonists exhibit either agonistic or antagonistic properties in adult rats depending on the state of dopaminergic tone (for a review, see Clark et al., 1985). More specifically, in adult rats, partial D2-like agonists have antagonistic effects under a state of high dopaminergic tone, and agonistic effects under a state of low dopaminergic tone (for a review, see Pulvirenti & Koob, 1994).

A somewhat different pattern of effects are observed in early ontogeny. In preweanling rats, partial D2-like agonists function as antagonists in states of high dopaminergic tone (Arnt, 1988; McDougall et al., 2005; Sibole et al., 2003). In states of low dopaminergic tone, however, partial D2-like agonists continue to function like antagonist drugs (McDougall et al., 2005). In other words, terguride consistently functioned like an antagonist drug in behavioral paradigms using the

preweanling rat: effects that were apparent during states of low or high dopaminergic tone.

In addition to employing behavioral paradigms, the effects of partial D2-like agonists have been examined by measuring autoreceptor-mediated changes in dopamine synthesis (Iyengar, Hausler, Kim, Marient, Alter, & Wood, 1989; Lahti et al., 1996; Li, Ichikawa, Dai, & Meltzer, 2004). In states of high dopaminergic tone (no reserpine or GBL treatment), partial D2-like agonists exhibit antagonistic (haloperidol-like) effects in adult rats (Ahlenius et al., 1991; Argiolas et al., 1982; Svensson et al., 1991). On the other hand, in states of low dopaminergic tone (i.e., after reserpine or GBL treatment) partial D2-like agonists exhibit agonistic (quinpirole-like) effects in adults.

In summary, in both behavioral and neurochemical paradigms involving adult rats, partial D2-like agonists function as antagonists during states of high dopaminergic tone, but function as agonists in states of low dopaminergic tone. In contrast, available behavioral evidence suggests that partial D2-like agonists function exclusively as antagonists during the preweanling period

(Arnt, 1983; McDougall et al., 2005; Sibole et al., 2003). However, no ontogenetic studies have directly examined the effects of partial D2-like agonists using neurochemical paradigms.

The purpose of this thesis, therefore, was to determine the effects of partial D2-like agonists on dorsal striatal dopamine synthesis during the preweanling period. To this end, preweanling rats were treated with saline or reserpine (either acutely or repeatedly) in Experiment 1. On the test day, the saline- or reserpine-pretreated rats were injected with the partial D2-like agonist terguride, the full D2-like agonist quinpirole, or the full D2-like antagonist haloperidol. Rats were then injected with NSD 1015. It was hypothesized that terguride would induce antagonistic (haloperidol-like) effects in a state of high dopaminergic tone (after saline treatment), while showing agonistic (quinpirole-like) effects in a state of low dopaminergic tone (after repeated reserpine treatment). It was also hypothesized that terguride would induce antagonistic effects after acute reserpine treatment.

The rationale for these hypotheses was based on the intensity and longevity of dopamine depletion. McDougall et al. (2005) showed that short-term or mild dopamine depletion was insufficient to cause terguride to exhibit agonist-like properties. Therefore, I hypothesized that prolonged dopamine depletion (i.e., after repeated reserpine treatment) would induce a state of dopaminergic tone sufficiently low to cause agonistic effects in terguride-treated rats. Because acute administration of AMPT did not induce agonist-like effects in terguride-treated rats (see McDougall et al., 2005), it was hypothesized that acute reserpine treatment would also be insufficient to induce a state of low dopaminergic tone. If the data do not support these hypotheses (i.e., if terguride causes antagonist-like effects in Experiment 1), then it is possible that preweanling rats have a smaller receptor reserve than adult rats. Alternatively, preweanling rats may not show adult-like changes in receptor conformation after dopamine depletion.

Experiment 2 was designed to examine the effects of terguride using GBL. The GBL model is a technique used to induce a state of low dopaminergic tone by inhibiting

nerve impulse flow (Walters & Roth, 1976). In adult rats, GBL-induced DOPA accumulation is inhibited by both partial and full D2-like agonists (Ahlenius et al., 1991; Clark et al., 1984; Kikuchi et al. 1995; Svensson et al., 1991). Importantly, the effects of partial D2-like agonists on GBL-induced DOPA accumulation have not been assessed in preweanling rats. Therefore, preweanling rats were injected with terguride, quinpirole, or haloperidol. Rats were subsequently injected with GBL prior to NSD 1015 treatment. It was predicted that terguride would exhibit agonistic (quinpirole-like) properties (i.e., reversing GBL-induced DOPA accumulation). This pattern of results would indicate that partial D2-like agonists cause agonistic effects during a state of low dopaminergic tone.

