2009

Role of dorsostriatal D1 and D2 receptors in modulating the kappa opioid-mediated locomotor activity of preweanling rats: Importance of synergistic activation

Sergios Charntikov

ROLE OF DORSOSTRIATAL D1 AND D2 RECEPTORS IN MODULATING THE KAPPA OPIOID-MEDIATED LOCOMOTOR ACTIVITY OF PREWEANLING RATS: IMPORTANCE OF SYNERGISTIC ACTIVATION

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

Sergios Charntikov

September 2009

ROLE OF DORSOSTRIATAL D1 AND D2 RECEPTORS IN MODULATING THE KAPPA OPIOID-MEDIATED LOCOMOTOR ACTIVITY OF PREWEANLING RATS: IMPORTANCE OF SYNERGISTIC ACTIVATION

A Thesis

Presented to the

Faculty of

California State University,

San Bernardino

---

by

Sergios Charntikov

September 2009

Approved by:

[redacted]

Dr. Sanders A. McDougall, Chair, Psychology

AUG 14, 2009
Date

[redacted]

Dr. Cynthia A. Crawford

[redacted]

Dr. Matt L. Riggs

ABSTRACT

Infusions of the nonselective dopamine agonist R(-)-propylnorapomorphine (NPA) into the dorsal striatum of preweanling rats attenuates kappa opioid-mediated locomotor activity. The purpose of this thesis was to ascertain which dopamine receptor subtype (D1 or D2) is responsible for this effect. It was hypothesized that a) D1, but not D2, receptors in the dorsal striatum underlie NPA's ability to attenuate the kappa opioid-mediated locomotor activity of preweanling rats, and b) microinjecting SKF38393 (a D1 agonist), and not quinpirole (a D2 agonist), would attenuate kappa opioid-mediated locomotion. To test these hypotheses, cannulae were bilaterally implanted into the dorsal striatum of preweanling rats on postnatal day (PD) 16. In Experiment 1, the dopamine receptor alkylating agent *N*-ethoxycarbonyl-2-ethoxy-1, 2-dihydroquinoline (EEDQ) was administered bilaterally into the dorsal striatum on PD 17 (EEDQ was not utilized in Experiment 2). On PD 18, NPA (Experiment 1) and SKF38393 or quinpirole (Experiment 2A) were infused into the dorsal striatum and the ability of these drugs to inhibit U50488 (a kappa opioid agonist) induced locomotor activity was measured. Results showed that a) EEDQ does not block NPA's ability to attenuate the

kappa opioid-mediated locomotor activity of preweanling rats, and b) neither SKF38393 nor quinpirole attenuated U50488-induced locomotion. These novel findings suggest that preweanling rats do not respond to dorsostriatal infusions of EEDQ in same manner as adult rats. Second, selective stimulation of D1 or D2 receptor is not responsible for attenuating the U50488-induced locomotor activity of preweanling rats. Our findings suggest that a synergistic interaction between dorsostriatal D1 and D2 receptors may be responsible for attenuating the kappa opioid-mediated locomotor activity of preweanling rats.

ACKNOWLEDGMENTS

I would like to thank Dr. Sanders A. McDougall for all the guidance and support that he has provided me during this thesis preparation and throughout my graduate studies. I am also very grateful for all the help and expertise that Dr. Cynthia A. Crawford has shared with me throughout this thesis and during my graduate work. I would also like to thank Dr. Matt L. Riggs for his support and advice during the thesis preparation.

TABLE OF CONTENTS

LIST OF FIGURES

CHAPTER ONE

INTRODUCTION

Behavior can vary qualitatively or quantitatively depending on the developmental stage in which it is assessed. These behavioral differences are often reflective of neurobiological changes in the central nervous system that take place across ontogeny. Understanding these neurobiological changes may provide important insight into a variety of developmental pathologies such as attention deficit hyperactivity disorder, pediatric bipolar disorder, pediatric obsessive-compulsive disorder, and Tourette's syndrome.

The basal ganglia is a prominent network of brain structures that modulates various behaviors, including motor control, motivation and reward, cognitive processes, and learning. The basal ganglia's neuronal circuitry undergoes substantial maturational changes, as the interaction of various neurotransmitter systems is responsible for many ontogenetic behavioral effects. One of the more prominent circuits within the basal ganglia is comprised of dopamine neurons of the nigrostriatal pathway. Stimulation of the dopamine system results in quantitatively different behavioral effects across

ontogeny. For example, psychostimulant treatment causes a more robust locomotor response in adult rats than preweanling animals (McDougall, Arnold, & Nonneman, 1990; McDougall, Duke, Bolanos, & Crawford, 1994; McDougall, Rodarte-Freeman, & Nazarian, 1999; Moody & Spear, 1992). Similarly, direct dopamine agonists produce progressively more robust behavioral effects as the animal matures (Broaddus & Bennett, 1990; Hedner & Lundborg, 1985; Lin & Walters, 1994; Moody & Spear, 1992; Shalaby & Spear, 1980).

In addition to the dopaminergic system, kappa opioid receptors play an important role in basal ganglia functioning. In comparison to the quantitative ontogenetic differences observed after dopaminergic stimulation, activation of kappa opioid receptors causes behavioral effects that vary qualitatively across ontogeny. One of the most compelling examples of a qualitative change in drug responsiveness is the paradoxical locomotor response after treatment with a selective kappa opioid agonist (e.g., U50488). Specifically, systemic administration of U50488 attenuates the locomotor activity of adult rats, while paradoxically causing a dramatic increase in the locomotion of preweanling rats (Collins et al., 1998; Collins, Zavala, Nazarian, & McDougall, 2000; Jackson &

Cooper, 1988; Leyton & Stewart, 1992; McDougall, Garmsen, Meier, & Crawford, 1997; Ukai & Kameyama, 1985).

During early ontogeny the kappa opioid and dopamine systems interact when modulating behavior. For example, the kappa opioid-mediated locomotor activity of preweanling rats can be attenuated by systemic administration of a dopamine agonist (e.g., NPA) (Duke, Meier, Bolanos, Crawford, & McDougall, 1997; McDougall et al., 1997, 1999; Nazarian, Rodarte-Freeman, & McDougall, 1999). Moreover, microinjecting NPA into the dorsal striatum is able to attenuate kappa opioid-induced locomotor activity of young rats (Charntikov, Halladay, Herbert, Marquez, & McDougall, 2008). Although the output structures involved in this behavior have been determined, the input pathways responsible for this kappa opioid/dopamine interaction have not been identified. Thus, the purpose of this thesis is to further investigate how dopaminergic input pathways regulate the kappa opioid-mediated locomotor activity of preweanling rats.

CHAPTER TWO

KAPPA OPIOID RECEPTORS

Introduction

Opioid receptors are seven transmembrane G-protein coupled receptors originally discovered in the early 1970s using radioligand binding techniques (Pert & Snyder, 1973; Simon, Hiller, & Edelman, 1973; Terenius, 1973). These early studies demonstrated that endogenous opioid peptides and opiates, such as morphine, act as ligands at opioid receptors and exert specific pharmacological and physiological effects. The pharmacological activity of these receptors, in particular the inability of nalorphine to antagonize various narcotic analgetics in a uniform manner, indicated the presence of receptor subtypes (Gilbert & Martin, 1976; Martin, Eades, Thompson, Huppler, & Gilbert, 1976). Based on different pharmacological actions of various ligands (morphine, ketocyclazocine, and enkephalin), three types of opioid receptors were proposed to exist - mu, kappa, and delta. Thereafter, molecular cloning of mu, kappa, and delta receptors has been completed (Chen, Mestek, Liu, Hurley, & Yu, 1993; Evans, Keith, Morrison, Magendzo, & Edwards, 1992; Fukuda, Kato, Mori, Nishi, & Takeshima, 1993; Kieffer, Befort,

Gaveriaux-Ruff, & Hirth, 1992; Li et al., 1993; Meng et al., 1993; Nishi, Takeshima, Fukuda, Kato, & Mori, 1993). In addition, other opioid receptors (X, ε, and orphan) have been identified and cloned (Marchese et al., 1994; Mollereau et al., 1994; Wang et al., 1994).

Based on hydrophobicity studies of opioid receptors, it has been established that opioid receptors are composed of seven transmembrane domains: a typical attribute of the G-protein coupled receptor family. Amino acid sequences of three cloned rodent opioid receptors are approximately 65% identical and exhibit significantly more similarities in the transmembrane regions than elsewhere (Reisine & Bell, 1993). This category of G-protein coupled receptors functions by activation or blockade of effector systems such as adenylyl cyclase, Ca^{2+} channels, K^{+} channels, or phosphoinositol turnover (Chen et al., 1993; Cox, 1993; North, 1993; Reisine & Bell, 1993; Tallent, Dichter, Bell, & Reisine, 1994; Yasuda et al., 1992). In addition, kappa opioid receptors localized in brain are able to influence N-type calcium currents, thus altering the ability of kappa agonists and dynorphin A to presynaptically inhibit neurotransmitter release (Gross & Macdonald, 1987; North, 1993).

Kappa Opioid Receptor Subtypes

Kappa opioid receptors were originally discovered utilizing *in vivo* pharmacological techniques (Martin et al., 1976). Cloning of kappa opioid receptors revealed their high affinity for exogenous and endogenous compounds such as dynorphin A, U50488, U69593, but not to the mu selective agonist DAMGO (D-Ala2, N-MePhea, Gly-olS-enkephalin) or the delta selective agonist DPDPE (D-Pen2, D-PenS-enkephalin) (Chavkin, James, & Goldstein, 1982; Fischli, Goldstein, Hunkapiller, & Hood, 1982; Goldstein, Tachibana, Lowney, Hunkapiller, & Hood, 1979; Kawasaki et al., 1993; Lemaire, Chouinard, Denis, Panico, & Morris, 1982). Kappa opioid receptors have at least two subtypes - κ_1 and κ_2 (Zukin, Eghbali, Olive, Unterwald, & Tempel, 1988). Kappa opioid ligands such as dynorphin A, U50488, bremzocine, thylketocyclazocine, and tifluadom bind to both κ_1 and κ_2 sites, while U69593 binds selectively to κ_1 sites and not to κ_2 sites (Zukin et al., 1988). At present, there are no selective κ_2 receptor ligands. Moreover, a third kappa binding site (κ_3) has been proposed and is characterized by high affinity to naloxone benoylhydrazone and low affinity for U50488 (Clark et al., 1989).

Kappa Opioid Receptor Localization

Kappa opioid receptor localization studies have been performed using standard autoradiographic techniques (Mansour, Khachaturian, Lewis, Akil, & Watson, 1987; Nock, Rajpara, O'Connor, & Cicero, 1988; Quirion, Pilapil, & Magnan, 1987). These studies utilize radiolabeled ligands to visualize kappa opioid receptors in brain slices. Results of these studies revealed that kappa opioid receptor populations are concentrated in the following areas of the brain: striatum, nucleus accumbens, superior colliculus, substantia nigra, and cerebral cortex. Localization of kappa opioid receptors in rat, mouse, and guinea pig brain has also been studied using *in situ* hybridization histochemistry (DePaoli, Hurley, Yasada, Reisine, & Bell, 1994; Mansour, Fox, Meng, Akil, & Watson, 1994; Minami et al., 1993; Xie et al., 1994). In rat brain, the distribution of kappa opioid receptor mRNA is high in the telencephalic regions of the brain, especially in the medial striatum and nucleus accumbens, with the exception of the globus pallidus where relatively low levels of kappa opioid receptor mRNAs were detected. In comparison, kappa opioid receptor mRNA varies from low to moderate levels in the septal nucleus, while cortical regions show intense signals in the VI layer of the

parietal, temporal, and occipital cortices. There are also high levels of kappa opioid receptor mRNA in amygdaloid nuclei.

In the rat diencephalon, kappa opioid receptor mRNA is dense in the paraventricular and supraoptic hypothalamic nuclei (Leander, Zerbe, & Hart, 1985). Furthermore, high concentrations of kappa opioid receptor mRNA have been detected in the dorsomedial and ventromedial hypothalamic nuclei (Olson, Olson, & Kastin, 1992). Mesencephalic regions of the rat brain express high levels of kappa opioid receptor mRNA in the substantia nigra and ventral tegmental area (Mansour, Hoversten, Taylor, Watson, & Akil, 1995; Mansour, Khachaturian, Lewis, Akil, & Watson, 1988; McLean, Rothman, & Herkenham, 1986). These brain regions give rise to dopaminergic pathways that project to the striatum, globus pallidus, nucleus accumbens, amygdala, and cerebral cortex (Le Moine & Bloch, 1995; Le Moine et al., 1990; Werling, Frattali, Portoghese, Takemori, & Cox, 1988). Finally, moderate levels of kappa opioid receptor mRNA have been found in the superior and inferior colluculi (Millan, Czlonkowski, Lipkowski, & Herz, 1989).

Kappa Opioid Receptor Ligands

Two families of ligands interact with opioid receptors: alkaloids and peptides (for a review, see Janecka, Fichna, & Janecki, 2004). Morphine is the oldest known alkaloid agonist, a compound which is derived from poppy seeds (Gulland & Robinson, 1923). Morphine and other alkaloid opiate agonists are commonly used to induce analgesia. In pharmacological studies, alkaloid agonists, and morphine specifically, are ligands that target mu opioid receptors with much higher affinity than delta or kappa opioid receptors (Takemori & Portoghese, 1987). Alkaloid antagonists include naloxone and naltrexone (Blumberg & Dayton, 1974). While both of these opioid antagonists are nonselective (i.e., they target all three opioid receptors) they have much higher affinity for the mu receptor (Magnan, Paterson, Tavani, & Kosterlitz, 1982). Consequently, for a ligand to be characterized as an opioid agonist its agonistic actions have to be "naloxone-reversible" (Leslie, 1987).

Peptide opioid receptor ligands have been divided into two categories - typical and atypical (Teschemacher, 1993). The typical opioid peptide receptor ligands include enkephalins, β-endorphin, and dynorphins. These ligands vary in their affinity for the three main opioid receptors

and all exhibit nonspecific properties by binding to more than one receptor type. In particular, [Met]- and [Leu]-enkephalin express much higher affinity for delta receptors than for kappa or mu receptors (Mansour et al., 1995; Mulder, Wardeh, Hogenboom, & Frankhuyzen, 1989; Schoffelmeer, Warden, Hogenboom, & Mulder, 1991). β-Endorphin binds with equal affinity to both mu and delta opioid receptors, while binding with much lesser affinity to the kappa receptor (Hollt, Sanchez-Blazquez, & Garzon, 1985). Furthermore, dynorphin A and B bind with high affinity to the kappa receptor and with lower affinity to mu and delta opioid receptors. The atypical opioid peptide ligands derive from various protein sources, such as milk, blood protein, hemoglobin, and even amphibian skin (Brantl, Teschemacher, Henschen, & Lottspeich, 1979; Lazarus, Bryant, Cooper, & Salvadori, 1999; Montecucchi, de Castiglione, Piani, Gozzini, & Erspamer, 1981; Nyberg, Sanderson, & Glamsta, 1997).

Kappa opioid receptor ligands can be divided into two categories: agonists and antagonists. Kappa opioid agonists are derived from the heptadecapeptide dynorphin A family of putative endogenous ligands for kappa opioid receptors (Chavkin et al., 1982). These ligands are nonselective agonists and bind to mu and delta receptors

with high affinity. At present, there is a limited pool of kappa opioid ligands with antagonistic properties (Gairin et al., 1988; Lemaire & Turcotte, 1986; Wan, Murray, & Aldrich, 1999). Among the notable nonpeptide kappa opioid antagonists are *nor*-binaltorphimine, 5'-guanidinonaltrindole (GNTI), and dynantin (Bennett, Murray, & Aldrich, 2002; Jones, Hjorth, Schwartz, & Portoghese, 1998; Larson, Jones, Hjorth, Schwartz, & Portoghese, 2000; Lin, Takemori, & Portoghese, 1993; Lu et al., 2001). These ligands exhibit both high selectivity and high affinity for kappa opioid receptors. Notably, dynantin is a relatively new and potent kappa opioid antagonist with subnanomolar kappa antagonistic potency (Lu et al., 2001).

Ontogeny of Kappa Opioid Receptors

The presence of kappa opioid receptors can be detected as early as the 14^{th} day of gestation in both mouse and rat brain (Kent, Pert, & Herkenham, 1981; Rius, Barg, Bem, Coscia, & Loh, 1991). A number of studies have investigated the ontogenesis of kappa opioid receptors and have reported somewhat consistent results (Kitchen, Kelly, & Viveros, 1990; Petrillo, Tavani, Verotta, Robson, & Kosterlitz, 1987; Volterra, Brunello, Restani, Galli, &

Racagni, 1986). Specifically, it has been shown that the number of kappa opioid receptors in neonatal rats (PD 4), as revealed through Scatchard analysis, is comparable to those of adults (Kitchen et al., 1990). However, further analysis revealed that the number of kappa opioid receptors is significantly higher (approximately 7-fold increase) on PD 10 in comparison to PD 5 (Kitchen et al., 1990). Kappa opioid receptor numbers remain consistently high until PD 20 after which a gradual decline is apparent, reaching adult like numbers on PD 30 (Kitchen et al., 1990). The time-course of these quantitative changes is comparable for both κ_1 and κ_2 opioid receptors (Petrillo et al., 1987; Spain, Roth, & Coscia, 1985; Tavani, Robson, & Kosterlitz, 1985).

Localization studies have shown that by late gestation the pattern of kappa opioid receptor distribution is comparable to that of adults (Zhu, Hsu, & Pintar, 1998). In particular, studies utilizing *in situ* hybridization have confirmed that kappa opioid receptors are present in rodent basal ganglia, thalamus, hypothalamus, raphe, and the ventral tegmental area during the mid- and late-gestation period (Zhu et al., 1998). Radioligand binding studies have reported similar results, with high densities of both κ_1 and κ_2 opioid receptors

being present in the striatum, nucleus accumbens, olfactory tubercle, amygdala, substantia nigra, midbrain, and ventral tegmental area (Kornblum, Hurlbut, & Leslie, 1987; Unterwald, Knapp, & Zukin, 1991).

Endogenous and exogenous opioid ligands are capable of affecting cell growth and functioning of the developing central nervous system (Crofford & Smith, 1973; Meriney, Gray, & Pilar, 1985; Simon, 1971; Slotkin, Seidler, & Whitmore, 1980; Smith, Hui, & Crofford, 1977; Zagon & McLaughlin, 1977, 1983). In fact, the endogenous neurotransmitter is necessary for the appropriate development of various receptor types (Mattson, 1988; Stiene-Martin, Mattson, & Hauser, 1993; Zagon & McLaughlin, 1983, 1987). Specifically, the appearance of peptides and opioid receptors has a close temporal relation, thus indicating a functional role for opioid ligands in opioid receptor development (Meriney et al., 1985; Zagon & McLaughlin, 1983). These findings suggest that kappa opioid receptors are functional during the prenatal period and continue to mature across neonatal stages (Herman & Panksepp, 1978; Jackson & Sewell, 1984; Panksepp, Siviy, Normansell, White, & Bishop, 1982).