Lastly, Experiment 3 was designed to examine whether haloperidol would block terguride's effects using the GBL model. Preweanling rats were injected with saline or haloperidol, followed by an injection of saline, terguride, or quinpirole. Rats were then treated with GBL followed by NSD 1015. It was predicted that haloperidol would block the ability of terguride and quinpirole to reverse GBL-induced DOPA accumulation. This pattern of results

would indicate that: 1) the actions of terguride are mediated by dopamine receptors; and 2) terguride and quinpirole are functioning like agonists, while haloperidol is functioning like an antagonist.

CHAPTER EIGHT

GENERAL METHODS

Subjects

Subjects were 240 male and female Sprague-Dawley rats (Charles River), born and raised in the animal colony at California State University, San Bernardino. All litters were culled to 10 by PD 3 and the pups remained with the dam throughout testing. Before the pretreatment period, rats were randomly assigned to treatment groups. All subjects were given food and water ad lib. The colony room was maintained at 21 - 23°C, and was on a 12 light/12 dark cycle. All subjects were treated in accordance with the ethical principles as outlined by the American Psychological Association (1992).

Drugs

Terguride, haloperidol, quinpirole, NSD 1015 (3-hydroxybenzylhydrazine hydrochloride), and GBL (γ -butyrolactone) were dissolved in saline. Reserpine was dissolved in a minimal amount of glacial acetic acid and diluted with saline. All drugs were purchased from Sigma

(St. Louis, MO) and were injected intraperitoneally (ip) at a volume of 5 ml/kg.

Apparatus

A high performance liquid chromatograph (582 pump and a MD-150 column; ESA, Chelmsford, MA) with an electrochemical detector (Coulochem II; ESA) was used to measure DOPA accumulation. The mobile phase consisted of 75 mM NaH_2PO_4 , 1.4 mM 1-octane sulfonic acid, 10 mM EDTA, and 10% acetonitrile [(pH 3.1) MD-TM Mobile Phase; ESA] and was pumped at a rate of 0.5 ml/min.

Assay Procedures

Frozen dorsal striatal sections were sonicated in 10 volumes of 0.1 N HClO_4 and centrifuged at $20,000 \times g$ for 30 min at 4°C . The supernatant was then filtered through a $0.22 \mu\text{m}$ centrifugation unit at $2,000 \times g$ for 5 min at 4°C . Twenty microliters of the resulting extract was assayed for DOPA accumulation using high performance liquid chromatography.

Statistical Analysis

Analysis of variance (ANOVA) was used to analyze neurochemical data. Litter effects were controlled by assigning no more than one subject per litter to a particular treatment group. Post-hoc comparison of the neurochemical data was conducted using Tukey tests ($p < .05$).

CHAPTER NINE

EXPERIMENT ONE

Overview

Experiment 1 examined whether terguride has agonistic-like effects during states of low dopaminergic tone and antagonistic-like effects during states of high dopaminergic tone. To that end, dopamine synthesis (i.e., DOPA accumulation after treatment with NSD 1015) was measured in saline- or reserpine-treated preweanling rats (acute or repeated treatment). Rats in the acute condition received one reserpine injection and rats in the repeated condition received reserpine treatment for five consecutive days (see procedure for more details). In control animals, it was predicted that terguride, like haloperidol, would enhance dopamine synthesis. Conversely, terguride was hypothesized to act like quinpirole in reserpinized rats (i.e., dopamine synthesis would be depressed). It was also predicted that terguride would inhibit dopamine synthesis in the repeated reserpine condition but not in the acute reserpine condition group.

Procedures

Preweanling rats (n = 144) were randomly divided into three conditions: control, repeated reserpine, and acute reserpine. Rats in the control condition received saline injections on PD 16 - PD 20; rats in the repeated reserpine condition received reserpine (1 mg/kg, ip) injections on PD 16 - PD 20; rats in the acute reserpine condition received a single injection of reserpine (1 mg/kg, ip) on PD 20. After 24 hr, all rats were injected with the full D2-like antagonist haloperidol (0.5 mg/kg, ip), the partial D2-like agonist terguride (0.1, 0.4, or 1.6 mg/kg, ip), the full D2-like agonist quinpirole (0.5 mg/kg, ip), or saline (n = 8 per group). After an additional 30 min, rats were injected with NSD 1015 (100 mg/kg, ip). Rats were then sacrificed 30 min later and their dorsal striata were stored at -70°C until time of assay (see Table 1).

Statistics

A 3 × 6 (pretreatment condition × post treatment) ANOVA was used to determine whether DOPA levels differed

Table 1. Injection paradigm of Experiment 1.

Condition	PD
Repeated Reserpine	16-20
Saline	16-20
Acute Reserpine	20

First Injection	Time	Second Injection	Time	
Terguride	30 min	NSD 1015	30 min	Sacrifice
Quinpirole	30 min	NSD 1015	30 min	Sacrifice
Haloperidol	30 min	NSD 1015	30 min	Sacrifice
Saline	30 min	NSD 1015	30 min	Sacrifice

Rats were pretreated with reserpine or saline. On the test day, rats were injected with terguride, quinpirole, haloperidol, or saline. All rats were then injected with NSD 1015.

according to treatment group. DOPA accumulation after NSD 1015 treatment was used as an index of dopamine synthesis.

Results

Pretreatment condition interacted with post treatment group to affect striatal DOPA accumulation [$F(10,90) = 20.19, p < 0.001$] (see Fig. 3). In the vehicle-pretreatment condition, the partial D2-like agonist terguride had antagonist-like effects in vehicle-pretreated rats (under high dopaminergic tone), because both haloperidol and terguride caused a significant increase in DOPA accumulation when compared to the control group [$F(5, 30) = 63.77, p < 0.001$]. In addition, haloperidol caused a greater increase in DOPA accumulation than did terguride. More specifically, haloperidol caused a 313% increase in DOPA accumulation, while terguride caused a 165% increase over control values. On the other hand, the D2-like agonist quinpirole significantly reduced DOPA accumulation in comparison to saline controls.

In the reserpine-pretreated conditions (acute and repeated), terguride caused a quinpirole-like effect. Both terguride and quinpirole significantly reduced DOPA

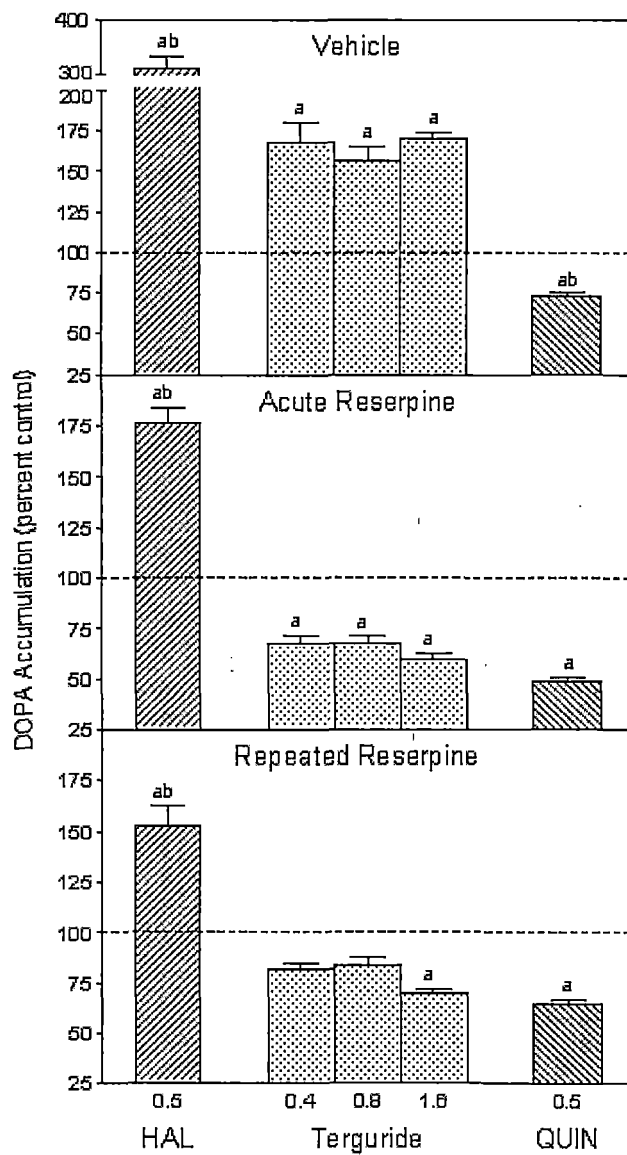


Figure 3. Results from Experiment 1. ^aSignificantly different from saline controls from the same pretreatment condition ($p < 0.05$). ^bSignificantly different from terguride groups from the same pretreatment condition ($p < 0.05$).

accumulation relative to the saline controls [acute reserpine: $F(5, 30) = 79.72, p < 0.0001$; repeated reserpine: $F(5, 30) = 27.86, p < 0.001$]. More specifically, all doses of terguride (0.4, 0.8, and 1.6mg/kg) significantly decreased DOPA accumulation in the acute reserpine condition; however, only 1.6 mg/kg terguride decreased DOPA accumulation in the repeated reserpine condition. Haloperidol significantly increased DOPA accumulation in both the acute and repeated reserpine conditions.

CHAPTER TEN

EXPERIMENT TWO

Overview

Experiment 2 examined whether terguride caused agonistic-like effects using the GBL model. GBL creates a state of low dopaminergic tone by inhibiting impulse flow; therefore, the effects of partial and full dopamine-acting drugs on DOPA accumulation was measured in GBL-treated rats. It was predicted that terguride would exhibit agonist-like (quinpirole-like) effects under a state of low dopaminergic tone (in GBL-treated animals). In other words, terguride, like quinpirole and opposite to haloperidol, was expected to reverse GBL-induced DOPA accumulation.