CHAPTER THREE

DOPAMINE RECEPTORS

Introduction

Dopamine is a chemical compound which functions as a neurotransmitter and as a neurohormone in a variety of organisms. Dopamine is a member of the catecholamine family that derives from the amino acid tyrosine and is itself a precursor to norepinephrine and epinephrine (Hess, Connamacher, Ozaki, & Udenfriend, 1961; Kaufman & Friedman, 1965; Levin, Levenberg, & Kaufman, 1960; Levitt, Spector, Sjoerdsma, & Udenfriend, 1965; Nagatsu, Levitt, & Udenfriend, 1964). Synthesis of dopamine occurs in nervous tissue and adrenal glands where the essential amino acid tyrosine is converted to DOPA through enzymatic reactions involving tyrosine hydroxylase. DOPA decarboxylase then converts DOPA to dopamine (Kandel, Schwartz, & Jessell, 2000). In the central nervous system, dopamine cell bodies are primarily located in the olfactory bulb, substantia nigra, ventral tegmental area, and hypothalamus (Calabresi et al., 2000; Montmayeur, Guiramand, & Borrelli, 1993; Snyder, Roberts, & Sealfon, 1991). Three major dopaminergic pathways originate from the substantia nigra and the ventral tegmental area: 1) the nigrostriatal

pathway, which is involved in motor control; 2) the mesolimbic pathway, which is involved in reward and motivation; and 3) the mesocortical pathway, which is involved in motivation and emotional processes.

Structure and Subtypes of Dopamine Receptors

Dopamine stimulates five dopamine receptor subtypes - D_1, D_2, D_3, D_4, and D_5 (Seeman & Van Tol, 1994). These five dopamine receptors can be categorized into two distinct families: D1 - which includes the D_1 and D_5 subtypes, and D2 - which includes the D_2, D_3, and D_4 subtypes. These two distinct families of dopamine receptors are classified based on their molecular properties. All known dopamine receptors are G-protein coupled receptors and their activation can either stimulate or inhibit adenylyl cyclase activity (Clark & White, 1987; Stoof & Kebabian, 1981). D1 receptor activation typically stimulates adenylyl cyclase and results in an excitatory cellular response, while D2 receptor activation leads to an inhibitory cellular response due to depression of adenylyl cyclase activity (Clark & White, 1987; Stoof & Kebabian, 1981). Specifically, activation of D1 receptors leads to the disengagement of the G-protein from its original site resulting in the stimulation of adenylyl cyclase and, as a

consequence, increased levels of the second messenger cyclic adenosine monophosphate (cAMP). Elevated levels of cAMP usually cause an excitatory response in the cell. Conversely, stimulation of the D2 family of dopamine receptors (D_2, D_3, and D_4) attenuates cellular responsiveness, because activation of an inhibitory G-protein leads to elevated levels of phosphodiesterase which breaks down cAMP (Clark & White, 1987; Stoof & Kebabian, 1981).

Distribution of Dopamine Receptors

Dopamine receptor localization studies employ various neurochemical techniques, including autoradiography and mRNA isolation. Autoradiographic studies provide compelling evidence for the regional distribution of dopamine receptors in the central nervous system. In particular, both D1 and D2 receptors are present in the striatum and nucleus accumbens of mammalian brain (Baldessarini & Tarazi, 1996; Tarazi, Campbell, Yeghiayan, & Baldessarini, 1998). Furthermore, radioligand binding studies have been able to localize dopamine receptors on pre- and postsynaptic elements. Specifically, D1 and D2 receptors are predominantly located on postsynaptic

neurons within the striatum and nucleus accumbens (Tarazi et al., 1998).

D_1 dopamine receptors are the most common subtype among the dopamine family (Dearry et al., 1990; Fremeau et al., 1991). D_1 receptor mRNA has been found in the striatum, nucleus accumbens, and olfactory tubercle (Gerfen et al., 1990; Le Moine, Normand, & Bloch, 1991). D_1 receptors are also present in the substantia nigra pars reticulata and entopeduncular nucleus, even though no D_1 receptor mRNA has been found in these structures (Dearry et al., 1990; Fremeau et al., 1991; Gerfen & Engber, 1992; Le Moine et al., 1991; Weiner et al., 1991). This discrepancy is due to the absence of dopamine cell bodies in the substantia nigra pars reticulata and entopeduncular nucleus and the presence of neuronal projections containing D_1 receptors. In fact, a number of studies have traced D_1 bearing projections to striatal GABAergic neurons that coexpress substance P (Gerfen & Engber, 1992; Le Moine et al., 1991).

D_5 receptors, in comparison to D_1 receptors, exist in significantly smaller populations and are mainly found in the hippocampus, lateral mamillary nucleus, and the parafascicular nucleus of the thalamus (Meador-Woodruff et al., 1992; Tiberi et al., 1991). In addition to these

structures, D_5 receptor mRNA is found in the striatum, substantia nigra, hippocampus, thalamus, and cerebral cortex (Huntley, Morrison, Prikhozhan, & Sealfon, 1992; Rappaport, Sealfon, Prikhozhan, Huntley, & Morrison, 1993).

D_1 and D_5 receptors are frequently colocalized on pyramidal neurons located in the prefrontal, premotor, entorhinal, and cingulate cortices. Both D_1 and D_5 receptors occur pre- and postsynaptically, with postsynaptic localization being more prevalent (Huang et al., 1992; Levey et al., 1993). Within individual pyramidal neurons, D_1 receptors tend to be located on dendritic spines, while D_5 receptors are primarily localized on dendritic shafts (Bergson et al., 1995; Smiley, Levey, Ciliax, & Goldman-Rakic, 1994). Although the pharmacological properties of D_1 and D_5 receptors are analogous their function partially depends on their dendritic localization.

The D2 family of dopamine receptors are G-protein coupled receptors that inhibit adenylyl cyclase activity. The D_2 receptor is predominantly located in the striatum, olfactory tubercle, and nucleus accumbens core, where it is expressed by neurons that co-release GABA and enkephalin (Bouthenet et al., 1991; Le Moine & Bloch,

1995; Le Moine et al., 1990). D_2 receptors can also be found in the shell of the nucleus accumbens, where they are expressed by GABAergic neurons that co-release neurotensin (Diaz et al., 1994). Cell bodies of neurons bearing D_2 receptors have been traced to various cortical areas (prefrontal, temporal, motor, somatosensory, posterior parietal, and occipital), septal nuclei, amygdala, and granule cells of the hippocampal formation (Bouthenet et al., 1991). D_2 receptor mRNA is also present in dopaminergic neurons located in the hypothalamus, substantia nigra pars compacta, and ventral tegmental area (Bouthenet et al., 1991; Weiner et al., 1991). Immunohistochemical analysis of D_2 receptors reveals that they are expressed by GABAergic medium spiny neurons of the striatum, with D_2 receptors being precisely positioned in spiny dendrites and spiny heads (Levey et al., 1993).

The D_3 receptor is located in a number of limbic areas, such as the ventromedial thalamus shell of the nucleus accumbens, olfactory tubercle, and islands of Calleja (Bouthenet et al., 1991; Diaz et al., 1994; Levesque et al., 1992). In addition, relatively low levels of D_3 receptors are detected in the hippocampus, septal area, medial temporal lobe, and a number of cortical areas (Bouthenet et al., 1991). In comparison, D_3 receptor mRNA

has been found in the substantia nigra pars compacta, the ventral tegmental area, and the cerebellum (Diaz et al., 1994, 1995).

The D_4 receptor is found in high levels in frontal cortex, hippocampus, amygdala, hypothalamus, and the mesencephalon (O'Malley, Harmon, Tang, & Todd, 1992; Van Tol et al., 1991). In contrast, low levels of D_4 receptor mRNA are detected in the basal ganglia (O'Malley et al., 1992; Van Tol et al., 1991). Immunohistochemical analysis of D_4 receptors in the cerebral cortex and hippocampus revealed that this receptor subtype is endogenous to GABAergic interneurons, both pyramidal and nonpyramidal, that modulate GABAergic transmission within those brain regions (Mrzljak et al., 1996).

Colocalization of D1 and D2 Receptors

The striatum gives rise to two distinct populations of GABAergic neurons that disproportionately contain D1 and D2 dopamine receptors (Bloch & Le Moine, 1994; Gerfen & Keefe, 1994). GABAergic neurons projecting to the substantia nigra and entopeduncular nucleus (i.e., striatonigral neurons) predominantly express D1 receptors and co-release substance P and dynorphin (Gerfen et al., 1990; Yung et al., 1995). In contrast, D2 receptors

preferentially occur on GABAergic neurons that project to the globus pallidus (i.e., striatopallidal neurons) and corelease enkephalin (Gerfen et al., 1990; Yung et al., 1995). Although numerical assessment varies, most studies agree that the majority of striatopallidal neurons express both D1 and D2 receptors, with D2 receptors predominating. Striatonigral neurons exhibit the opposite characteristics, because they possess both D1 and D2 receptors, with the majority of receptors being D1 (Aizman et al., 2000; Deng, Lei, & Reiner, 2006; Hersch et al., 1995b; Surmeier et al., 1992; Surmeier, Reiner, Levine, & Ariano, 1993). These findings have been confirmed by electrophysiological studies measuring Ca^{2+} and Na^{+} currents within striatal neurons (Cepeda, Buchwald, & Levine, 1993; Surmeier et al., 1992).

Dopamine Receptor Stimulation and Dopamine Transmission

Neurons are capable of expressing dopamine receptors on both pre- and postsynaptic elements. On nigrostriatal dopamine terminals, presynaptic D2 receptors are called autoreceptors because of their ability to regulate the synthesis and release of dopamine from the terminal. Stimulation of synthesis-modulating D2 autoreceptors, via dopamine agonists or endogenous dopamine, activates a

second messenger system that decreases dopamine synthesis (Stoof & Kebabian, 1984; Surmeier et al., 1992). Release-modulating D2 autoreceptors, on the other hand, alter dopamine release by regulating Ca^{2+} and K^{+} conductance (Bigornia et al., 1990; Lacey, Mercuri, & North, 1987). Blockade of D2 autoreceptors either increases dopamine synthesis or release depending on the type of autoreceptor affected (Hakansson et al., 2004; Stoof & Kebabian, 1984).

Activation of postsynaptic D2 receptors depresses adenylyl cyclase activity and results in an inhibitory response (Clark & White, 1987; Stoof & Kebabian, 1981). Stimulation of postsynaptic D2 receptors, which predominate on striatal medium spiny neurons projecting to the globus pallidus, causes inhibitory postsynaptic potentials in the distal neurons (Mottola et al., 2002). Stimulation of postsynaptic D1 receptors, which are predominantly located on striatal neurons projecting to the substantia nigra and endopeduncular nucleus, typically increases adenylyl cyclase activity and results in excitatory postsynaptic potentials (Pereda, Triller, Korn, & Faber, 1992; Seamans, Durstewitz, Christie, Stevens, & Sejnowski, 2001). In summary, dopamine exerts an inhibitory effect by stimulating postsynaptic D2 receptors

located on striatopallidal neurons (which comprise the indirect pathway); whereas, dopamine has an excitatory effect by stimulating postsynaptic D1 receptors located on striatonigral neurons (which comprise the direct pathway).

Ontogeny of Dopamine Receptors

Dopamine neurons start developing at embryonic day 12, with the initial topographical epicenter being the midbrain and medial forebrain bundle (Gates, Coupe, Torres, Fricker-Gates, & Dunnett, 2004; Nakamura, Ito, Shirasaki, & Murakami, 2000; Smidt & Burbach, 2007). Dopamine neurons originating from the substantia nigra and ventral tegmental area complete striatal innervation around embryonic day 19 and cortical innervation by the end of the first postnatal week (Kalsbeek, Voorn, Buijs, Pool, & Uylings, 1988; Specht, Pickel, Joh, & Reis, 1981; Van Eden et al., 1987; Voorn, Kalsbeek, Jorritsma-Byham, & Groenewegen, 1988). Dopamine can be detected in the rat embryo as early as the second half of the gestation period (Golden, 1973; Lauder & Bloom, 1974).

Studies examining D1 receptor development in striatal regions have reported contradictory results ranging from: a) a gradual increase of D1 receptors from birth to adulthood; b) a gradual increase of D1 receptors from

birth to postnatal days 35-40, followed by a gradual decrease of receptors (pruning) into adulthood; to c) no age-dependent changes in receptor numbers (Broaddus & Bennett, 1990; Gelbard, Teicher, Faedda, & Baldessarini, 1989; Giorgi et al., 1987; Murrin & Zeng, 1990; Zeng, Hyttel, & Murrin, 1988). Although there is a lack of consensus about prenatal and postnatal development of D1 receptors, there is agreement about the modulators of that development. A number of studies have confirmed that receptor stimulation during development is necessary for the proper maturation of the system. Support for this hypothesis is two- fold: a) normal development of D1 receptors is disrupted by removal of endogenous dopamine using 6-hydroxydopamine, and b) normal postnatal development of D1 receptors, following 6-hydroxydopamine treatment, is reinstated by administration of the D1 agonist SKF38393 (Frohna, Neal-Beliveau, & Joyce, 1995; Gelbard et al., 1990; Neal & Joyce, 1992; Teicher et al., 1991). Thus, stimulation of D1 receptors via either endogenous or exogenous ligands is sufficient and necessary for their normal development.

Studies examining D2 receptor proliferation during prenatal and postnatal stages typically focus on the striatal complex in the rat. Using the *in situ*

hybridization technique of localizing mRNA signals in developing rat brain, it has been shown that D2 dopamine receptor mRNA can be detected in the prenatal striatum as early as gestation day 14 with further proliferation peaking at PD 16, followed by a slight decline into adulthood (Chen & Weiss, 1991). However, a more precise estimation of D2 dopamine receptors, employing receptor autoradiography, shows a gradual increase from low levels at birth to adult levels by PD 30 (Chen & Weiss, 1991; Hartley & Seeman, 1983; Pardo, Creese, Burt, & Snyder, 1977; Rao, Molinoff, & Joyce, 1991; Schambra et al., 1994). Unlike D1 receptors, D2 receptors seem to proliferate independent of endogenous dopaminergic stimulation, although development of D2 receptors can be impaired by spiperone (a D2 receptor antagonist) administed from birth to postnatal day 32 (Breese et al., 1987; Kostrzewa & Saleh, 1989; Neal & Joyce, 1992; Thomas, Neal-Beliveau, & Joyce, 1998).

The dopamine system is a complex and important mediator of a variety of neurochemical and physiological mechanisms. Understanding the processes underlying the development of the dopamine system can elucidate a number of pathologies involving neural networks. Efforts have been made to explicate the ontogeny of the dopamine

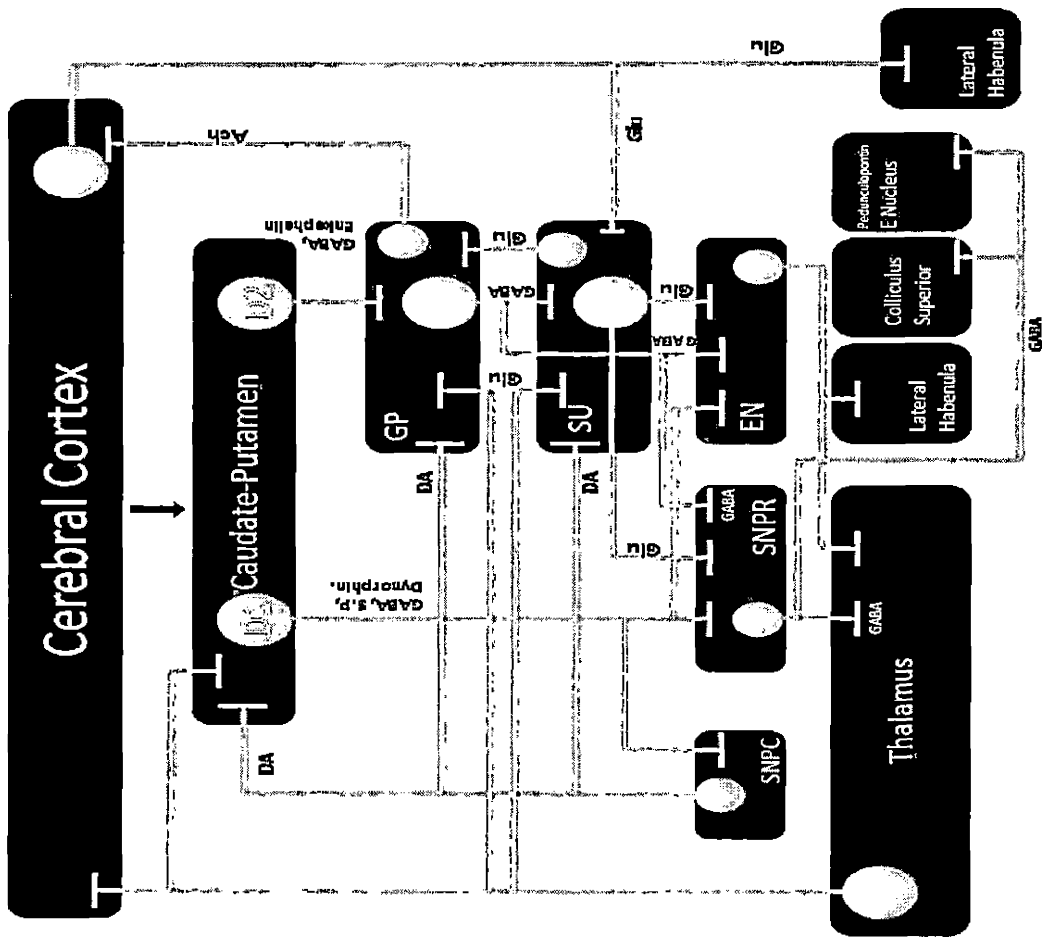
system, including the development and functioning of receptors, the role of endogenous and exogenous ligands, and the extent of neuronal proliferation. Although studies have occasionally yielded inconsistent results, it is clear that the dopamine system develops rapidly during early ontogeny and continues to mature across the preweanling period.

CHAPTER FOUR

BASAL GANGLIA

Introduction

The basal ganglia is a group of nuclei found in the telencephalon, diencephalon, and midbrain which are interconnected through a set of networks with the cerebral cortex, thalamus, and brain stem (see Figure 1) (Hauber, 1998; Mello & Villares, 1997). It is thought that the basal ganglia evolved from a relatively simple motor structure to a complex system that is not only responsible for a variety of motor behaviors but also plays a cardinal role in cognition, learning, reward, and motivation (Albin, Young, & Penney, 1989; Graybiel, Aosaki, Flaherty, & Kimura, 1994; Kimura, 1995; Knowlton, Mangels, & Squire, 1996; Schultz, 1994). The basal ganglia is composed of a group of structures interconnected through a series of reciprocal regulatory pathways. Anatomical structures comprising the basal ganglia vary from species to species, but typically consist of the striatum (caudate and putamen), globus pallidus, subthalamic nucleus, entopeduncular nucleus, and the substantia nigra (Hauber, 1998; McGeorge & Faull, 1989; Parent & Hazrati, 1994). The striatum is a critical relay station that mainly receives



The striatonigral (direct) pathway projects from the caudate-putamen to the substantia nigra pars reticulata and entopeduncular nucleus. The striatopallidal (indirect) pathway projects from the caudate-putamen and carries signals via GABAergic connections to the globus pallidus and, subsequently, to the substantia nigra pars reticulata and entopeduncular nucleus by way of the subthalamic nucleus. GP, globus pallidus; SU, subthalamic nucleus; EN, entopeduncular nucleus; SNPR, substantia nigra pars reticulata; SNPC, substantia nigra pars compacta; DA, dopamine; ACh, acetylcholine; Glu, glutamate; S.P., substance P. Partially adapted from Hauber (1998).