Procedures

On PD 21, preweanling rats ($n = 48$) were injected with the full D2-like antagonist haloperidol (0.5 mg/kg, ip), the partial D2-like agonist terguride (0.1, 0.4, or 1.6 mg/kg, ip), the full D2-like agonist quinpirole (0.5 mg/kg, ip), or saline. After 25 min later, they were

injected with GBL (625 mg/kg, ip). After an additional 5 min, an injection of NSD 1015 (100 mg/kg, ip) was given. Rats were sacrificed 30 min later and their dorsal striata were stored at -70°C until time of assay (see Table 2).

Table 2. Injection paradigm for Experiment 2.

First Injection	Time	Second Injection	Time	Third Injection	Time	
Terguride	25 min	GBL	5 min	NSD 1015	30 min	Sacrifice
Quinpirole	25 min	GBL	5 min	NSD 1015	30 min	Sacrifice
Haloperidol	25 min	GBL	5 min	NSD 1015	30 min	Sacrifice
Saline	25 min	GBL	5 min	NSD 1015	30 min	Sacrifice

Rats were first injected with terguride, quinpirole, haloperidol, or saline. They were then given an injection GBL prior to NSD 1015.

Statistics

A one-way (treatment group) ANOVA was used to determine whether DOPA levels differed according to treatment group. DOPA accumulation after NSD 1015 treatment was used as an index of dopamine synthesis.

Results

As expected, the partial D2-like agonist terguride (0.1, 0.2, 0.8, and 1.6 mg/kg) and the full D2-like agonist quinpirole significantly reduced DOPA accumulation (see Fig. 4) [$F(7, 40) = 16.27, p < 0.001$].

Interestingly, quinpirole caused a greater reduction in DOPA accumulation than terguride. On the other hand, haloperidol significantly increased DOPA accumulation relative to saline controls.

Surprisingly there were no dose-dependent effects observed among the terguride groups. More specifically, DOPA accumulation did not vary across the extended dose range (0.1-1.6 mg/kg) of terguride. This result may be due to a "ceiling effect" of the partial D2-like agonist, with 0.1 mg/kg terguride producing a maximal effect on

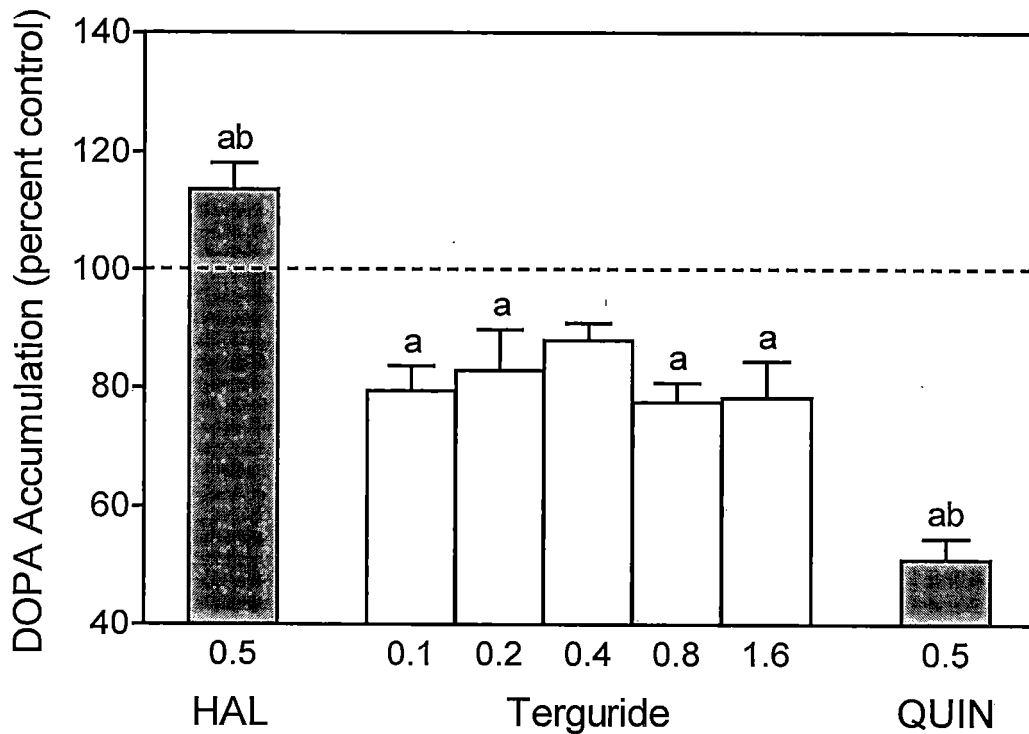


Figure 4. Results from Experiment 2. ^aSignificantly different from saline controls ($p < 0.05$). ^bSignificantly different from terguride groups ($p < 0.05$).