Figure 1. The Circuitry of the Basal Ganglia

input from the cerebral cortex. This input is further relayed, via the direct and indirect pathways, to the major processing and output areas. Processing areas, such

as the globus pallidus and subthalamic nucleus, receive signals from the striatum and redistribute them to the major basal ganglia output areas - entopeduncular nucleus and substantia nigra pars reticulata (see Figure 1). In turn, the substantia nigra pars compacta provides dopaminergic innervation to the striatum, globus pallidus, and subthalamic nucleus. Output from the entopeduncular nucleus and substantia nigra pars reticulata is distributed to major motor areas, such as motor nuclei of the brainstem, via the thalamus and cortical motor areas.

Striatum

The striatum (caudate-putamen) is a chief component of basal ganglia circuitry due to the fact that it relays signals received from the cerebral cortex to major processing (globus pallidus and subthalamic nucleus) and output structures of the basal ganglia (substantia nigra pars reticulata and entopeduncular nucleus) via the striatonigral (direct) and striatopallidal (indirect) pathways (Bolam, Hanley, Booth, & Bevan, 2000; Fisone, Håkansson, Borgkvist, & Santini, 2007; Hauber, 1998). The striatonigral pathway is composed predominantly of D1 bearing neurons (D2 receptors are coexpressed in lower concentrations) that originate in the striatum and project

to the substantia nigra pars compacta along with the entopeduncular nucleus. These striatonigral neurons corelease GABA, substance P, and dynorphin (Gerfen, 1992).

In addition, the striatum connects with the globus pallidus via neurons that corelease GABA and enkephalin (Fink et al., 1992; Gerfen, 1992; Schiffmann, Jacobs, & Vanderhaeghen, 1991). These striatopallidal neurons express D2 receptors (D1 receptors are coexpressed in lower concentrations) and form the initial part of the indirect pathway, which further extends to the substantia nigra pars reticulata and the entopeduncular nucleus by way of the subthalamic nucleus (Hauber, 1998). Although the direct pathway is activated by D1 receptor stimulation and the indirect pathway is inhibited by D2 receptor stimulation, there is a small degree of colocalization of these receptors on neurons forming either pathway (Aizman et al., 2000; Deng et al., 2006; Hersch et al., 1995b; Surmeier et al., 1992, 1993).

The functioning of striatal neurons is affected by a number of neurotransmitters and modulators. For instance, the neuronal activity of D1 expressing neurons can be regulated pre- and postsynaptically via dynorphin, while the functional properties of the dopamine receptor can be affected by the neuromodulator adenosine (Ferre et al.,

1996; Steiner & Gerfen, 1996). In comparison, D2 expressing neurons of the indirect pathway can be modulated by stimulating adenosine A_{2A} receptors in the striatum (Ferre, O'Connor, Fuxe, & Ungerstedt, 1993; Ferre et al., 1996). Activity of both the direct and indirect pathways is also affected by serotonergic inputs from the dorsal nucleus of the raphe and caudal linear nucleus (Imai, Steindler, & Kitai, 1986; Soghomonian, Descarries, & Watkins, 1989; Vertes, 1991). Finally, it is important to note that the striatal neurons forming the direct and indirect pathway can be influenced by small intrinsic interneurons releasing acetylcholine (Di Chiara, Morelli, & Consolo, 1994).

Globus Pallidus

The globus pallidus is part of a signal processing network in the core of the basal ganglia. Major input to the globus pallidus is provided via striatal GABA and enkephalin releasing neurons making up the indirect pathway. In addition to these striatopallidal corrections, the globus pallidus receives glutamatergic input from the thalamus and subthalamic nucleus (Feger, 1997). Dopamine receptors are also present in the globus pallidus (Richfield, Young, & Penney, 1987) and are activated by

dopamine released from neurons projecting from the substantia nigra pars compacta (Lindvall & Bjorklund, 1979). The globus pallidus sends signals to most basal ganglia structures via GABAergic outputs. The subthalamic nucleus, substantia nigra pars reticulata, and the entopeduncular nucleus are among those brain areas influenced by the globus pallidus through its inhibitory transmission (Carter & Pycock, 1978; DeVito & Anderson, 1982; DeVito, Anderson, & Walsh, 1980; Parent & Hazrati, 1995). In addition to the GABAergic outputs, the globus pallidus gives rise to cholinergic neurons that project to the cortex (Heimer, Zahm, & Alheid, 1995). Overall, the globus pallidus is in a unique position to control a wide variety of basal ganglia functions because of its (a) direct connections to the substantia nigra pars compacta and the entopeduncular nucleus, (b) indirect projections to proximal areas via the subthalamic nucleus, and (c) its inhibitory connections with thalamic nuclei.

Subthalamic Nucleus

The subthalamic nucleus receives most of its incoming projections in the form of glutamatergic input (Fujimoto & Kita, 1993) from pyramidal cell collaterals (Ryan & Clark, 1991). These pyramidal cells primarily project from

frontal areas of the cerebral cortex (Canteras, Shammah-Lagnado, Silva, & Ricardo, 1990). Additional input to the subthalamic nucleus comes in the form of inhibitory GABAergic signals from the globus pallidus (Feger, 1981) and dopaminergic signals from the substantia nigra pars compacta (Hassani, Francois, Yelnik, & Feger, 1997). Output from the subthalamic nucleus is predominantly excitatory in nature and is mediated by glutamatergic neurons. The subthalamic nucleus uses this excitatory output to communicate with the globus pallidus, substantia nigra pars reticulata, and entopeduncular nucleus. Many of these outputs originate from the same population of neurons and further collateralize to different locales (Deniau, Hammond, Riszk, & Feger, 1978). Thus, the subthalamic nucleus is structurally and functionally situated to modulate basal ganglia functioning through signal processing and relaying signals between input and output areas.

Substantia Nigra Pars Reticulata

The substantia nigra pars reticulata is one of two basal ganglia output structures (the other being the entopeduncular nucleus). It plays an important role in controlling motor related behavior because of its

GABAergic connections with various premotor structures, including the thalamus, superior colliculus, and the pedunculopontine tegmental nucleus (Deniau & Chevalier, 1992; Gerfen, Staines, Arbuthnott, & Fibiger, 1982; Kita & Kitai, 1987; Nakanishi, Kita, & Kitai, 1987). The two major inputs to the substantia nigra pars reticulata are the striatonigral (direct) and the striatopallidal (indirect) pathways. As previously mentioned, neurons comprising the striatonigral pathway originate in the caudate-putamen and corelease GABA, dynorphin, and substance P (Chevalier & Deniau, 1990). In contrast, GABA neurons of the striatopallidal pathway corelease enkephalin (Fink et al., 1992; Schiffmann et al., 1991).

The striatopallidal pathway projects from the striatum to the substantia nigra pars reticulata by way of the globus pallidus and subthalamic nucleus. Specifically, the substantia nigra pars reticulata is modulated by excitatory glutamatergic inputs from the subthalamic nucleus (Hammond, Deniau, Rizk, & Feger, 1978; Nakanishi et al., 1987) and inhibitory GABAergic inputs from the globus pallidus (Smith & Bolam, 1989). GABAergic inputs from the direct and indirect pathways converge on one site in the substantia nigra pars reticulata (Bolam, Smith, Ingham, von Krosigk, & Smith, 1993), thus allowing for an

integration of inputs from the two parallel pathways. The substantia nigra pars reticulata, in turn, serves as one of the chief output structures of the basal ganglia, modulating various premotor nuclei via its GABAergic outputs. Moreover, its strategic location at the point of convergence of the two major pathways makes the substantia nigra pars reticulata a critical component involved in the information processing and signal discrimination of the basal ganglia.

Entopeduncular Nucleus

The entopeduncular nucleus, also referred to as the internal segment of the globus pallidus, is an important output structure of the basal ganglia and functions in much the same way as the substantia nigra pars reticulata. For example, the globus pallidus inhibits the entopeduncular nucleus via GABAergic transmission (Fonnum, Gottesfeld, & Grofova, 1978; Nagy, Carter, Lehmann, & Fibiger, 1978), while the subthalamic nucleus stimulates the entopeduncular nucleus through glutamatergic connections (Nakanishi et al., 1987). Dopaminergic input to the entopeduncular nucleus is provided by the substantia nigra pars compacta (Lindvall & Bjorklund, 1979). As a major output system, GABAergic fibers from the

entopeduncular nucleus project throughout the forebrain. This GABAergic activity provides inhibitory signals to several important motor structures, including the thalamus (Carter & Fibiger, 1978; van der Kooy & Carter, 1981), pedunculopontine nucleus (Nauta, 1979; Takada, Tokuno, Ikai, & Mizuno, 1994), and superior colliculus (Takada et al., 1994). Therefore, the entopeduncular nucleus is a critical component of the basal ganglia, acting as an output structure that distributes an inhibitory signal to a number of important motor areas.

Substantia Nigra Pars Compacta

The substantia nigra pars compacta supplies dopaminergic modulation to the major input (striatum) and processing (globus pallidus and subthalamic nucleus) areas of the basal ganglia. These dopamine neurons coexpress cholecystokinin and neurotensin (Seroogy et al., 1988), which may serve as modulators for several feedback loops carrying GABAergic signals via the direct and indirect pathways (Fuxe et al., 1995; O'Connor, 2001; Tanganelli et al., 1993). The presence of NMDA and nonNMDA glutamate receptors in the substantia nigra pars compacta (Kalivas, 1993) indicates possible excitatory input from the prefrontal cortex and subthalamic nucleus. This

glutamatergic input probably regulates the firing rates of dopamine neurons in the substantia nigra pars compacta and may be part of a feedback system. Hence, the substantia nigra pars compacta is in position to control the functioning of major input and processing structures of the basal ganglia via dopaminergic modulation of the direct and indirect pathways.

Summary

The basal ganglia is a massive brain network that is involved in receiving incoming information from the cerebral cortex, distributing that signal to specialized processing structures, and providing output signals to subcortical and cortical areas. The basal ganglia employs an intricate array of pathways and feedback networks ensuring accurate signal processing. Both inhibitory and excitatory signals are utilized by the basal ganglia. For instance, glutamatergic and GABAergic neurons are found throughout the indirect pathway, while GABA is the primary neurotransmitter of the direct pathway. The interaction of these systems creates a complex environment where excitation, inhibition, and disinhibition are used to modulate behavioral processes. In summary, the basal ganglia is a complex set of structures, with a number of

ganglia-thalamocortical loops which employ redundant feedback systems and competitive networks, that are involved in information processing related to motor, cognitive, and emotional processes.

CHAPTER FIVE

DOPAMINE MEDIATED BEHAVIOR

Introduction

Dopamine modulates a variety of behaviors including, but not limited to, learning, motivation and reward, cognition, and motoric function. Dopamine modulates behavior by altering an intricate array of mechanisms, such as varying the intensity of dopaminergic tone, stimulating various dopamine receptor subtypes, affecting pre- and postsynaptic receptors, and by synergistically activating opposing dopaminergic networks. Exogenous agonism and antagonism has been used to elucidate the role of dopaminergic systems for behavioral functioning. Administration of pharmacoagents varies from systemic treatment to precisely targeted intracranial injections. In addition, brain lesioning techniques are employed in combination with pharmacological testing to reveal the functional properties of dopamine systems.

Systemic Administration of Dopamine Agonists

Selective D1 and D2 receptor agonists differentially affect the unlearned behaviors of adult rats and mice. Systemic administration of the selective D1 agonist SKF38393 to normosensitive rats does not produce robust

locomotor activity nor is it capable of inducing stereotyped behaviors, although low levels of locomotion are sometimes reported (Arnt, 1985; Molloy & Waddington, 1984; Neisewander, Lucki, & McGonigle, 1991). However, animals depleted of monoamines (i.e., reserpinized rats) or 6-OHDA-treated rats exhibit elevated levels of locomotion following systemic SKF38393 treatment (Arnt, 1985; Breese, Baumeister, Napier, Frye, & Mueller, 1985; Breese et al., 1987; Neisewander et al., 1991). The enhanced locomotor activity of reserpine-treated rats can be blocked by either systemic administration of a selective D1 antagonist (SCH23390) or a nonselective D1/D2 antagonist (haloperidol) (Starr, Starr, & Kilpatrick, 1987; Zarrindast & Eliassi, 1991; Zarrindast & Minaian, 1991).

Systemic administration of selective D2 agonists, such as quinpirole or pergolide, affects motor behavior of rodents in a biphasic manner (Bradbury, Cannon, Costall, & Naylor, 1984; Costall, Lim, & Naylor, 1981; Eilam & Szechtman, 1989; Frantz & Van Hartesveldt, 1995; Koller & Herbster, 1988). Low doses of quinpirole attenuate locomotor activity, while high doses of this D2 agonist augment locomotion (Eilam & Szechtman, 1989; Frantz & Van Hartesveldt, 1995; Van Hartesveldt, Meyer, & Potter,

1994). This disparity in behavioral responsiveness can be explained by the selective affinity of pre- and postsynaptic D2 receptors. Specifically, presynaptic D2 receptors exhibit a higher affinity for quinpirole than postsynaptic D2 receptors. Therefore, at lower doses a quinpirole-induced reduction of dopamine levels is responsible for the decreased locomotion (i.e., a presynaptic effect), while stimulation of postsynaptic receptors at higher doses is responsible for the increased locomotor activity. Furthermore, although selective D2 agonists are not capable of producing intense stereotypies, high doses of quinpirole induce low level stereotypies such as sniffing and rearing (Christensen, Arnt, & Svendsen, 1985; Meller, Bordi, & Bohmaker, 1988).

Systemic administration of nonselective dopamine agonists, which stimulate both D1 and D2 receptors, causes behavioral effects that are somewhat similar to the effects of a selective D2 agonist. Specifically, nonselective D2 agonists affect the locomotor activity of rodents in a biphasic manner: locomotion is attenuated at low concentrations and enhanced at higher concentrations of the drug (Bradbury et al., 1984; Costall et al., 1981; Tossman et al., 1983). At even higher doses, however, nonselective D1/D2 agonists induce more intense behaviors

that are not observed after treatment with a selective D2 agonist alone (Bradbury et al., 1984; Ljungberg, 1986; Vaccheri, Dall'Olio, Gandolfi, & Montanaro, 1986). For example, high doses of apomorphine (2-4 mg/kg) induce a full range of stereotyped behaviors ranging from sniffing and rearing to intense repetitive movements such as licking, biting, and gnawing (Costall & Naylor, 1973; Lepekhina & Tsitsurina, 2007; Ljungberg, 1986; Schiorring, 1971; Szechtman, Ornstein, Teitelbaum, & Golani, 1985). A full range of stereotyped behaviors also occur after coadministration of selective D1 and D2 agonists. Not surprisingly, these behavioral effects can be attenuated by systemic treatment with either a selective D1 or D2 receptor antagonist (Arnt, 1987; Braun & Chase, 1986).

Precision Targeted Intracranial Microinjection of Dopamine Agonists

Microinjection of D1 Agonists

Microinjection of selective D1 agonists into the nucleus accumbens induces a variety of motor behaviors, including locomotor activity, climbing, and contralateral circling, among others. The behaviors induced by D1 agonism can be antagonized by either a selective D1 (e.g., SCH23390) or D2 (e.g., spiperone) receptor antagonist (Dreher & Jackson, 1989).

In contrast, microinjection of D1 agonists into the striatum does not produce locomotor activity, but it does cause contralateral circling when administered unilaterally in normosensitive rats (Costall, Kelly, & Naylor, 1984a; Worms, Gueudet, & Biziere, 1986). This circling behavior can be attenuated by systemic administration of either a D1 or D2 antagonist (Worms et al., 1986). Importantly, microinjection of SKF38393 into the striatum does not produce stereotyped behaviors (Gower & Marriott, 1982).

Microinjection of D2 Agonists

Microinjection of D2 agonists into the nucleus accumbens results in a moderate dose-dependent increase in locomotor activity (Breese et al., 1987; Mogenson & Wu, 1991a, 1991b; Plaznik, Stefanski, & Kostowski, 1989). This locomotor activation can be blocked by depletion of monoamines through reserpine pretreatment or by systemic treatment with SCH23390 (Dreher & Jackson, 1989). In comparison, microinjecting D2 agonists into the striatum of 6-OHDA-treated rats induces vigorous locomotion that can be attenuated by systemic D2 antagonism and cannot be augmented with further infusion of a D1 agonist (LaHoste, 1990).

Microinjection of Nonselective or Indirect Agonists

Anatomical and behavioral studies have shown that the striatum is responsible for the stereotypical effects of dopamine agonists in rodents. Specifically, early studies showed that microinjecting dopamine into the dorsal striatum is able to elicit stereotyped motor responses that can be inhibited by D2 antagonism (Costall, Marsden, Naylor, & Pycock, 1976; Jackson, Anden, & Dahlstrom, 1975; Pijnenburg, Honig, Van der Heyden, & Van Rossum, 1976). Furthermore, microinjecting a combination of quinpirole and SKF38393, or the nonselective dopamine agonist apomorphine, into the dorsal striatum also results in the expression of stereotypy (Gower & Marriott, 1982). These findings have been further confirmed by a number of lesion studies showing that nigrostriatal projections are necessary for the expression of dopamine-mediated stereotypy (Asher & Aghajanian, 1974; Iversen & Koob, 1977; Joyce, Stinus, & Iversen, 1983; Kelly, Seviour, & Iversen, 1975).

The nucleus accumbens is a critical mesolimbic structure modulating rodent locomotor behavior through its dopaminergic connections. For example, coadministration of D1 and D2 receptor agonists, but not either agonist alone,

into the nucleus accumbens results in a synergistic increase in locomotion and, when injected unilaterally, contralateral circling (Canales & Iversen, 1998; Colle & Wise, 1991; Dreher & Jackson, 1989; Fog, 1972; Kelly et al., 1975; Mrabet, Messier, & Destrade, 1989; Solomon & Staton, 1982). Although dopamine agonist studies indicate that the striatum mediates stereotypy and the nucleus accumbens is associated with locomotor activity, their functions are not exclusively independent. It seems that multiple neuronal networks, segregated in a number of proximal regions, are responsible for the behavioral response to dopamine agonism; therefore, these motor responses are not solely mediated by one particular brain region or circuit.