DOPA accumulation. This possibility seems unlikely, because terguride has previously been shown to produce dose-dependent effects across the same range of doses used in the present experiment (Clark et al., 1991). In the latter study, however, terguride's effects were assessed in a behavioral paradigm using adult rats.

CHAPTER ELEVEN

EXPERIMENT THREE

Overview

Experiment 3 examined the combined effects of terguride and haloperidol using the GBL model. Preweanling rats were pretreated with both GBL and NSD 1015. Rats were then injected with saline or haloperidol followed by a later injection of saline, terguride, or quinpirole. It was predicted that terguride and quinpirole would reverse GBL-induced DOPA accumulation, and that this effect would be blocked by haloperidol. This pattern of results would indicate that the actions of terguride are mediated by dopamine receptors. It would also indicate that terguride and quinpirole were exhibiting agonistic properties during a state of low dopaminergic tone, while haloperidol was acting as an antagonist.

Procedures

On PD 21, preweanling rats ($n = 48$) were injected with saline or the full D2-like antagonist haloperidol

(0.5 mg/kg, ip) followed, 30 min later, by an injection of the partial D2-like agonist terguride (dose to be determined in Experiment 2), the full D2-like agonist quinpirole (0.5 mg/kg, ip), or saline. After an additional 25 min, rats were injected with GBL (625 mg/kg, ip), followed, 5 min later, by an injection of NSD 1015 (100 mg/kg, ip). Rats were sacrificed 30 min later and their dorsal striata were stored at -70°C until time of assay (see Table 3).

Statistics

A 2 × 3 (pretreatment condition × post treatment) ANOVA was used to determine whether DOPA levels differed according to treatment group. DOPA accumulation after NSD 1015 treatment was used as an index of dopamine synthesis.

Results

As expected, both terguride (0.8 and 1.6 mg/kg) and quinpirole significantly reduced DOPA accumulation when compared to control values [$F(4, 50) = 7.66, p < 0.001$] (see Fig. 5), with quinpirole's effects being more robust.

Table 3. Injection paradigm for Experiment 3.

First Injection	Time	Second Injection	Time	Third Injection	Time	Fourth Injection	Time	
Haloperidol	30 min	Terguride	25 min	GBL	5 min	NSD 1015	30 min	Sacrifice
Saline	30 min	Quinpirole	25 min	GBL	5 min	NSD 1015	30 min	Sacrifice
		Saline	25 min	GBL	5 min	NSD 1015	30 min	Sacrifice

On the test day (PD 21), rats were first injected with haloperidol or saline. After the first drug administration, they were injected with terguride, quinpirole, or saline. They were then injected with GBL and NSD 1015.

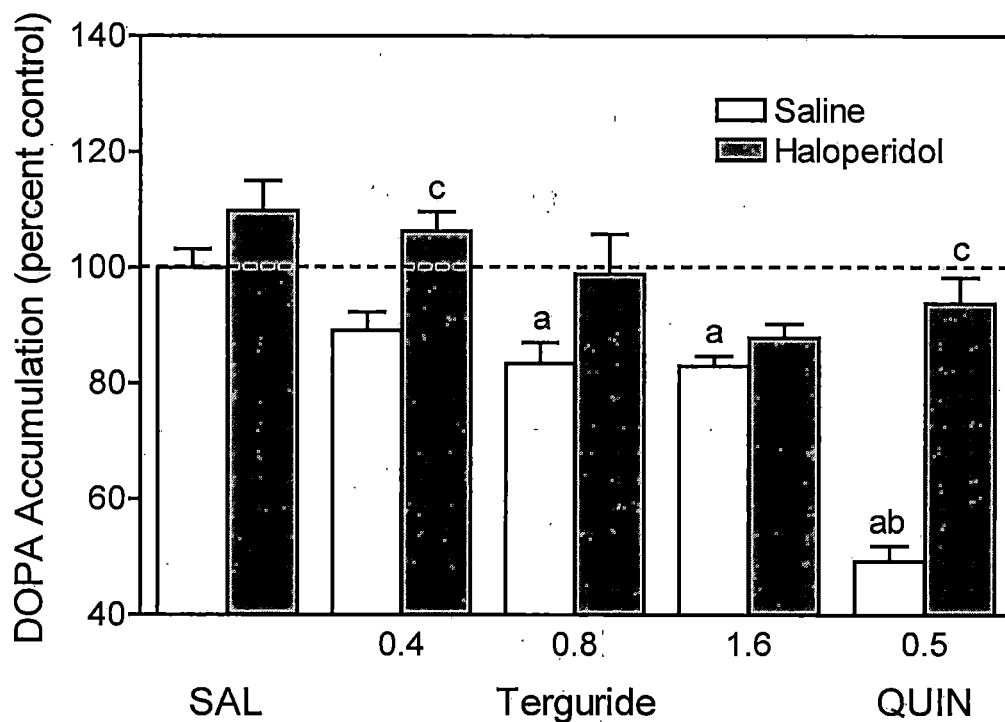


Figure 5. Results from Experiment 3. ^aSignificantly different from saline controls ($p < 0.05$). ^bSignificantly different from terguride groups ($p < 0.05$). ^cSignificantly different from saline-pretreated rats receiving the identical dose of terguride and quinpirole ($p < 0.05$).