D1/D2 Synergism

The interaction between the D1 and D2 family of receptors is an important factor affecting the expression of dopamine-mediated behaviors. There are several studies showing that synergistic activation of D1 and D2 receptors is required for a variety of behaviors to be expressed. For example, selective D2 receptor agonists (e.g., quinpirole) are capable of inducing locomotion and mild stereotypes, although they fail to produce intense

stereotyped behavior. However, intense stereotypy is apparent when selective D1 and D2 receptor agonists are coadministered (Arnt, 1987; Braun & Chase, 1986). More importantly, the behavioral effects of combined D1 and D2 administration can be attenuated by either a D1 or D2 receptor antagonist (Arnt, 1987).

An interaction between the two families of dopamine receptors is further apparent because administration of a selective D1 antagonist (SCH23390) not only blocks the effects of SKF38393 but exhibits a profile similar to a selective D2 or nonselective dopamine antagonist. More specifically, systemic administration of SCH23390 is capable of attenuating locomotion and conditioned avoidance responding, while producing catalepsy (Amalric, Koob, Creese, & Swerdlow, 1986; Gerhardt, Gerber, & Liebman, 1985; Gessa et al., 1985). In addition, SCH23390 modulates the effects of a variety of selective and nonselective dopamine agonists. For example, SCH23390 attenuates locomotion, stereotypy, and turning induced by selective D2 agonists such as quinpirole or pergolide (Arnt, 1985; Breese & Mueller, 1985; Pugh, O'Boyle, Molloy, & Waddington, 1985). Thus, it is evident that the D1 and D2 family of dopamine receptors interacts when mediating a variety of behavioral responses.

The synergistic effects of D1 and D2 receptors have been further studied in monoamine depleted (i.e., reserpinized) rats. In dopamine depleted animals, administration of a nonselective dopamine receptor agonist (apomorphine) is capable of inducing locomotion and stereotyped behavior (Arnt, 1987; Braun & Chase, 1986). The synergistic relationship between the D1 and D2 families of receptors becomes further apparent since D2 agonists alone (quinpirole and bromocriptine) do not elicit a comparable response even though they are capable of augmenting locomotion in normosensitive animals (Arnt, 1987; Braun & Chase, 1986). Interestingly, locomotion of reserpinized rats can be reinstated using D2 agonists but only when it is combined with a low, and otherwise behaviorally ineffective, dose of SKF38393 (Arnt, 1987). Thus, it is evident that tonic activation of D1 receptors is required for the expression of D2 mediated behaviors.

Neurochemical and Behavioral Effects of Irreversible Dopamine Receptor Alkylation

N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ) has been used extensively to study the functional characteristics of dopamine receptors. EEDQ functions by nondiscriminative alkylation of dopaminergic receptors

rendering them functionless (Adler, Meller, & Goldstein, 1985; Nowak, Arnt, & Hyttel, 1988). Since EEDQ irreversibly blocks only unprotected monoamine receptors, and does not damage neurons as a whole, it has proven to be a useful tool for studying receptors, individual cells, and neural pathways (Crawford, McDougall, & Bardo, 1994b; Giorgi & Biggio, 1990a; Hamblin & Creese, 1983).

Dopamine-mediated behavior have also been successfully studied using EEDQ irreversible antagonism. Since EEDQ is not selective to any particular dopamine receptor subtype, dopamine receptor subtypes can be selectively protected with exogenous antagonists (Crawford, McDougall, & Bardo, 1994a; Crawford et al., 1994b; McDougall, Crawford, & Nonneman, 1993; Nowak et al., 1988). Sulpiride and raclopride are commonly used to protect D2 dopamine receptors, whereas SCH23390 is used to protect D1 dopamine receptors (Meller, Bohmaker, Goldstein, & Friedhoff, 1985; Miller, Lumpkin, Galpern, Greenblatt, & Shader, 1991). Systemic administration of EEDQ induces severe catalepsy and attenuates amphetamine-induced stereotypy of adult rats (Belleau et al., 1968; Hamblin & Creese, 1983; Henry, Joseph, Kochman, & Roth, 1987). Rats treated systemically with EEDQ also exhibit attenuated levels of NPA-induced sniffing and oral

activities for 4-8 days, after which responsiveness returns to normal (Bordi, Carr, & Meller, 1989). In addition, systemic EEDQ treatment (25 mg/kg) has been shown to reliably and substantially reduce the percentage of D1 (down to 7% of controls) and D2 (down to 8% of controls) dopamine receptors in striatal samples (Crawford et al., 1994b; Crawford, McDougall, Rowlett, & Bardo, 1992).

Functional properties of dopamine receptors have also been studied after unilateral administration of EEDQ into various motor related brain regions. In this model, nonselective unilateral inactivation of dopamine receptors is responsible for a marked dose-dependent increase in ipsilateral movement following quinpirole treatment (Giorgi & Biggio, 1990a). Interestingly, systemic SKF38393 treatment did not cause ipsilateral rotation but did potentiate quinpirole-induced locomotion (Giorgi & Biggio, 1990a). This effect may be due to a more extensive D1 receptor reserve or deactivation of a larger percentage of D1 receptors may be required for ipsilateral movement. In summary, irreversible inactivation of dopamine receptors via EEDQ alkylation is a useful technique to study the functional properties of D1 and D2 dopamine receptors. It allows one to examine the role of D1 and D2 receptors

without relying on the acute presence of a reversible dopamine receptor antagonist.

Ontogeny of Dopamine-Mediated Behavior

Dopamine-mediated behavior varies across ontogeny due to maturational changes in dopamine system functioning (Broaddus & Bennett, 1990; Hedner & Lundborg, 1985; Lin & Walters, 1994). Like adults, young animals are capable of responding to D1 and D2 agonists and the synergism between receptors is apparent at birth. Some quantitative behavioral differences are apparent, however, because the D1 agonist SKF38393 elicits more pronounced locomotor activity in preweanling animals than adults (McDevitt & Setler, 1981; Moody & Spear, 1992). Furthermore, greater doses of SKF38393 are needed to evoke grooming responses in young rats, thus suggesting quantitative changes in either D1 receptors or the pharmacokinetics of SKF38393 (McDougall, Arnold, & Nonneman, 1990; Moody & Spear, 1992).

Systemically administered quinpirole is capable of producing forward locomotion and stereotyped behavior (intermittent licking, sniffing, and reversed locomotion), which is comparable to adult rats (Lal & Sourkes, 1973; Moody & Spear, 1992). Moreover, like adults, preweanling

rats display a biphasic behavioral reaction to quinpirole, with lower doses augmenting and higher doses attenuating locomotion (Moody & Spear, 1992; Van Hartesveldt et al., 1994). This biphasic effect is also apparent when R(-)-propylnorapomorphine (NPA) is infused into the striatum of young rats. Specifically, low doses of NPA (0.1 mg/kg) increase forward locomotion, while higher doses of NPA (1.0 mg/kg) do not (Charntikov et al., 2008). Adult-like stereotyped behavior has also been reported following apomorphine administration in neonatal, infant, and preweanling rats (Lal & Sourkes, 1973). Therefore, it seems that young rats behave in a qualitatively similar manner to adults when treated systemically with D1, D2, or nonselective dopamine agonists, or when intracerebrally injected with the D2 agonist NPA.

Age-dependent differences in dopamine receptor functioning and turnover have also been studied using EEDQ. In young animals systemic EEDQ (25 mg/kg) treatment is capable of significantly reducing the number of available D1 (down to 21% of controls) and D2 (down to 35% of controls) dopamine receptors in striatal tissue samples (Crawford et al., 1992, 1994b). Furthermore, EEDQ has been used successfully to study a variety of agonist-induced behaviors in animals (Cameron & Crocker, 1989; Double &

Crocker, 1990). Like adults, preweanling rats pretreated with SCH23390 and sulpiride, in order to preserve D1 and D2 dopamine receptors, do not exhibit typical amphetamine-induced behaviors (Crawford et al., 1994b). Unfortunately, EEDQ has only been administered systemically to preweanling rats, thus the advantages inherent to site-specific microinjections of EEDQ have not been utilized in young animals.

CHAPTER SIX

KAPPA OPIOID-MEDIATED BEHAVIOR

Introduction

Kappa opioid receptors are capable of modulating a variety of physiological and behavioral responses in adult rats and mice, including analgesia, reward, and unlearned motoric behaviors (e.g., locomotion, grooming, rearing, and sniffing). In terms of analgesia, systemic administration of exogenous (e.g. U50488 and U69593) or endogenous (dynorphin) kappa opioid agonists is capable of inducing antinociception (Gogas, Levine, & Basbaum, 1996; Herman & Goldstein, 1985; Millan et al., 1989). In addition, systemic administration of U50488 or dynorphin attenuates morphine- and β-endorphin-induced analgesia in a dose-dependent manner when tested on the hot plate or tail flick task (Friedman, Jen, Chang, Lee, & Loh, 1981; Ramarao, Jablonski, Rehder, & Bhargava, 1988; Tao, Hwang, & Chen, 1994; Tulunay, Jen, Chang, Loh, & Lee, 1981). In terms of reward, kappa opioid agonists lack reinforcing properties and are neither self administered or induce a conditioned place preference (Dykstra, Preston, & Bigelow, 1997). However, systemic administration of U50488 is able to attenuate the rewarding effects of morphine (a kappa

opioid agonist) and cocaine (an indirect dopamine agonist) on self administration and conditioned place preference tasks (Crawford, McDougall, Bolanos, Hall, & Berger, 1995; Funada et al., 1993; Kuzmin, Semenova, Gerrits, Zvartau, & Van Ree, 1997). Importantly, these U50488-induced behavioral effects are sensitive to kappa opioid antagonists (e.g., *nor*-binaltorphimine), thus confirming that U50488's actions are mediated by the kappa opioid receptor (Funada et al., 1993; Glick, Maisonneuve, Raucci, & Archer, 1995).

Adult Rats and Mice: Unlearned Motor Movement

Systemic Kappa Opioid Administration: Striatal Actions

Stimulation of kappa opioid receptors in adult rodents produces a marked reduction in motoric activity (Crawford et al., 1995; Jackson & Cooper, 1988; Leyton & Stewart, 1992; Ukai & Kameyama, 1985). Specifically, systemic administration of U50588 results in decreased levels of forward movement, rearing, and grooming (Jackson & Cooper, 1988; Leyton & Stewart, 1992; Ukai & Kameyama, 1985). In addition to its ability to reduce basal locomotor activity, U50488 attenuates cocaine-induced locomotion (Crawford et al., 1995). The locomotor inhibiting properties of kappa opioid receptor agonism can

be reversed by *nor*-binaltorphimine, thus indicating that kappa opioid receptors are responsible for modulating these unlearned behaviors (Kuzmin, Sandin, Terenius, & Ogren, 2000).

The ability of kappa opioid agonists to attenuate the locomotion of adult animals appears to result from the modulation of the mesolimbic and nigrostriatal dopamine pathways. These dopaminergic pathways project to the striatum and nucleus accumbens and are known to mediate locomotor activity as well as other unlearned motoric behaviors (Costall et al., 1976; Pijnenburg et al., 1976; Solomon & Staton, 1982). Interestingly, perfusion of kappa opioid agonists into the striatum and nucleus accumbens of adult rats attenuates dopamine release and, most importantly, decreases locomotion (Di Chiara & Imperato, 1988; Donzanti, Althaus, Payson, & Von Voigtlander, 1992; Maisonneuve, Archer, & Glick, 1994; Spanagel, Herz, & Shippenberg, 1990). The locomotor-inhibiting effects of kappa opioid agonists are observed in both normosensitive and psychostimulant-treated adult rats (Crawford et al., 1995; Di Chiara & Imperato, 1988; Jackson & Cooper, 1988; Leyton & Stewart, 1992; Waddell & Holtzman, 1998). The neural mechanisms responsible for these behavioral effects appear to involve presynaptic kappa opioid receptors.

Stimulation of presynaptic kappa opioid receptors, located on the terminals of mesolimbic and nigrostriatal dopamine neurons, results in decreased dopamine release from the host terminal fibers (Di Chiara & Imperato, 1988; Maisonneuve et al., 1994; Spanagel et al., 1990; Spanagel, Herz, & Shippenberg, 1992). Thus, decreased dopaminergic transmission seems to be responsible for the reduction of locomotion following kappa opioid agonist administration.

Central Kappa Opioid Administration: Nigral Actions

Surprisingly, microinjecting kappa opioid agonists into the substantia nigra pars reticulata, a nucleus in the basal ganglia, cause a dramatic increase in the locomotor activity of adult rats. Specifically, unilateral administration of U50488 or dynorphin produces a marked increase in the contralateral circling of adult rats (Friederich, Friederich, & Walker, 1987; Herrera-Marschitz et al., 1986; Herrera-Marschitz, Hokfelt, Ungerstedt, & Terenius, 1983; Herrera-Marschitz, Hokfelt, Ungerstedt, Terenius, & Goldstein, 1984; Matsumoto, Brinsfield, Patrick, & Walker, 1988; Morelli & Di Chiara, 1985). This effect seems unrelated to dopaminergic activity, since lesioning the nigrostriatal pathway does not disrupt the contralateral circling induced by unilateral

administration of a kappa opioid agonist into the substantia nigra pars reticulata (Matsumoto et al., 1988; Morelli & Di Chiara, 1985; Walker, Thompson, Frascella, & Friederich, 1987). Kappa opioid receptors within the substantia nigra pars reticulata are predominantly located on GABAergic output neurons that project to the superior colliculus and ventromedial thalamus (Di Chiara, Morelli, Imperato, & Porceddu, 1982; Morelli & Di Chiara, 1985).

Summary

Kappa opioid receptor systems seem to be indirectly involved in modulating locomotion of rodents. Adult animals treated systemically with a kappa opioid agonist exhibit reduced levels of locomotion, which seems to be the result of decreased striatal and accumbal dopamine release. Animals given a unilateral microinjection of a kappa opioid agonist into the substantia nigra pars reticulata exhibit an augmented locomotor response. Specifically, stimulating kappa opioid receptors in the substantia nigra pars reticulata inhibits GABAergic output neurons which, in turn, causes the disinhibition of the tectal and thalamic premotor systems. Depressed GABAergic output to the premotor areas, such as the superior colliculus and thalamus, results in disinhibition of these

systems and, as a consequence, elevated locomotor activity.

Preweanling Rats and Mice: Overview

In young animals the central nervous system undergoes maturational changes that result in different behavioral patterns, which can vary depending on the stage of development (Broaddus & Bennett, 1990; Clark, Garret, & Platt, 2001; Leslie & Loughlin, 1993). The maturation of neuronal circuits produces both quantitative and qualitative behavioral changes which can be revealed through various pharmacological interventions (Myslivecek & Hassmannova, 1979; Spear, 1979; Zhang & Pasternak, 1981). One of the clearest examples of an ontogenetic pharmacological effect involves activation of the kappa opioid system. Specifically, stimulation of kappa opioid receptors produces dramatically different effects in young and adult rats. Systemic administration of selective kappa opioid agonists (e.g., U50488) attenuates locomotor activity of adult rats, while paradoxically causing a dramatic increase in the locomotion of preweanling rats (Carden, Barr, & Hofer, 1991; Collins et al., 1998, 2000; Di Chiara & Imperato, 1988; Duke et al., 1997; Jackson &

Cooper, 1988; Kehoe & Boylan, 1994; Leyton & Stewart, 1992; McDougall et al., 1997; Ukai & Kameyama, 1985).

Kappa opioid-mediated locomotion in preweanling animals is not mediated by the dopaminergic system, but rather seems to be dependent on GABAergic outputs from the substantia nigra pars reticulata to premotor systems, such as the superior colliculus and ventromedial thalamus (Collins et al., 2000; Zavala, Yoshida, Osburn, & McDougall, 2002). The substantia nigra pars reticulata has been established as an activation site for U50488-induced behavior in 18-day-old rats (Collins et al., 2000). Specifically, bilateral microinjections of *nor*-binaltorphimine, a kappa opioid antagonist, into the substantia nigra pars reticulata attenuates the locomotor activating effects of systemically administered U50488 (Collins et al., 2000). The elevated motor response to kappa opioid receptor agonism is due to GABAergic disinhibition of motor pathways projecting from substantia nigra pars reticulata to the ventromedial thalamus and superior colliculus (Zavala et al., 2002). Thus, the kappa opioid-induced locomotor activity of preweanling rats is mediated by nigrotectal and nigrothalamic GABAergic projections originating in the substantia nigra pars reticulata and is not due to kappa opioid receptor

stimulation within accumbal and striatal areas (Collins et al., 2000; Morelli & Di Chiara, 1985; Thompson & Walker, 1992).

CHAPTER SEVEN

CONCLUSION

Although much is known about the early ontogeny of the dopamine and kappa opioid systems, how these systems interact is not fully understood. Interestingly, it appears that the dopamine system is capable of modulating the U50488-induced locomotor activity of preweanling rats. For example, stimulation of D2 receptors, but not D1 receptors, fully attenuates the locomotion induced by kappa opioid receptor agonists (Collins et al., 1998; McDougall et al., 1997, 1999). Specifically, systemic administration of the D2/D3 agonist quinpirole blocks U50488-induced locomotor activity, suggesting that these receptor subtypes are important for the dopamine/kappa opioid interaction.

Furthermore, systemic or intracranial administration of NPA into the dorsal striatum is able to attenuate the kappa opioid-induced locomotor activity of young rats (Charntikov et al., 2008; Duke et al., 1997; McDougall et al., 1997, 1999; Nazarian et al., 1999). This effect cannot be attributed to NPA's ability to induce stereotypy, since coadministration of NPA and U50488 has been shown to reduce stereotypy relative to when NPA is

administered alone (Duke et al., 1997; McDougall et al., 1999). Since NPA is somewhat selective for D2 dopamine receptors, it appeared likely that this kappa opioid-induced locomotion is mediated, at least partially, by dorsal striatal neuronal populations expressing D2 receptors. Paradoxically, however, the indirect pathway, which has mainly D2 receptor input, does not seem to mediate kappa opioid-induced locomotion. For example, lesions to critical regions of the indirect pathway (i.e., the globus pallidus and subthalamic nucleus) were unable to disrupt NPA's ability to attenuate the kappa opioid-induced locomotor activity of young rats (Charntikov et al., 2008).

There are three possible explanations for why bilateral lesions of the indirect pathway were unable to disrupt NPA's locomotor modulating effect. First, it is feasible that electrolytic lesions of the indirect pathway were not complete, leaving small populations of neurons within that pathway intact and operational. This possibility seems unlikely, however, because additional behavioral data from that study suggest that lesions to the globus pallidus and subthalamic nucleus were sufficient to disrupt the indirect pathway (see also Dewar, Jenner, & Marsden, 1983; Joel et al., 1998).