Haloperidol significantly reversed quinpirole-induced DOPA accumulation, however, this effect was only observed for one of the terguride groups (0.4 mg/kg). More specifically, haloperidol reversed the DOPA accumulation caused by 0.4 mg/kg terguride, but haloperidol did not significantly reverse the effects of the higher terguride doses (0.8 or 1.6 mg/kg).

CHAPTER TWELVE

DISCUSSION

Effects of Terguride After Acute and Repeated Reserpine Treatment on Dopamine Synthesis in Preweanling Rats

The purpose of present study was to examine the neurochemical effects of terguride under high or low dopaminergic tone using preweanling rats. In adult rats, partial D2-like agonists function as antagonists during states of high dopaminergic tone, but function as agonists in states of low dopaminergic tone using both behavioral and neurochemical paradigms. In contrast, available behavioral evidence suggests that partial D2-like agonists function exclusively as antagonists during the preweanling period (Arnt, 1983; McDougall et al., 2005; Sibole et al., 2003); however, no ontogenetic studies have directly examined the effects of partial D2-like agonists using neurochemical paradigms.

In the present study, therefore, dopamine synthesis (i.e., DOPA accumulation after treatment with NSD 1015) was measured in saline- or reserpine-pretreated rats (acute or repeated treatment) (Experiment 1). Rats in the

acute condition received one reserpine injection on PD 20, while rats in the repeated condition received reserpine treatment for five consecutive days (PD 16 - PD 20). It was predicted that terguride would depress dopamine synthesis after repeated reserpine treatment (low dopaminergic tone). Conversely, it was hypothesized that terguride would enhance dopamine synthesis in control animals (high dopaminergic tone). It was also predicted that terguride would not affect dopamine synthesis in the acute reserpine condition.

These hypotheses were partially supported by the results. As hypothesized, under a state of high dopaminergic tone (i.e., in the vehicle-pretreated condition), the partial D2-like agonist terguride had antagonist-like effects. Like haloperidol, terguride caused significant increases in DOPA accumulation when compared to the control group. In addition, haloperidol caused a greater increase in DOPA accumulation than terguride. In a state of low dopaminergic tone (i.e., after acute or repeated reserpine treatment), terguride caused the opposite effect (i.e., terguride had agonist-like actions). Like the full D2-like agonist quinpirole,

terguride reduced DOPA accumulation after acute or repeated reserpine treatment. The reduction in DOPA accumulation was more robust in the quinpirole group than the terguride groups.

That terguride causes agonist-like effects after repeated reserpine treatment was expected, but I originally hypothesized that terguride would still act like an antagonist after acute reserpine treatment. The basis for the latter hypothesis was that short-term dopamine depletion using AMPT did not cause agonistic behavioral effects in terguride-treated rats (McDougall et al., 2005). Therefore, I hypothesized that repeated, but not acute, administration of reserpine would produce a state where terguride induced agonistic neurochemical effects. However, the results from the present study showed that acute administration of reserpine was sufficient to create a state of low dopaminergic tone that would allow terguride to exhibit agonistic effects. Perhaps, the ability of AMPT and reserpine to induce a state of low dopaminergic tone differs in young animals.

Effects of Terguride on DOPA
Accumulation in Preweanling
Rats Using the GBL Model

In addition to using reserpine to induce a state of low dopaminergic tone, GBL was used to examine the effects of autoreceptor-mediated changes in neurotransmitter synthesis. GBL creates a state of low dopaminergic tone by inhibiting impulse flow; therefore, the effects of partial and full dopamine-acting drugs on DOPA accumulation was measured in GBL-treated rats. In Experiment 2, it was predicted that terguride would exhibit agonistic (quinpirole-like) effects in GBL-treated animals. In Experiment 3, it was hypothesized that terguride would reverse GBL-induced DOPA accumulation, and that this effect would be blocked by haloperidol. This pattern of results would indicate that the actions of terguride were mediated by dopamine receptors.

As predicted, terguride (0.1, 0.2, 0.8, and 1.6 mg/kg), like quinpirole, significantly reversed GBL-induced DOPA accumulation. Surprisingly, there were no dose-dependent effects observed among the terguride groups. Although they were not significantly different from each other, there was a dose-dependent trend (i.e., an increase

in DOPA accumulation) up to 0.4 mg/kg and then a transient decline above 0.4 mg/kg. This transient effect may be due to the unique properties of partial D2-like agonists. As indicated before, partial D2-like agonists have high affinity and low intrinsic activity at presynaptic sites (Carlson, 1983). Therefore, when a partial D2-like agonist was injected at a low dose, it showed "true" partial agonist effects (showing high affinity but low intrinsic effect), however, when it was given at a higher dose, it showed more full agonist-like effects (quinpirole-like effects). In addition, this nonsignificant dose-dependent effect may also be due to a "ceiling effect" of the partial D2-like agonist. As indicated before, since there were no significant differences among the terguride groups, it may be possible that 0.1 mg/kg terguride was sufficient to induce a maximal effect. Once again, quinpirole had a more robust effect on dopamine accumulation than terguride did.

Haloperidol significantly increased DOPA accumulation relative to the control values (see Fig. 4). Haloperidol also significantly reversed the quinpirole-induced reductions in DOPA accumulation. Interestingly, this

effect was only observed in one of the terguride groups (0.4 mg/kg). More specifically, haloperidol only blocked the effects of 0.4 mg/kg terguride, while the effects of 0.8 or 1.6 mg/kg terguride were not attenuated by the antagonist drug.

The inability of haloperidol to block the effects of 0.8 or 1.6 mg/kg terguride suggests that some of terguride's effects may be mediated by other receptor systems. Unlike adult rats, preweanling rats have a D1 autoreceptor that modulates dopamine synthesis (Teicher, Gallitano, Gelbard, Marsh, Booth, & Baldessarini, 1991). Teicher and colleagues (1991) examined the ontogeny of D1 autoreceptor-mediated effects by comparing young and adult rats using the GBL model. They found that D1-like agonists, SKF 38393 and CY 208243, significantly reduced the GBL-induced increase in DOPA accumulation in young (PD 15-16) but not adult rats. This transient expression of D1-like autoreceptors suggests that both D1- and D2-like autoreceptors are present and functional in developing brains. In the present study, therefore, it is possible that terguride may have been affecting DOPA accumulation by binding to both D2 and D1 autoreceptors. If true, it

might explain why haloperidol did not fully antagonize terguride's effects on DOPA accumulation, because haloperidol has almost no affinity for D1 receptors.

GBL Model

GBL is used to induce a state of low dopaminergic tone by inhibiting nerve impulse flow (Walters & Roth, 1976). When impulse flow is inhibited, release of dopamine at the terminals is disrupted, resulting in a decrease in the synaptic levels of dopamine. Decreased levels of synaptic dopamine result in disinhibition of autoreceptors, which leads to increased DOPA accumulation (Wolf & Roth, 1987). In other words, blocking impulse flow increases dopamine synthesis by modulating presynaptic receptors (Walters & Roth, 1976). This GBL-induced DOPA accumulation is capable of being altered by dopamine-acting drugs. For example, amphetamine, which increases dopamine levels, causes a significant reduction in GBL-induced DOPA accumulation (Walters & Roth, 1976). Conversely, haloperidol significantly increases GBL-induced DOPA accumulation when compared to controls. In addition, haloperidol reverses the amphetamine-induced

reduction in GBL-induced DOPA accumulation (Walters & Roth, 1976).

In the present thesis, preweanling rats exhibited adult-like neurochemical effects. Specifically, quinpirole (a full D2-like agonist) caused a significant reduction in GBL-induced DOPA accumulation, while haloperidol (a D2-like antagonist) enhanced DOPA accumulation. These results provide additional evidence that autoreceptors are functionally mature during the late preweanling period.

Autoreceptors in Preweanling Rats

Early studies suggested that the autoreceptors of young animals were not functional during the early adolescent period (Shalaby & Spear, 1980; Hedner & Lundborg, 1985). However, results from the present study indicate that autoreceptors function in an adult-like manner during the late preweanling period (i.e., on PD 21). This conclusion is consistent with a study conducted by Andersen et al. (1997) using full D2-like agonists. Andersen et al. (1997) measured DOPA accumulation in the striatum, nucleus accumbens, and prefrontal cortex after

rats were treated with (+)-7-OH-DPAT, GBL, and NSD 1015 on PD 10, PD 15, PD 20, PD 30, and PD 40. The full D2-like agonist (+)-7-OH-DPAT inhibited striatal GBL-induced DOPA accumulation at all ages. These results support our contention that autoreceptors are present and functional during the late preweanling period.

Interestingly, Andersen et al. (1997) also found that GBL-induced DOPA accumulation was inhibited in the prefrontal cortex after (+)-7-OH-DPAT treatment in 10-, 15-, 20-, and 30-day-old rats. Although the present thesis only tested the effects of terguride in the striatum, it would be interesting to determine whether a partial D2-like agonist affects DOPA accumulation similarly in the prefrontal cortex of preweanling rats. In any event, the present study was the first to show that a partial D2-like agonist would induce adult-like neurochemical effects during the preweanling period.