Second, it is possible that D2 receptors located on the striatonigral neurons of the direct pathway are responsible for NPA's ability to attenuate U50488-induced locomotor activity in preweanling rats. Although D1 receptors predominate on striatonigral neurons, previous studies have shown that both striatonigral and striatopallidal pathways exhibit some level of colocalization (Aizman et al., 2000; Deng et al., 2006; Hersch et al., 1995a; Lester, Fink, Aronin, & DiFiglia, 1993; Meador-Woodruff et al., 1991; Surmeier et al., 1992, 1993). Even though it has been established that D2 receptors are located on striatonigral neurons, the functional properties of these receptors are not known.

Lastly, it is possible that NPA's ability to stimulate D1 receptors in the dorsal striatum may be responsible for modulating kappa opioid-mediated locomotion. Although NPA is more selective for the D2 receptor subtype, it also has affinity for the D1 dopamine receptor. The ability of NPA to induce intense stereotypy, relative to quinpirole for example, is evidence of NPA's ability to stimulate both D1 and D2 receptors (Bordi et al., 1989; Meller et al., 1988). Since the direct (striatonigral) pathway is mainly composed of neurons expressing D1 receptors and projects from the dorsal

striatum to the substantia nigra pars compacta (i.e., the brain area mediating U50488-induced locomotion) it is possible that D1 receptors of the direct pathway are responsible for modulating kappa opioid-mediated locomotor activity.

The purpose of this thesis was to further investigate the relationship between dopamine and kappa opioid networks in the preweanling rat. Specifically, I attempted to answer whether D1 or D2 receptors (or both) are responsible for modulating the kappa opioid-mediated locomotor activity of preweanling rats. To test this experimental idea I employed EEDQ, which irreversibly inactivates dopamine receptors. I wanted to use this pharmacological agent because it can later be adapted for studying the underlying pathways mediating dopamine/kappa opioid interactions. I also employed the straight forward procedure of administering selective D1 and D2 agonists in order to determine what receptor type modulates kappa opioid-mediated locomotor activity.

In Experiment 1, I tested whether intrastriatal administration of EEDQ (an irreversible monoamine receptor antagonist) blocked NPA's ability to attenuate U50488-induced locomotion. It was hypothesized that microinjecting EEDQ into the dorsal striatum would block

NPA's actions. In Experiment 2, I originally planned to test whether D1 or D2 receptor stimulation, or concomitant stimulation of D1 and D2 receptors, by NPA is responsible for attenuating the U50488-induced locomotor activity of preweanling rats. However, because EEDQ did not block NPA's actions in Experiment 1, an alternate follow-up experiment was done. Specifically, in Experiment 2A, I microinjected distilled water, quinpirole (a selective D2/D3 agonist), or SKF38393 (a selective D1 agonist) into the dorsal striatum following systemic saline or U50488 administration. It was hypothesized that microinjecting SKF38393, but not quinpirole, would attenuate the kappa opioid-mediated locomotor activity of preweanling rats.

CHAPTER EIGHT

METHODS

Experimental Procedures

Subjects

Subjects were 240 (n = 8 per group) male and female rats of Sprague-Dawley descent (Charles River), born and raised at California State, San Bernardino (CSUSB). Litters were culled to 10 at PD 3 and were kept with dam until the end of experiment (PD 18). Rats were kept in the colony room under a 12 hour light/dark schedule and were maintained at 21-23 °C. All rats were treated according to the "Guide for the Care and Use of Mammals in Neuroscience and Behavioral Research" (National Research Council, 2003) under a research protocol approved by the Institutional Animal Care and Use Committee of CSUSB.

Apparatus

Behavioral assessment was performed in commercially available automated locomotor activity chambers (25 × 25 × 41 cm; Coulbourn Instruments) consisting of four transparent Plexiglas walls, a gray plastic composite floor, and an open top. Locomotion was measured by interruption of two sets of photobeam arrays horizontally positioned to measure rodent locomotor activity.

Drugs

U50488 methanesulfonate was dissolved in saline and administered intraperitonealy (i.p.) at a volume of 5 ml/kg. R(-)-propylnorapomorphine hydrochloride (NPA), quinpirole, and SKF38393 were dissolved in distilled water and administered intracranially (i.c.) at a volume of 0.5 µl per side. EEDQ was dissolved in DMSO and injected intracranially (i.c.) at a volume of 0.5 µl per side (Giorgi & Biggio, 1990b). All drugs were purchased from Sigma-Aldrich (St. Louis, MO).

Surgery

All animals underwent cannulae implantation surgery on PD 16. Anesthesia was induced by administering isoflurane (5%/5 min in 100% oxygen during the induction phase and 2-3% in 100% oxygen during the maintenance phase) via a nose mask. Prior to surgeries, all rats were administered ketoprofen 2 mg/kg (i.p.) and a topical lidocaine solution (1%) for pain management. A Cunningham Neonatal Rat Adapter attached to a standard Kopf stereotaxic apparatus was used to immobilize subjects during all surgical procedures. Microinjection guide cannulae (C232G; 22-gauge, 5 mm length; Plastics One; Roanoke, VA) were implanted 1 mm above the dorsal striatum (A +6.5, L 2.4, V 5.6). Coordinates for the dorsal

striatum were obtained from the developing rat brain atlas of Sherwood and Timiras (1970). Guide cannulae were anchored to the scull using cyanoacrylate gel followed by dental cement (Lang Dental; Wheeling, IL). Following cranioplasty, all animals were sutured and placed in a heated incubation chamber until fully recovered; subjects were then returned to dam. Post-operative monitoring was performed in order to assess subject responsiveness and dam acceptance. All rats underwent behavioral assessment 48 hr later.

Microinjection Procedure

Stainless steel stylets were replaced by an internal injection cannulae (C2321-5-SPC; 28-gauge, 1 mm projection length; Plastics One; Roanoke, VA), which protruded 1 mm below the tip of the guide cannula. Injection cannulae were attached via polyethylene tubing (i.d.: 28 mm; Becton Dickinson; Sparks, MD) to a 10 µl syringe (1801N, Hamilton; Reno, NV), which was mounted onto the microinjection pump (SP210IW; World Precision Instruments; Sarasota, FL). Cannulae were left in place for 1 min and the compound was then delivered at a constant rate over a 60 s period. Following microinjection, cannulae were left in place for an additional 1 min after which rats were

returned to the activity chambers. During the injection procedure all animals were gently hand-held.

Behavioral Procedures

Experiment 1

The first experiment tested the ability of intrastriatal EEDQ to block the NPA-induced reduction of kappa opioid-mediated locomotor activity. In addition, this experiment was designed to determine whether dopamine receptor inactivation alters U50488-induced locomotion. This was a mixed between/within factorial design with four independent variables: condition (EEDQ or saline), pre-drug (U50488 or saline), post-drug (0, 5, 10, or 20 µg NPA), and time block (see Figure 2). The dependent variable was distance traveled scores. A total of 128 rats (n = 8 per group) were used in Experiment 1.

On PD 17 (24 hr after surgery), rats received bilateral infusions of vehicle or EEDQ (200 µg; 0.5 µl per side). After an additional 24 hr (i.e., on PD 18), EEDQ- and vehicle-treated rats were placed for 20 min in the automated locomotor activity chambers (see Figure 3). Immediately following this 20 min baseline period, subjects were injected (i.p.) with U50488 (5 mg/kg) or saline and returned to the activity chambers for

additional behavioral assessment. After 20 min, rats were microinjected with either distilled water or NPA (5, 10, or 20 µg) into the dorsal striatum and returned to the activity chambers for another 40 min. Immediately following behavioral testing all subjects underwent histological examination to determine the accuracy of cannulae placement.

Experiment 2

The second experiment was designed to test whether D1, D2, or D1+D2 receptors located in the dorsal striatum mediated the U50488-induced locomotor activity of preweanling rats. All animals in Experiment 2 would have received one of four receptor protection treatments on PD 17 (24 hr after cannulae implantation). Specifically, different groups of rats would have been systemically treated (i.p.) with either SCH23390 (1 mg/kg), sulpiride (100 mg/kg), SCH23390 + sulpiride, or saline (Cameron & Crocker, 1989; Crawford et al., 1992; Giorgi et al., 1990). These drug combinations would have been used to protect D1 receptors, D2 receptors, or both D1 and D2 receptors.

Experiment 2A

As mentioned in the introduction, because Experiment 1 failed (i.e., EEDQ did not block NPA-induced behaviors)

Experiment 2 was not conducted. Instead, Experiment 2A was designed to assess whether stimulation of D1 or D2 receptors, via intracranial administration of highly selective dopamine agonists, modulates the U50488-induced locomotor activity of preweanling rats. This was a mixed between/within factorial subject design with three independent variables: pre-drug (saline or U50488), post-drug (distilled water, quinpirole, or SKF38393), and time block (see Figure 4). The dependent variable was distance traveled scores. A total of 112 rats (n = 8 per group) were used in Experiment 2A.

On PD 16 preweanling rats received intracranial cannulations. On PD 18, these rats were placed for 20 min in the testing chambers for assessment of locomotor activity (see Figure 5). Immediately afterwards, rats were injected (i.p.) with either saline or U50488 and placed back in the testing chambers for an additional 20 min. Rats then received dorsal striatal infusions of distilled water, quinpirole (10, 20, or 30 µg; 0.5 µl per side), or SKF38393 (10, 20, or 30 µg; 0.5 µl per side) and were returned to the chambers for an additional 40 min of testing. Histological assessment of cannulae placement immediately followed completion of behavioral testing.

Histology

All rats received an overdose of pentobarbital after which brains were removed and perfused with 4% paraformaldehyde solution. Following a fixation period (48-72 hr), tissue was cryoprotected in a 20% sucrose solution for an additional 24-48 hr. Coronal brain sections (70 µm) were taken using a cryostat. All tissue samples were stained with thionin for cannulae placement verification.

Statistical Analysis

Analysis of variance (ANOVA) for repeated measures (using SPSS general linear model) was used for the statistical analysis of locomotor activity. Data were analyzed in 5-min time blocks. Statistically significant higher order interactions were further analyzed by one- or two-way ANOVAs and followed, if necessary, by Tukey's HSD (for between group comparisons) or Dunnett's (for comparison to a control group) post hoc tests ($p < 0.05$). Violations of sphericity (as determined by Mauchly's sphericity test) were further corrected using Huynh-Feldt degrees of freedom adjustments and are indicated in the Results section using a superscripted "a". In order to control for litter effects, no more than one subject from

a litter was assigned to a particular group. An equal number of male and female rats were assigned to each group.

For Experiment 1, there was four independent variables: a) condition (EEDQ or vehicle), b) pre-drug (U50488 or saline), c) post-drug (0, 5, 10, or 20 µg of NPA), and d) time blocks (see Figure 2). Because of ongoing experimental manipulations, separate ANOVAs were used to analyze time blocks 1-4 (habituation), time blocks 5-8 (U50488 vs saline), and time blocks 9-16 (NPA vs vehicle). The first four time blocks (0-20 min) were analyzed using a 2 × 4 (condition × time block) ANOVA. Time blocks 5-8 (20-40 min) were analyzed by a 2 × 2 × 4 (condition × pre-drug × time block) ANOVA. Time blocks 9-16 (40-80 min) were analyzed using a 2 × 2 × 4 × 8 (condition × pre-drug × post-drug × time block) ANOVA. Significant higher order interactions were further assessed using one- or two-way ANOVAs.

For Experiment 2A, there were three independent variables: a) pre-drug (saline or U50488), b) post-drug (distilled water, quinpirole, or SKF38393), and c) time blocks (see Figure 4). Separate ANOVAs were used to analyze time blocks 1-4 (habituation), time blocks 5-8 (U50488 vs saline), and time blocks 9-16 (quinpirole vs

SKF38393 vs distilled water). The first four time blocks (0-20 min) were analyzed using a one-way (time block) ANOVA. Time blocks 5-8 (20-40 min) were analyzed using a 2 × 4 (pre-drug × time block) ANOVA. Time blocks 9-16 (40-80 min) were analyzed using a 2 × 7 × 8 (pre-drug × post-drug × time block) ANOVA.

Histological assessment of cannulae placement was performed by two observers blind to experimental conditions. Cannulae placements were graphically mapped on coronal sections taken from Paxinos and Watson's *The rat brain: in stereotaxic coordinates* (1998). Only subjects with accurate cannulae placements were included in the statistical analysis.

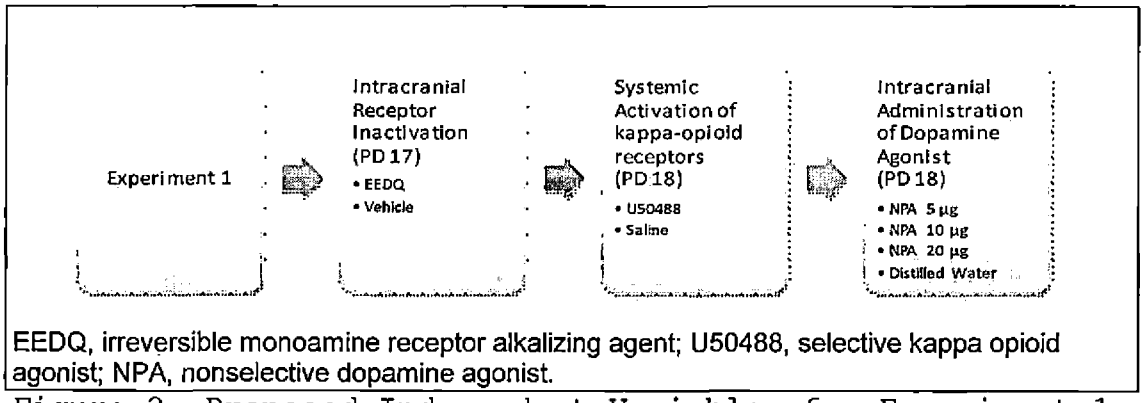
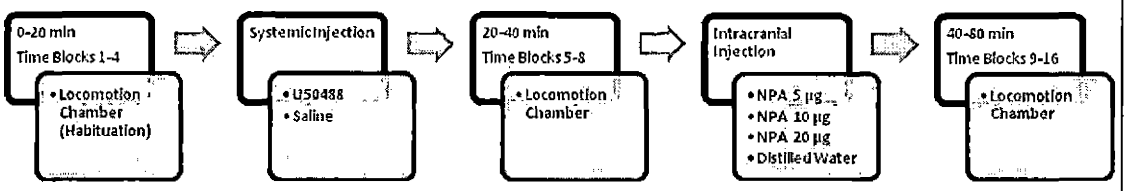
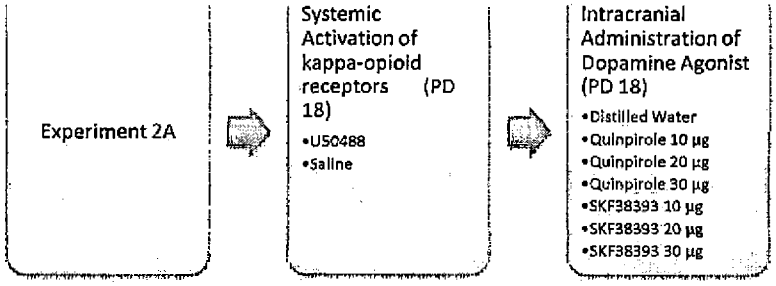


Figure 2. Proposed Independent Variables for Experiment 1 (2 × 2 × 4 Design)



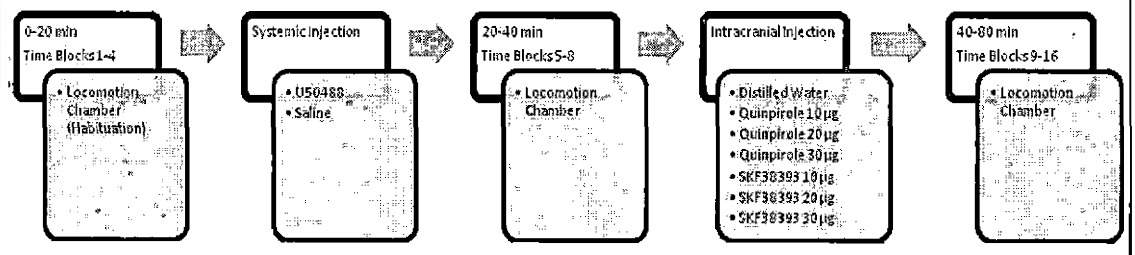
Habituation occurred during the first 20 min (time blocks 1-4) after which rats were injected (i.p.) with either U50488 or saline. Rats were then immediately returned to the testing chamber for an additional 40 min of locomotor testing. At the end of time block 8 all rats were given striatal infusions (i.c.) of NPA (0, 5, 10, or 20 µg) and returned to the chamber for 40 min of additional behavioral testing.

Figure 3. Representation of the Timeline for Experiment 1



Quinpirole, selective D2 agonist; SKF38393, selective D1 agonist; U50488, selective kappa opioid agonist.

Figure 4. Diagram of Independent Variables for Experiment 2A (2 × 7 Design)



Rats were habituated to the apparatus during the first 20 min (time blocks 1-4). At the end of the time block 4 all rats were injected (i.p.) with either U50488 or saline. Rats were then immediately returned to the locomotor chambers for an additional 20 min of behavioral testing. At the end of time block 8 all rats were infused (i.c.) with either quinpirole (10, 20, or 30 µg), SKF38393 (10, 20, or 30 µg), or distilled water and returned to the chambers for 40 min of additional behavioral testing.

Figure 5. Representation of the Timeline for Experiment 2A

CHAPTER NINE

RESULTS

Experiment 1

Habituation (Time Blocks 1-4)

Overall, rats treated with EEDQ had greater distance traveled scores (i.e., locomotor activity) than rats treated with DMSO (see Figures 6 and 7, compare left panels) [condition main effect, $F(1, 126) = 4.85$, $p < 0.05$]. Specifically, the locomotor activity of DMSO-treated rats declined progressively across time blocks 1-4, while the locomotor activity of EEDQ-treated rats was significantly lower than controls on time block 1 and higher than controls on time blocks 3 and 4 [[a]condition × time interaction, $F(2, 233) = 31.48$, $p < 0.001$; Tukey HSD tests].

U50488 Systemic Treatment (Time Blocks 5-8)

DMSO Condition. Among the DMSO-pretreated rats, U50488 significantly enhanced locomotor activity when compared to saline-treated controls (see Figure 6, compare top and bottom middle panels) [pre-drug main effect, $F(1, 62) = 102.35$, $p < 0.001$]. Specifically, U50488-treated rats showed significantly greater locomotor activity on time blocks 5-8 in comparison to

saline-treated rats [[a]pre-drug × time interaction, $F(2, 107) = 35.80$, $p < 0.001$; Tukey HSD tests].

EEDQ Condition. Among the EEDQ-pretreated rats, U50488 significantly enhanced locomotor activity when compared to saline controls, with differences between the U50488- and saline-treated rats being apparent on time blocks 6-8 (see Figure 7, compare upper and lower middle panels) [pre-drug main effect, $F(1, 62) = 59.11$, $p < 0.001$; [a]pre-drug × time interaction, $F(2, 112) = 36.86$, $p < 0.001$; Tukey HSD tests]. In addition, rats receiving U50488 showed a progressive increase in locomotor activity across time blocks 5-8 [Tukey HSD tests].

DMSO vs. EEDQ. On time blocks 5-7, rats pretreated with EEDQ and saline showed significantly greater locomotor activity than rats treated with DMSO and saline (see Figures 6 and 7, compare upper middle panels) [condition main effect, $F(1, 62) = 20.05$, $p < 0.001$; [a]condition × time interaction, $F(2, 111) = 7.26$, $p < 0.001$; Tukey HSD tests].

EEDQ-pretreated rats given U50488 showed significantly greater locomotor activity than rats given DMSO and U50488 (see Figures 6 and 7, compare lower middle panels) [condition main effect, $F(1, 62) = 12.57$,

$p < 0.001$]. Differences between the EEDQ-U50488 and DMSO-U50488 groups were apparent on time blocks 6-8 (see Figures 6 and 7, compare lower middle panels) [^{a}condition × time interaction, $F(2, 109) = 11.56$, $p < 0.001$; Tukey HSD tests].

Dorsostriatal NPA Infusions (Time Blocks 9-16)

An omnibus ANOVA assessing time blocks 9-16 resulted in a significant four-way interaction [^{a}condition × pre-drug × post-drug × time block interaction, $F(10, 392) = 3.43$, $p < 0.05$). Because of the significant interaction separate ANOVA's were conducted.

DMSO Condition: Saline Pretreatment. Among the DMSO rats pretreated with saline, NPA (5, 10 or 20 µg) infusions resulted in greater locomotor activity when compared to controls (see Figure 6, right upper panel) [post-drug main effect, $F(3, 28) = 22.48$, $p < 0.001$; Dunnett tests]. This effect did not differ according to dose or time block.

DMSO Condition: U50488 Pretreatment. On time block 9, U50488-pretreated rats infused with NPA (5, 10, and 20 µg) had significantly greater locomotor activity than controls (0 µg NPA) (see Figure 6, lower right panel) [^{a}post-drug × time block interaction, $F(16, 150) = 8.32$, $p < 0.001$; Dunnett tests]. Rats infused with 20 µg NPA

showed significantly less locomotor activity than controls on time blocks 11-16 (see Figure 6, lower right panel). Rats infused with the lower doses of NPA (5 or 10 µg) did not differ from controls on time blocks 10-16.

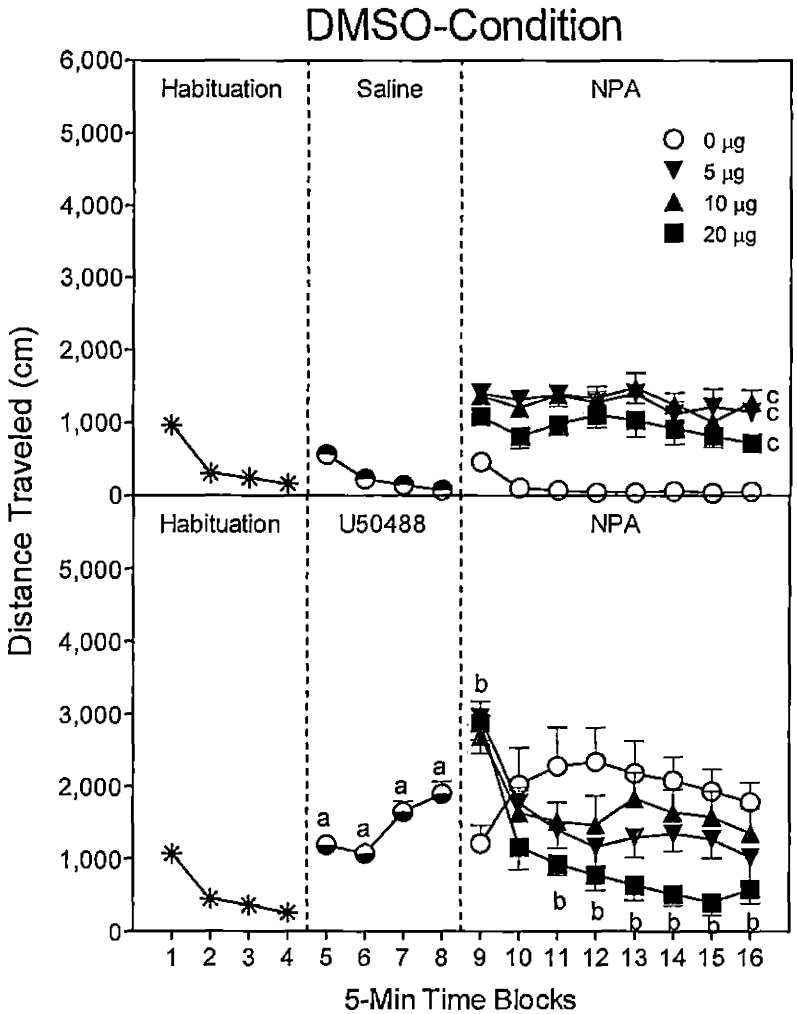
EEDQ Condition: Saline Pretreatment. Among the EEDQ rats pretreated with saline, NPA (5, 10 or 20 µg) infusions resulted in significantly greater locomotor activity than control rats (0 µg NPA) when collapsed across time blocks 9-16 (see Figure 7, upper right panel) [post-drug main effect, $F(3, 28) = 11.00$, $p < 0.001$; Dunnett tests]. This effect did not differ according to time block.

EEDQ Condition: U50488 Pretreatment. Among the EEDQ rats pretreated with U50488, infusions of NPA (5, 10 or 20 µg) significantly increased locomotor activity when collapsed across time blocks 9-16 (see Figure 7, lower right panel) [post-drug main effect, $F(3, 28) = 8.11$, $p < 0.001$; Dunnett tests]. This effect did not vary according to time block.

EEDQ versus DMSO Condition: Saline Pretreatment. Among the saline groups, EEDQ-pretreated rats showed significantly greater locomotor activity than DMSO-pretreated rats (see Figures 6 and 7, compare upper right panels) [condition main effect, $F(1, 56) = 47.43$,

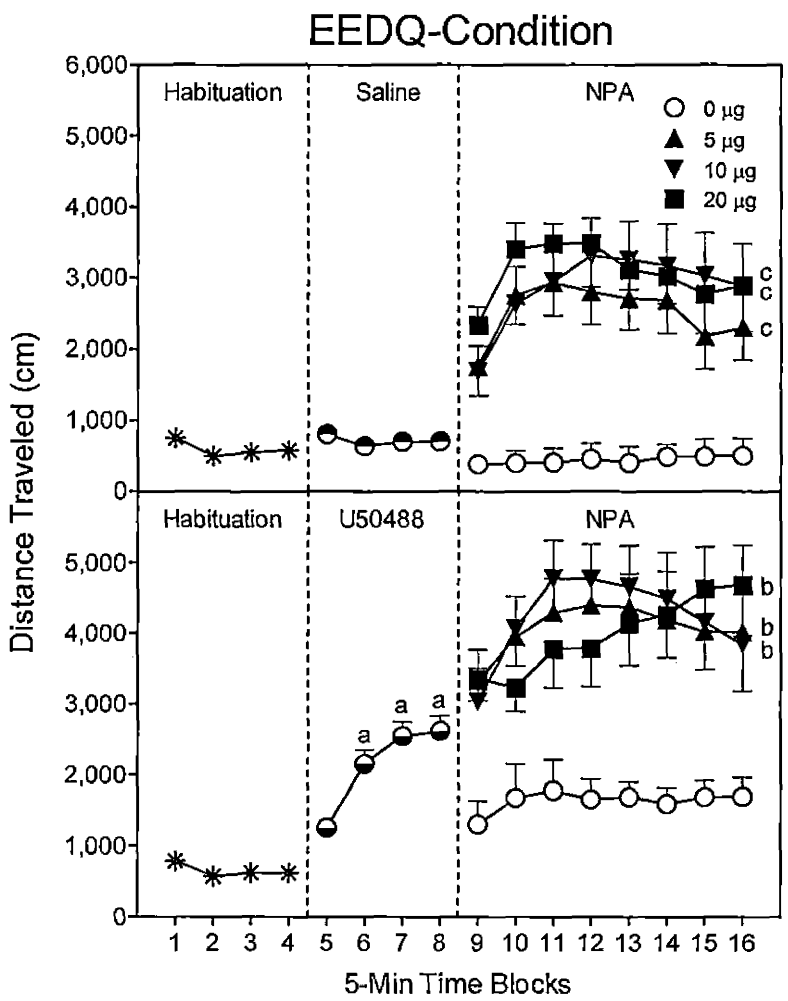
$p < 0.001$]. When collapsed across time blocks 9-16, EEDQ-pretreated rats infused with NPA (5, 10, or 20 µg) were significantly more active than DMSO-pretreated rats in the same treatment groups (see Figures 6 and 7, compare upper right panels) [condition × post-drug interaction, $F(3, 56) = 3.88$, $p < 0.05$; Tukey HSD tests].

EEDQ versus DMSO Condition: U50488 Pretreatment. Among the U50488 groups, EEDQ-pretreated rats showed greater locomotor activity than DMSO-pretreated rats (see Figures 6 and 7, compare lower right panels) [condition × post-drug interaction, $F(1, 56) = 57.59$, $p < 0.001$]. On time blocks 10-16, EEDQ-pretreated rats infused with NPA (5, 10 or 20 µg) exhibited significantly greater locomotor activity than DMSO-pretreated rats infused with the same doses of NPA (see Figures 6 and 7, compare right lower panels) [[a]condition × post-drug × time block interaction, $F(10, 195) = 6.15$, $p < 0.001$; Tukey HSD tests). Among the control groups (i.e., rats given 0 µg NPA), distance traveled scores did not vary after EEDQ pretreatment.



All rats were habituated to the testing chambers for 20 min (time blocks 1-4) and received systemic injections of either saline or U50488 at the end of time block 4. All rats were infused with NPA (0, 5, 10, or 20 µg) at the end of time block 8 and immediately returned to the testing chamber for an additional 40 min. [a]Significantly different from rats in saline pre-drug condition at the same time block (pre-drug × time interaction). [b]Significantly different from rats given U50488 and 0 µg NPA (post-drug × time block interaction). [c]Significantly different from rats given saline and 0 µg NPA (post-drug main effect).

Figure 6. Mean Distance Traveled Scores of DMSO-Pretreated Rats during the Testing Session



All rats were habituated to the testing chambers for 20 min (time blocks 1-4) and received systemic injections of either saline or U50488 at the end of time block 4. All rats were injected with NPA (0, 5, 10, or 20 µg) at the end of time block 8 and immediately returned to the testing chamber for an additional 40 min. [a]Significantly different than rats in the saline pre-drug condition at the same time block (pre-drug × time interaction). [b]Significantly different from rats given U50488 and 0 µg NPA (post-drug main effect). [c]Significantly different from rats given saline and 0 µg NPA (post-drug main effect).

Figure 7. Mean Distance Traveled Scores of EEDQ-Pretreated Rats during the Testing Session

Experiment 2A

Habituation (Time Blocks 1-4)

During habituation, rats showed a decline in locomotor activity that was evident across time blocks 1-4 (see Figures 8 and 9, left panels) [[a]time block main effect, $F(2, 271) = 398.90$, $p < 0.001$].

U50488 Systemic Treatment (Time Blocks 5-8)

Overall, rats treated with U50488 showed significantly greater locomotor activity than controls when collapsed across time blocks 5-8 (see Figures 8 and 9, compare upper and lower panels) [pre-drug main effect, $F(1, 110) = 39.26$, $p < 0.001$]. This effect varied according to time block, because the locomotion of U50488-treated rats gradually increased across time blocks 5-8, while the locomotion of controls gradually declined [[a]pre-drug × time block interaction, $F(2, 166) = 10.45$, $p < 0.001$].

Omnibus ANOVA Including SKF38393 and Quinpirole Groups (Time Blocks 9-16)

An omnibus ANOVA assessing time blocks 9-16 resulted in a significant three-way interaction [[a]pre-drug × post-drug × time block interaction, $F(27, 449) = 10.45$, $p < 0.001$]. Because of the significant interaction separate ANOVA's were conducted.

Dorsostriatal SKF38393 Infusions (Time Blocks 9-16)

Among rats infused with SKF38393, systemic pretreatment with U50488 resulted in significantly greater locomotor activity than saline (see Figure 8, compare upper and lower right panels) [pre-drug main effect, $F(1, 56) = 78.32$, $p < 0.001$]. Specifically, locomotor activity of U50488-pretreated rats increased over time blocks 9-11 and then stabilized, while the locomotion of saline-pretreated rats was minimal on all time blocks [^{a}pre-drug × time block interaction, $F(4, 220) = 27.28$, $p < 0.001$]. SKF38393 (0, 10, 20, or 30 µg) infusions did not affect locomotor activity on time blocks 9-16.

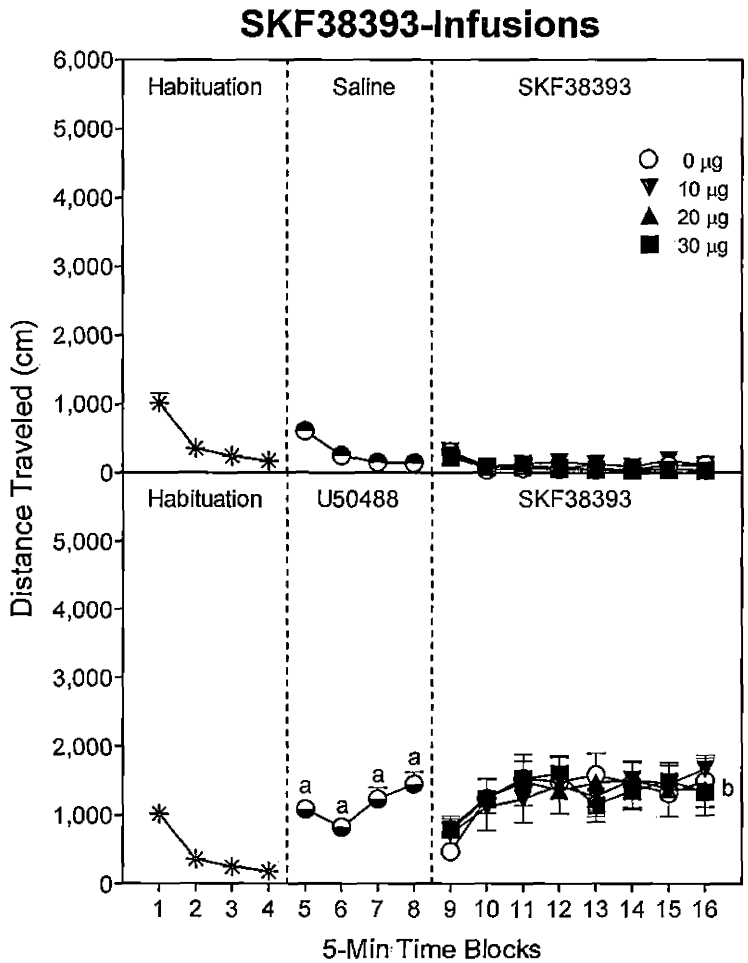
Dorsostriatal Quinpirole Infusions (Time Blocks 9-16)

An overall ANOVA assessing the locomotor activity of quinpirole-pretreated rats on time blocks 9-16 resulted in a significant three-way interaction [^{a}pre-drug × post-drug × time block interaction, $F(14, 258) = 8.35$, $p < 0.001$]. Because of the significant interaction separate ANOVA's were conducted.

Dorsostriatal Quinpirole Infusions: Saline-Pretreatment. Among rats pretreated with saline, quinpirole (10, 20, and 30 µg) infusions significantly augmented locomotor activity when compared to controls on

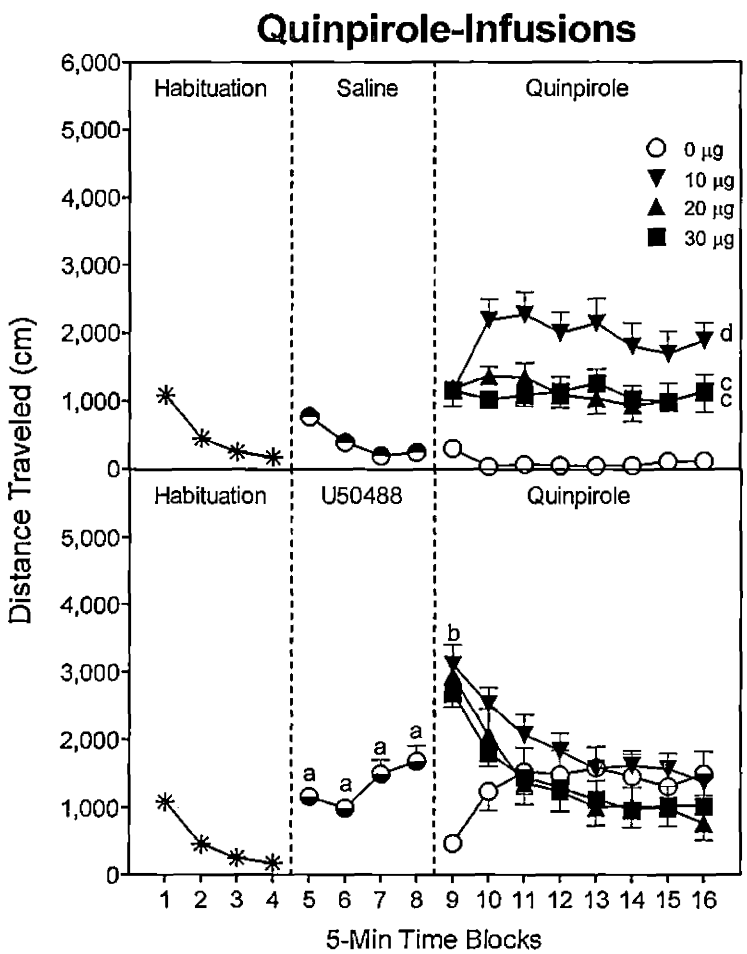
time blocks 9-16 (see Figure 9, upper right panel) [post-drug main effect, $F(3, 28) = 13.66$, $p < 0.001$; [a]post-drug × time block interaction, $F(12, 111) = 2.98$, $p < 0.001$; Tukey HSD tests]. Furthermore, rats infused with 10 µg quinpirole exhibited greater locomotor activity on time blocks 10-16 than rats infused with 20 or 30 µg quinpirole [Tukey HSD tests].

Dorsostriatal Quinpirole Infusions: U50488-Pretreatment. When collapsed over time blocks 9-16, quinpirole (0, 10, 20, or 30 µg) infusions did not significantly alter the locomotor activity of U50488-pretreated rats (see Figure 9, lower right panel) [post-drug main effect, $F(3, 28) = 1.44$, $p > 0.05$]. However, rats infused with quinpirole (10, 20, and 30 µg) showed a progressive decline in locomotor activity across time blocks 9-11, while controls showed a progressive increase across the same time blocks [[a]post-drug × time block interaction, $F(15, 138) = 9.85$, $p < 0.001$; Tukey HSD tests].