Conformational Theory

In the present study, partial agonists had opposite neurochemical effects depending on the state of dopaminergic tone. According to Carlsson (1983), the

conformation of a receptor changes depending on intrinsic activity (see also Clark et al., 1985; Drukarch & Stoof, 1990). More specifically, responsiveness of a receptor to different agonist drugs varies depending on the state of the receptor. The intrinsic activity and previous occupancy of the receptor plays a very critical role. For example, after high receptor occupancy, partial D2-like agonists act as antagonists; whereas after low receptor occupancy, partial D2-like agonists act as agonists. These changes in receptor occupancy slowly induce a conformational change in the receptor, thus influencing the responsiveness of the receptor. In other words, the adaptability of receptor molecules alters the responsiveness to partial D2-like agonists.

In the present study, the partial D2-like agonist terguride induced agonistic effects under low receptor occupancy (low dopaminergic tone) and antagonistic effects under high receptor occupancy (high dopaminergic tone). This is an important finding because it has not been previously shown that partial agonists will induce this pattern of effects in preweanling rats. For such effects

to occur, dopamine autoreceptors must be functioning in an adult-like manner by PD 21.

Receptor Reserve Theory

An alternative explanation for the actions of partial D2-like agonists is provided by the receptor reserve theory. This theory suggests that partial D2-like agonists only exhibit agonistic actions in the presence of a large receptor reserve (Meller et al., 1987). More specifically, because partial D2-like agonists possess low intrinsic efficacies, they cannot stimulate a receptor-mediated response in the absence of a substantial receptor reserve. For example, when a full agonist (NPA) and partial agonist ((-)-3-PPP) are administered under high receptor reserve conditions, both drugs elicit a maximal tissue response that is indistinguishable from one another. Thus, with a large receptor reserve, partial D2-like agonists act like agonists (e.g., decrease DOPA accumulation). On the other hand, partial D2-like agonists act like antagonists (e.g., increase DOPA accumulation) when there is little or no receptor reserve.

In the present study, a partial D2-like agonist elicited agonist-like and antagonist-like effects under low and high dopaminergic tone, respectively. These results suggest that both acute and repeated reserpine treatment produced a large receptor reserve. Conversely, little or no receptor reserve was present after vehicle treatment.

When considered together, I believe that the receptor reserve theory better explains the results of the present study. This conclusion is largely drawn from results of the reserpine experiment (Experiment 1). According to Carlsson (1983), changes in receptor occupancy are only capable of slowly inducing a conformational change in the receptor. However, terguride caused similar effects in rats treated acutely or repeatedly with reserpine. Thus, reserpine must either be capable of inducing more rapid conformational changes than Carlsson suggests or the conformational theory cannot fully explain the present results.

Clinical Aspects of Partial D2-Like Agonists

Before partial D2-like agonists were commercially available to the public, D2-like antagonists were used to treat schizophrenia, motor dysfunction, and drug addiction (for a review, see Wetzell & Benkert, 1992). However, due to their severe side effects (e.g., vomiting, diarrhea, dizziness, drowsiness, and motor dysfunction), researchers have been searching for drugs that do not possess these types of extrapyramidal side effects.

Recently, partial DA agonists (e.g., aripiprazole, preclamol, terguride, SDZ 208-911, and SDZ 208-912) have drawn much clinical attention because of their unique ability to "normalize" dopamine functioning, without causing extrapyramidal side effects (Carson, Kane, Ali, Dunber, & Ingenito, 2000; Pulvirenti et al., 1998). Partial D2-like agonists alleviate drug withdrawal symptoms, decrease motor dysfunction, and reduce symptoms of schizophrenia and delusional disorders (for a review, see Benkert, Muller-Siecheneder, & Wetzell, 1995). For example, in a study using schizophrenic subjects, terguride reduced both positive and negative psychotic behaviors (Filip, Marsalek, Halkova, & Karen, 1991). In

addition, motor dysfunction was reduced after taking the same drug. More specifically, when terguride was given to patients with restless leg syndrome, symptomology was significantly reduced, and their restless leg syndrome symptoms were improved without major side effects (Sonka, Pretl, & Kranda, 2003). Therefore, the unique neurochemical properties of partial agonists (i.e., the ability to induce agonistic and antagonistic effects) have proven to be of great therapeutic benefit.

Conclusion

In preweanling rats, partial D2-like agonists act as agonists under low dopaminergic tone and as antagonists under high dopaminergic tone. This conclusion is based on experiments using the dopamine depleting agent reserpine and the impulse flow inhibitor GBL. Both of these drugs were able to create a state of low dopaminergic tone thus causing terguride to exhibit agonist (quinpirole-like) properties.

Results from the present thesis also indicate that dopamine autoreceptors are present and functional by PD 21. It remains unknown whether the responsiveness of partial

agonist drugs is altered by previous receptor occupancy (conformational theory) or changes in receptor reserve. Future investigation is necessary to determine which theory accurately explains the actions of partial D2-like agonists during the preweanling period.

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