All rats were habituated to the testing chambers for 20 min (time blocks 1-4) and received systemic injections of either saline or U50488 at the end of time block 4. All rats were infused with SKF38393 (0, 10, 20, or 30 µg) at the end of time block 8 and immediately returned to the testing chamber for an additional 40 min. [a]Significantly different from rats in saline pre-drug condition at the same time block (pre-drug × time block interaction). [b]Significantly different from rats given saline and SKF38393 (pre-drug main effect).

Figure 8. Mean Distance Traveled Scores of Rats Receiving Infusions of SKF38393 during the Testing Session



All rats were habituated to the testing chambers for 20 min (time blocks 1-4) and received systemic injections of either saline or U50488 at the end of time block 4. All rats were infused with quinpirole (0, 10, 20, or 30 µg) at the end of time block 8 and immediately returned to the testing chamber for an additional 40 min. [a]Significantly different from rats in saline pre-drug condition at the same time block (pre-drug × time block interaction). [b]Significantly different from rats given U50488 and 0 µg quinpirole (post-drug × time block interaction). [c]Significantly different from rats given saline and 0 µg quinpirole (post-drug main effect). [d]Significantly different from rats given saline and 0, 20, or 30 µg quinpirole (post-drug main effect).

Figure 9. Mean Distance Traveled Scores of Rats Receiving Infusions of Quinpirole during the Testing Session

CHAPTER TEN

DISCUSSION

The purpose of this thesis was to determine which dopamine receptor subtype (D1 or D2) is responsible for modulating the U50488-induced locomotor activity of preweanling rats. It was predicted that a) infusions of the irreversible dopamine antagonist EEDQ into the dorsal striatum would block NPA's ability to modulate U50488-induced locomotion; and b) infusions of SKF38393, but not quinpirole, into the dorsal striatum would block U50488-induced locomotion.

Effects of U50488 on the Locomotor Activity of Preweanling Rats

Systemic administration of U50488 increased the locomotor activity of DMSO- and EEDQ-treated rats on PD 18 (see Figures 6 and 7, bottom middle panels). The ability of kappa opioid agonists to enhance the locomotor activity of preweanling rats and mice has been reported before (Duke et al., 1997; Karper, Nazarian, Crawford, Drago, & McDougall, 2000; Kehoe & Boylan, 1994; McDougall et al., 1997, 1999) and is in sharp contrast to what is observed in adult animals. Specifically, systemic administration of a kappa opioid agonist decreases the locomotor activity,

rearing, and grooming of adult rats (Jackson & Cooper, 1988; Leyton & Stewart, 1992; Ukai & Kameyama, 1985). The neuroanatomical basis for this age-dependent effect is not fully understood, but it is known that U50488 induces locomotor activity by stimulating kappa opioid receptors in the substantia nigra pars reticulata (Collins et al., 2000; Zavala et al., 2002).

Effects of Dorsostriatal NPA Infusions on U50488-Induced Locomotion

My results showed that infusing NPA into the dorsal striatum dose-dependently attenuated U50488-induced locomotor activity on PD 18 (see Figure 6, lower right panel). When considered together with past studies (Charntikov et al., 2008), it appears that stimulating dorsostriatal D2 receptors is sufficient to attenuate the kappa opioid-mediated locomotor activity of preweanling rats. For various reasons, NPA's ability to cause a dose-dependent reduction in U50488-induced locomotion cannot be attributed to the onset of stereotypies. First, when NPA is given alone, either via striatal infusions or systemic administration, locomotor activity and not stereotypy is preferentially induced (see Figure 6, upper right panel; see also Charntikov et al., 2008). Second, when NPA is coadministered with U50488 fewer stereotypies

are evident than when NPA is administered alone (Duke et al., 1997; McDougall et al., 1999).

Inability of EEDQ to Attenuate NPA-Induced Behaviors

Contrary to our expectations, EEDQ pretreatment did not attenuate NPA-induced behavioral effects in preweanling rats. For example, EEDQ/U50488-pretreated rats showed greater locomotor activity than DMSO/U50488-pretreated rats after intrastriatal infusions of NPA. Second, NPA infusions did not reduce the locomotor activity of U50488-treated rats but, instead, potentiated U50488-induced locomotion. These results were counterintuitive, because infusing EEDQ into the dorsal striatum of adult rats significantly reduces dopamine receptor content (Giorgi & Biggio, 1990a). In any event, the inability of EEDQ to block the NPA-induced behaviors of preweanling rats means that EEDQ cannot be used as a tool for determining which dopamine receptor subtype is responsible for attenuating kappa opioid-mediated locomotion. Instead, I directly assessed this experimental question by microinjecting selective D1 and D2 agonists into the dorsal striatum of U50488- and saline-pretreated rats.

Effects of Dorsostriatal Infusions of D1 and D2 Agonists

The results of Experiment 2A indicate that neither quinpirole nor SKF38393, when infused into the dorsal striatum, were able to attenuate the U50488-induced locomotor activity of preweanling rats (see Figures 8 and 9, lower right panels). The inability of SKF38393 to inhibit U50488-induced locomotion was unexpected because the striatonigral pathway, which is activated by striatal D1 receptors, was hypothesized to modulate U50488-induced locomotion (Charntikov et al., 2008). The present findings, however, are consistent with adult rat studies showing that striatal administration of SKF38393 does not affect locomotor activity (Costall, 1984; Worms, 1986).

The inability of quinpirole to attenuate the U50488-induced locomotor activity of preweanling rats was expected because lesions of the indirect pathway, which is disinhibited by D2 receptors, do not disrupt kappa opioid-mediated locomotion (Charntikov et al., 2008). Even so, these results are not consistent with a previous study showing that systemic administration of quinpirole reduces the U50488-induced locomotor activity of preweanling rats (McDougall et al., 1997). This disparity could be explained by the regional non-selectivity of systemic drug

administration. For example, quinpirole may activate additional brain regions that comodulate the U50488-induced locomotor activity of preweanling rats. In summary, contrary to my hypotheses, selective activation of D1 or D2 receptors in the dorsal striatum was unable to attenuate the U50488-induced locomotor activity of preweanling rats.

Neuronal Mechanisms Responsible for Dopamine/Kappa Opioid Interactions

Systemic administration of a kappa opioid agonist induces locomotor activity in preweanling rats by activating postsynaptic kappa opioid receptors located on neurons projecting from the substantia nigra pars reticulata to the ventromedial thalamus and superior colliculus (Collins et al., 2000; Zavala et al., 2002). Evidence for this assertion is twofold: first, microinjecting a kappa opioid antagonist (e.g., *nor*-binaltorphimine) into the substantia nigra pars reticulata fully attenuates U50488-induced locomotion (Collins et al., 2000). Second, lesions to the ventromedial thalamus and superior colliculus abolish the kappa opioid-mediated locomotor activity of preweanling rats (Zavala et al., 2002).

The dopamine system modulates kappa opioid-mediated locomotor activity, because dopamine agonists attenuate U50488-induced locomotion when given systemically (NPA and quinpirole) or when infused into the dorsal striatum (NPA) (Charntikov et al., 2008; Duke et al., 1997; McDougall et al., 1997, 1999; Nazarian et al., 1999). Although the mechanism responsible for this effect is not fully understood, we have hypothesized that activation of dopamine receptors (D1 and D2) in the dorsal striatum may disinhibit GABAergic neurons projecting from the substantia nigra pars reticulata to premotor areas. The dopamine receptors modulating kappa opioid-mediated locomotor activity do not appear to be a component of the indirect striatonigral pathway. Evidence for this is twofold: 1) infusions of NPA into the dorsal striatum attenuate U50488-induced locomotion, and 2) lesioning key areas of the indirect striatonigral pathway does not disrupt this NPA-induced effect (Charntikov et al., 2008).

Results of Experiment 1 and 2A demonstrated that dorsostriatal administration of NPA, but not quinpirole or SKF38393, attenuated the U50488-induced locomotor activity of preweanling rats. Although quinpirole is selective for the D2 receptor and SKF38393 is selective for the D1 receptor, NPA is capable of stimulating both D1 and D2

receptors (albeit NPA has greater affinity for D2 receptors). The different receptor affinities of these drugs provides a potential explanation for the present results, because it is well established that many D2-mediated behavioral effects require the coactivation of D1 receptors (Canales & Iversen, 1998; Colle & Wise, 1991; Dreher & Jackson, 1989; Fog, 1972; Kelly et al., 1975; Mrabet et al., 1989; Solomon & Staton, 1982). In this regard, it appears that D1 receptors have a "permissive" or "enabling" effect (Arnt, 1987; Braun & Chase, 1986). Based on this explanation, I predict that coadministration of quinpirole and SKF38393, either systemically or in the dorsal striatum, would attenuate the U50488-induced locomotor activity of preweanling rats.

Effects of Dorsostriatal Infusion of Quinpirole on the Locomotor Activity of Preweanling Rats

Locomotor activity is not typically associated with selective activation of dorsostriatal D2 receptors in adult rats. Instead, the majority of studies report that infusing quinpirole (3-40 µg) into the dorsal striatum of adult rats elicits behavioral sedation (i.e., reduced locomotion and yawning) (Bordi & Meller, 1989; Canales & Iversen, 1998; Delfs & Kelley, 1990). The only exception is a study showing a biphasic locomotor effect after

quinpirole infusion (Van Hartesveldt, Cottrell, Potter, & Meyer, 1992). More specifically, Van Hartesveldt et al. (1992) reported that lower doses (10-20 µg) of quinpirole reduced locomotor activity, while higher doses (40 µg) increased locomotion. Interestingly, adult rats are capable of exhibiting intense forward locomotion after dorsostriatal administration of quinpirole, but this effect is only observed in dopamine denervated animals (i.e., rats given 6-OHDA nigral lesions) (LaHoste, 1990).

Contrary to these adult rat studies, we showed for the first time that selective stimulation of D2 receptors in the dorsal striatum is capable of eliciting significant locomotor activity in preweanling rats. The ability of quinpirole to augment the locomotor activity of preweanling rats is consistent with data showing that dorsostriatal infusions of NPA increase the locomotor activity of preweanling rats (see Figure 6, upper right panel; Charntikov et al., 2008). This age-dependent difference in responsivity to quinpirole is indicative of ontogenetic differences in motor processing and regulation within the striatonigral motor circuits of the basal ganlia.

Dorsostriatal Infusions: SKF38393

Infusions of SKF38393 into the dorsal striatum did not affect locomotor activity of saline-pretreated rats on PD 18. This effect is comparable to the behavioral response observed in adult rats (Costall, Kelly, & Naylor, 1984b; Worms et al., 1986). Therefore, we were able to show for the first time that the locomotor activity of preweanling rats, like adults, is not affected by direct stimulation of D1 receptors in the dorsal striatum.

Paradoxical Actions of EEDQ in Preweanling Rats

EEDQ pretreatment potentiated the locomotor activity of NPA-treated rats in both the saline and U50488 conditions. There are several possible explanations for these findings: First, EEDQ infusions into the dorsal striatum may not have irreversibly inactivated D2 receptors. Second, striatal infusions of EEDQ may have increased the sensitivity of the remaining D2 receptors. Third, EEDQ may have disproportionately inactivated one of the dopamine receptor subtypes, thus creating an imbalance in excitatory and inhibitory outputs from the striatum. Fourth, infusions of EEDQ into the dorsal striatum may have disrupted the activity of acetylcholine medium spiny neurons, which regulate activity of the striatonigral and

striatopallidal pathways (Galarraga et al., 1999; Harsing & Zigmond, 1998; Marti et al., 2003).

The first possibility (i.e., that EEDQ did not inactivate a sufficient number of D2 receptors) is not very probable since previous studies have consistently reported that EEDQ significantly reduces striatal dopamine receptors in both adult and preweanling rats (Crawford et al., 1992, 1994b, 1994c; Giorgi & Biggio, 1990a; Hamblin & Creese, 1983). Although this is the first study to infuse EEDQ into the striatum of preweanling rats, evidence from adult studies suggests that this procedure should result in a substantial decrease of dopamine receptors (Giorgi & Biggio, 1990a). More specifically, systemically administered EEDQ reduces striatal dopamine receptors by as much as 80-90% in adults, and 70-80% in preweanling rats (Crawford et al., 1992, 1994c).

A second possibility, that striatal infusions of EEDQ increased the sensitivity of either existing or newly regenerated dopamine receptors, is only conjecture based on dopamine denervation studies. Denervation of the substantia nigra results in limited dopaminergic input to the striatum (Calabresi, Mercuri, Sancesario, & Bernardi, 1993). Denervated rats display a hyper-sensitive response (10-40 fold more sensitive) to dopamine agonists (Marshall

& Ungerstedt, 1977; Schultz & Ungerstedt, 1978; Schwarcz, Fuxe, Agnati, Hokfelt, & Coyle, 1979; Thornburg & Moore, 1975). Because EDDQ inactivates a variety of monoamine receptors, it is conceivable that dorsostriatal EEDQ infusions reduced dopamine levels in the striatum, thus sensitizing dopamine receptors to NPA. It is also conceivable that newly generated D2 receptors, created as a consequence of EEDQ treatment, would be super-sensitive. Thus, NPA may induce a potentiated response in preweanling rats because the remaining dopamine receptors are super-sensitive.

A third possible explanation for EEDQ's potentiating effect is that there is an imbalance in striatal D1 and D2 outputs. Excitatory (glutamate) and inhibitory (GABA) projections to the major output areas (substantia nigra pars reticulata and internal globus pallidus) of the basal ganglia work in concert to execute a wide variety of motor functions (Canales & Iversen, 1998; Colle & Wise, 1991; Dreher & Jackson, 1989; Fog, 1972; Kelly et al., 1975; Mrabet et al., 1989; Solomon & Staton, 1982). Specifically, D2 receptor stimulation removes the inhibition from the indirect pathway, while D1 receptor stimulation activates the direct pathway. It seems likely that disproportional inactivation of D1 and D2 receptors

by EEDQ would result in an imbalance of inputs affecting the direct and indirect pathways. Moreover, since most studies report that EEDQ disproportionately inactivates D1 and D2 receptors (Crawford et al., 1992, 1994b; Giorgi & Biggio, 1990a), it seems that this hypothetical D1/D2 imbalance could be responsible for EEDQ's paradoxical behavioral effect.

A fourth possibility is that dorsostriatal EEDQ infusions dramatically alter the activity of acetylcholine neurons modulating striatal functioning. These medium spiny interneurons, which innervate the striatum, provide a powerful cholinergic signal that modulates striatal output (Bernard, Dumartin, Lamy, & Bloch, 1993; Di Chiara et al., 1994; Robertson, Vincent, & Fibiger, 1992). Dopamine is the chief regulator of these cholinergic interneurons (Gerfen et al., 1990). Specifically, nigral dopaminergic output stimulates D2 receptors located on the cell bodies of striatal cholinergic interneurons (Claustre, Fage, Zivkovic, & Scatton, 1985). Stimulation of these D2 receptors inhibits cholinergic output and, in this way, alters the activity of GABAergic medium spiny neurons that form the striatonigral and striatopallidal pathways. Because EEDQ not only alters dopaminergic input, but also inactivates acetylcholine receptors (Drazen &

Schneider, 1978; Norman & Creese, 1986; Norman, Eubanks, & Creese, 1989), it is perhaps not surprising that EEDQ's behavioral effects were not as predicted in the present study.

In summary, it remains unclear why dorsostriatal infusions of EEDQ did not diminish NPA's behavioral effects in preweanling rats. Moreover, there is no definitive explanation for why NPA caused a potentiated locomotor response in EEDQ-pretreated rats. Although unexplained, these results are consistent with previous studies showing that systemic administration of EEDQ attenuated the NPA-induced locomotor activity and stereotypies of adult rats, while leaving the behaviors of preweanling rats unaffected (McDougall et al., 1993; Mestlin & McDougall, 1993).

Conclusion

Contrary to our prediction, EEDQ did not block NPA's ability to attenuate the kappa opioid-mediated locomotor activity of preweanling rats. This result suggests that selective inactivation of dopamine receptors utilizing EEDQ cannot be achieved in preweanling rats. Dorsostriatal infusions of selective dopamine agonists (SKF38393 and quinpirole) did not attenuate U50488-induced locomotion.

Thus, it appears that a synergistic interaction between dorsostriatal D1 and D2 receptors may be responsible for attenuating the kappa opioid-mediated locomotor activity of preweanling rats.

REFERENCES

Adler, C. H., Meller, E., & Goldstein, M. (1985). Recovery of α_2-adrenoceptor binding and function after irreversible inactivation by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ). *European Journal of Pharmacology, 116*(1-2), 175-178.

Aizman, O., Brismar, H., Uhlen, P., Zettergren, E., Levey, A. I., Forssberg, H., Greengard, P., & Aperia, A. (2000). Anatomical and physiological evidence for D1 and D2 dopamine receptor colocalization in neostriatal neurons. *Nature Neuroscience, 3*(3), 226-230.

Albin, R. L., Young, A. B., & Penney, J. B. (1989). The functional anatomy of basal ganglia disorders. *Trends in Neurosciences, 12*(10), 366-375.

Amalric, M., Koob, G. F., Creese, I., & Swerdlow, N. R. (1986). "Selective" D-1 and D-2 receptor antagonists fail to differentially alter supersensitive locomotor behavior in the rat. *Life Sciences, 39*(21), 1985-1993.

Arnt, J. (1985). Behavioural stimulation is induced by separate dopamine D-1 and D-2 receptor sites in reserpine-pretreated but not in normal rats. *European Journal of Pharmacology, 113*(1), 79-88.

Arnt, J. (1987). Behavioral studies of dopamine receptors: Evidence for regional selectivity and receptor multiplicity. In I. Creese & C. M. Fraser (Eds.), *Dopamine Receptors* (pp. 199-231). New York: Liss.

Asher, I. M., & Aghajanian, G. K. (1974). 6-Hydroxydopamine lesions of olfactory tubercles and caudate nuclei: effect on amphetamine-induced stereotyped behavior in rats. *Brain Research, 82*(1), 1-12.

Baldessarini, R. J., & Tarazi, F. I. (1996). Brain dopamine receptors: a primer on their current status, basic and clinical. *Harvard Review of Psychiatry, 3*(6), 301-325.

Belleau, B., Martel, R., Lacasse, G., Menard, M., Weinberg, N. L., & Perron, Y. G. (1968). N-carboxylic acid esters of 1,2- and 1,4-dihydroquinolines. A new class of irreversible inactivators of the catecholamine alpha receptors and potent central nervous system depressants. *Journal of the American Chemical Society, 90*(3), 823-824.

Bennett, M. A., Murray, T. F., & Aldrich, J. V. (2002). Identification of arodyn, a novel acetylated dynorphin A-(1-11) analogue, as a kappa opioid receptor antagonist. *Journal of Medicinal Chemistry, 45*(26), 5617-5619.

Bergson, C., Mrzljak, L., Smiley, J. F., Pappy, M., Levenson, R., & Goldman-Rakic, P. S. (1995). Regional, cellular, and subcellular variations in the distribution of D1 and D5 dopamine receptors in primate brain. *Journal of Neuroscience, 15*(12), 7821-7836.

Bernard, V., Dumartin, B., Lamy, E., & Bloch, B. (1993). Fos immunoreactivity after stimulation or inhibition of muscarinic receptors indicates anatomical specificity for cholinergic control of striatal efferent neurons and cortical neurons in the rat. *European Journal of Neuroscience, 5*(9), 1218-1225.

Bigornia, L., Allen, C. N., Jan, C. R., Lyon, R. A., Titeler, M., & Schneider, A. S. (1990). D2 dopamine receptors modulate calcium channel currents and catecholamine secretion in bovine adrenal chromaffin cells. *Journal of Pharmacology and Experimental Therapeutics, 252*(2), 586-592.

Bloch, B., & Le Moine, C. (1994). Neostriatal dopamine receptors. *Trends in Neurosciences, 17*(1), 3-4; author reply 4-5.

Blumberg, H., & Dayton, H. B. (1974). Naloxone, naltrexone, and related noroxymorphones in narcotic antagonists. *Advances in Biochemical Psychopharmacology, 8*, 33-43.

Bolam, J. P., Hanley, J. J., Booth, P. A., & Bevan, M. D. (2000). Synaptic organisation of the basal ganglia. *Journal of Anatomy, 196 (Pt 4)*, 527-542.

Bolam, J. P., Smith, Y., Ingham, C. A., von Krosigk, M., & Smith, A. D. (1993). Convergence of synaptic terminals from the striatum and the globus pallidus onto single neurones in the substantia nigra and the entopeduncular nucleus. *Progress in Brain Research, 99*, 73-88.

Bordi, F., Carr, K. D., & Meller, E. (1989). Stereotypies elicited by injection of N-propylnorapomorphine into striatal subregions and nucleus accumbens. *Brain Research, 489*(2), 205-215.

Bordi, F., & Meller, E. (1989). Enhanced behavioral stereotypies elicited by intrastriatal injection of D1 and D2 dopamine agonists in intact rats. *Brain Research, 504*(2), 276-283.

Bouthenet, M. L., Souil, E., Martres, M. P., Sokoloff, P., Giros, B., & Schwartz, J. C. (1991). Localization of dopamine D3 receptor mRNA in the rat brain using in situ hybridization histochemistry: comparison with dopamine D2 receptor mRNA. *Brain Research, 564*(2), 203-219.

Bradbury, A. J., Cannon, J. G., Costall, B., & Naylor, R. J. (1984). A comparison of dopamine agonist action to inhibit locomotor activity and to induce stereotyped behaviour in the mouse. *European Journal of Pharmacology, 105*(1-2), 33-47.

Brantl, V., Teschemacher, H., Henschen, A., & Lottspeich, F. (1979). Novel opioid peptides derived from casein (beta-casomorphins). I. Isolation from bovine casein peptone. *Hoppe-Seylers Zeitschrift fur Physiologische Chemie, 360*(9), 1211-1216.

Braun, A. R., & Chase, T. N. (1986). Obligatory D-1/D-2 receptor interaction in the generation of dopamine agonist related behaviors. *European Journal of Pharmacology, 131*(2-3), 301-306.

Breese, G. R., Baumeister, A., Napier, T. C., Frye, G. D., & Mueller, R. A. (1985). Evidence that D-1 dopamine receptors contribute to the supersensitive behavioral responses induced by L-dihydroxyphenylalanine in rats treated neonatally with 6-hydroxydopamine. *Journal of Pharmacology and Experimental Therapeutics, 235*(2), 287-295.

Breese, G. R., Duncan, G. E., Napier, T. C., Bondy, S. C., Iorio, L. C., & Mueller, R. A. (1987). 6-Hydroxydopamine treatments enhance behavioral responses to intracerebral microinjection of D1- and D2-dopamine agonists into nucleus accumbens and striatum without changing dopamine antagonist binding. *Journal of Pharmacology and Experimental Therapeutics, 240*(1), 167-176.

Breese, G. R., & Mueller, R. A. (1985). SCH-23390 antagonism of a D-2 dopamine agonist depends upon catecholaminergic neurons. *European Journal of Pharmacology, 113*(1), 109-114.

Broaddus, W. C., & Bennett, J., J. P. (1990). Postnatal development of striatal dopamine function. I. An examination of D1 and D2 receptors, adenylate cyclase regulation and presynaptic dopamine markers. *Developmental Brain Research, 52*(1-2), 265-271.

Calabresi, P., Centonze, D., Gubellini, P., Marfia, G. A., Pisani, A., Sancesario, G., & Bernardi, G. (2000). Synaptic transmission in the striatum: from plasticity to neurodegeneration. *Progress in Neurobiology, 61*(3), 231-265.

Calabresi, P., Mercuri, N. B., Sancesario, G., & Bernardi, G. (1993). Electrophysiology of dopamine-denervated striatal neurons. Implications for Parkinson's disease. *Brain, 116 (Pt 2)*, 433-452.

Cameron, D. L., & Crocker, A. D. (1989). Localization of striatal dopamine receptor function by central injection of an irreversible receptor antagonist. *Neuroscience, 32*(3), 769-778.

Canales, J. J., & Iversen, S. D. (1998). Behavioural topography in the striatum: differential effects of quinpirole and D-amphetamine microinjections. *European Journal of Pharmacology, 362*(2-3), 111-119.

Canteras, N. S., Shammah-Lagnado, S. J., Silva, B. A., & Ricardo, J. A. (1990). Afferent connections of the subthalamic nucleus: a combined retrograde and anterograde horseradish peroxidase study in the rat. *Brain Research, 513*(1), 43-59.

Carden, S. E., Barr, G. A., & Hofer, M. A. (1991). Differential effects of specific opioid receptor agonists on rat pup isolation calls. *Developmental Brain Research, 62*(1), 17-22.

Carter, C. J., & Pycock, C. J. (1978). A study of the sites of interaction between dopamine and 5-hydroxytryptamine for the production of fluphenazine-induced catalepsy. *Naunyn-Schmiedeberg's Archives of Pharmacology, 304*(2), 135-139.

Carter, D. A., & Fibiger, H. C. (1978). The projections of the entopeduncular nucleus and globus pallidus in rat as demonstrated by autoradiography and horseradish peroxidase histochemistry. *Journal of Comparative Neurology, 177*(1), 113-123.

Cepeda, C., Buchwald, N. A., & Levine, M. S. (1993). Neuromodulatory actions of dopamine in the neostriatum are dependent upon the excitatory amino acid receptor subtypes activated. *Proceedings of the National Academy of Sciences, United States of America, 90*(20), 9576-9580.

Charntikov, S., Halladay, L. R., Herbert, M. S., Marquez, E. M., & McDougall, S. A. (2008). Effects of dorsal striatal infusions of R(-)-propylnorapomorphine on κ-opioid-mediated locomotor activity in the young rat: Possible role of the indirect pathway. *Neuroscience, 155*(3), 603-612.

Chavkin, C., James, I. F., & Goldstein, A. (1982). Dynorphin is a specific endogenous ligand of the kappa opioid receptor. *Science, 215*(4531), 413-415.

Chen, J. F., & Weiss, B. (1991). Ontogenetic expression of D2 dopamine receptor mRNA in rat corpus striatum. *Developmental Brain Research, 63*(1-2), 95-104.

Chen, Y., Mestek, A., Liu, J., Hurley, J. A., & Yu, L. (1993). Molecular cloning and functional expression of a mu-opioid receptor from rat brain. *Molecular Pharmacology, 44*(1), 8-12.

Chevalier, G., & Deniau, J. M. (1990). Disinhibition as a basic process in the expression of striatal functions. *Trends in Neurosciences, 13*(7), 277-280.

Christensen, A. V., Arnt, J., & Svendsen, O. (1985). Pharmacological differentiation of dopamine D-1 and D-2 antagonists after single and repeated administration. *Psychopharmacology. Supplementum, 2*, 182-190.

Clark, D., & White, F. J. (1987). D1 dopamine receptor--the search for a function: a critical evaluation of the D1/D2 dopamine receptor classification and its functional implications. *Synapse, 1*(4), 347-388.

Clark, J. A., Liu, L., Price, M., Hersh, B., Edelson, M., & Pasternak, G. W. (1989). Kappa opiate receptor multiplicity: evidence for two U50,488-sensitive κ_1 subtypes and a novel kappa κ_3 subtype. *Journal of Pharmacology and Experimental Therapeutics, 251*(2), 461-468.

Clark, S. E., Garret, M., & Platt, B. (2001). Postnatal alterations of GABA receptor profiles in the rat superior colliculus. *Neuroscience, 104*(2), 441-454.

Claustre, Y., Fage, D., Zivkovic, B., & Scatton, B. (1985). Relative selectivity of 6,7-dihydroxy-2-dimethylaminotetralin, N-n-propyl-3-(3-hydroxyphenyl)piperidine, N-n-propylnorapomorphine and pergolide as agonists at striatal dopamine autoreceptors and postsynaptic dopamine receptors. *Journal of Pharmacology and Experimental Therapeutics, 232*(2), 519-525.

Colle, L. M., & Wise, R. A. (1991). Circling induced by intra-accumbens amphetamine injections. *Psychopharmacology, 105*(2), 157-161.

Collins, R. L., Zavala, A. R., Ingersoll, V. Y., Duke, M. A., Crawford, C. A., & McDougall, S. A. (1998). Kappa opioid-mediated behavioral sensitization in the preweanling rat: relationship to Fos immunoreactivity. *Psychopharmacology (Berl), 137*(3), 282-291.

Collins, R. L., Zavala, A. R., Nazarian, A., & McDougall, S. A. (2000). κ-Opioid receptors in the substantia nigra pars reticulata mediate the U-50,488-induced locomotor activity of preweanling rats. *Developmental Brain Research, 119*(1), 97-103.

Costall, B., Kelly, M. E., & Naylor, R. J. (1984a). The antidyskinetic action of dihomo-gamma-linolenic acid in the rodent. *British Journal of Pharmacology, 83*(3), 733-740.

Costall, B., Kelly, M. E., & Naylor, R. J. (1984b). Unilateral striatal dopamine denervation: reduced motor inhibitory effects of dopamine antagonists revealed in models of asymmetric and circling behaviour. *Naunyn-Schmiedeberg's Archives of Pharmacology, 326*(1), 29-35.

Costall, B., Lim, S. K., & Naylor, R. J. (1981). Characterisation of the mechanisms by which purported dopamine agonists reduce spontaneous locomotor activity of mice. *European Journal of Pharmacology, 73*(2-3), 175-188.

Costall, B., Marsden, C. D., Naylor, R. J., & Pycock, C. J. (1976). The relationship between striatal and mesolimbic dopamine dysfunction and the nature of circling responses following 6-hydroxydopamine and electrolytic lesions of the ascending dopamine systems of rat brain. *Brain Research, 118*(1), 87-113.

Costall, B., & Naylor, R. J. (1973). The role of telencephalic dopaminergic systems in the mediation of apomorphine-stereotyped behaviour. *European Journal of Pharmacology, 24*(1), 8-24.

Cox, B. M. (1993). Opioid receptor-G protein interactions: acute and chronic effects of opioids. In A. Herz (Ed.), *Opioids I, Handbook of Experimental Pharmacology* (Vol. 104, pp. 145-148). Berlin: Springer.

Crawford, C. A., McDougall, S. A., & Bardo, M. T. (1994a). Effects of EEDQ on the synthesis and metabolism of dopamine in preweanling and adult rats. *Neuropharmacology, 33*(12), 1559-1565.

Crawford, C. A., McDougall, S. A., & Bardo, M. T. (1994b). Ontogenetic effects of EEDQ on amphetamine-induced behaviors of rats: role of presynaptic processes. *Psychopharmacology, 116*(2), 152-160.

Crawford, C. A., McDougall, S. A., Bolanos, C. A., Hall, S., & Berger, S. P. (1995). The effects of the kappa agonist U-50,488 on cocaine-induced conditioned and unconditioned behaviors and Fos immunoreactivity. *Psychopharmacology, 120*(4), 392-399.

Crawford, C. A., McDougall, S. A., Rowlett, J. K., & Bardo, M. T. (1992). Depletion of dopamine binding sites and changes in dopamine and dihydroxyphenylacetic acid levels in 17- and 90-day-old rat striatum after irreversible receptor antagonism. *Neuroscience Letters, 137*(2), 265-269.

Crofford, M., & Smith, A. A. (1973). Growth retardation in young mice treated with dl-methadone. *Science, 181*(103), 947-949.

Dearry, A., Gingrich, J. A., Falardeau, P., Fremeau, R. T., Jr., Bates, M. D., & Caron, M. G. (1990). Molecular cloning and expression of the gene for a human D1 dopamine receptor. *Nature, 347*(6288), 72-76.

Delfs, J. M., & Kelley, A. E. (1990). The role of D1 and D2 dopamine receptors in oral stereotypy induced by dopaminergic stimulation of the ventrolateral striatum. *Neuroscience, 39*(1), 59-67.

Deng, Y.-P., Lei, W.-L., & Reiner, A. (2006). Differential perikaryal localization in rats of D1 and D2 dopamine receptors on striatal projection neuron types identified by retrograde labeling. *Journal of Chemical Neuroanatomy, 32*(2-4), 101-116.

Deniau, J. M., & Chevalier, G. (1992). The lamellar organization of the rat substantia nigra pars reticulata: distribution of projection neurons. *Neuroscience, 46*(2), 361-377.

Deniau, J. M., Hammond, C., Riszk, A., & Feger, J. (1978). Electrophysiological properties of identified output neurons of the rat substantia nigra (pars compacta and pars reticulata): evidences for the existence of branched neurons. *Experimental Brain Research, 32*(3), 409-422.

DePaoli, A. M., Hurley, K. M., Yasada, K., Reisine, T., & Bell, G. (1994). Distribution of kappa opioid receptor mRNA in adult mouse brain: an in situ hybridization histochemistry study. *Molecular and Cellular Neurosciences, 5*(4), 327-335.

DeVito, J. L., & Anderson, M. E. (1982). An autoradiographic study of efferent connections of the globus pallidus in Macaca mulatta. *Experimental Brain Research, 46*(1), 107-117.

DeVito, J. L., Anderson, M. E., & Walsh, K. E. (1980). A horseradish peroxidase study of afferent connections of the globus pallidus in Macaca mulatta. *Experimental Brain Research, 38*(1), 65-73.

Dewar, D., Jenner, P., & Marsden, C. D. (1983). Lesions of the globus pallidus, entopeduncular nucleus and substantia nigra alter dopamine mediated circling behaviour. *Experimental Brain Research, 52*(2), 281-292.

Di Chiara, G., & Imperato, A. (1988). Opposite effects of mu and kappa opiate agonists on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats. *Journal of Pharmacology and Experimental Therapeutics, 244*(3), 1067-1080.

Di Chiara, G., Morelli, M., & Consolo, S. (1994). Modulatory functions of neurotransmitters in the striatum: ACh/dopamine/NMDA interactions. *Trends in Neurosciences, 17*(6), 228-233.

Di Chiara, G., Morelli, M., Imperato, A., & Porceddu, M. L. (1982). A re-evaluation of the role of superior colliculus in turning behaviour. *Brain Research, 237*(1), 61-77.

Diaz, J., Levesque, D., Griffon, N., Lammers, C. H., Martres, M. P., Sokoloff, P., & Schwartz, J. C. (1994). Opposing roles for dopamine D2 and D3 receptors on neurotensin mRNA expression in nucleus accumbens. *European Journal of Neuroscience, 6*(8), 1384-1387.

Diaz, J., Levesque, D., Lammers, C. H., Griffon, N., Martres, M. P., Schwartz, J. C., & Sokoloff, P. (1995). Phenotypical characterization of neurons expressing the dopamine D3 receptor in the rat brain. *Neuroscience, 65*(3), 731-745.

Donzanti, B. A., Althaus, J. S., Payson, M. M., & Von Voigtlander, P. F. (1992). Kappa agonist-induced reduction in dopamine release: site of action and tolerance. *Research Communications in Chemical Pathology and Pharmacology, 78*(2), 193-210.

Double, K. L., & Crocker, A. D. (1990). Effects of inactivation of D1 dopamine receptors on stereotypic and thermic responses to quinpirole (LY 171555). *Neuroscience Letters, 115*(1), 81-85.

Drazen, J. M., & Schneider, M. W. (1978). Comparative responses of tracheal spirals and parenchymal strips to histamine and carbachol in vitro. *Journal of Clinical Investigation, 61*(6), 1441-1447.

Dreher, J. K., & Jackson, D. M. (1989). Role of D1 and D2 dopamine receptors in mediating locomotor activity elicited from the nucleus accumbens of rats. *Brain Research, 487*(2), 267-277.

Duke, M. A., Meier, T. L., Bolanos, C. A., Crawford, C. A., & McDougall, S. A. (1997). Paradoxical effects of kappa-opioid stimulation on the locomotor activity and Fos immunoreactivity of the preweanling rat: role of dopamine receptors. *Behavioral Neuroscience, 111*, 1114-1122.

Dykstra, L. A., Preston, K. L., & Bigelow, G. E. (1997). Discriminative stimulus and subjective effects of opioids with mu and kappa activity: data from laboratory animals and human subjects. *Psychopharmacology, 130*(1), 14-27.

Eilam, D., & Szechtman, H. (1989). Biphasic effect of D-2 agonist quinpirole on locomotion and movements. *European Journal of Pharmacology, 161*(2-3), 151-157.

Evans, C. J., Keith, D. E., Jr., Morrison, H., Magendzo, K., & Edwards, R. H. (1992). Cloning of a delta opioid receptor by functional expression. *Science, 258*(5090), 1952-1955.

Feger, J. (1981). Electrophysiological studies of GABAergic neurons in the basal ganglia: nigro-collicular, nigro-thalamic, and pallido-subthalamic neurons. *Advances in Biochemical Psychopharmacology, 30*, 53-68.

Feger, J. (1997). Updating the functional model of the basal ganglia. *Trends in Neurosciences, 20*(4), 152-153.

Ferre, S., O'Connor, W. T., Fuxe, K., & Ungerstedt, U. (1993). The striopallidal neuron: a main locus for adenosine-dopamine interactions in the brain. *Journal of Neuroscience, 13*(12), 5402-5406.

Ferre, S., O'Connor, W. T., Svenningsson, P., Bjorklund, L., Lindberg, J., Tinner, B., Stromberg, I., Goldstein, M., Ogren, S. O., Ungerstedt, U., Fredholm, B. B., & Fuxe, K. (1996). Dopamine D1 receptor-mediated facilitation of GABAergic neurotransmission in the rat strioentopenduncular pathway and its modulation by adenosine A1 receptor-mediated mechanisms. *European Journal of Neuroscience, 8*(7), 1545-1553.

Fink, J. S., Weaver, D. R., Rivkees, S. A., Peterfreund, R. A., Pollack, A. E., Adler, E. M., & Reppert, S. M. (1992). Molecular cloning of the rat A2 adenosine receptor: selective co-expression with D2 dopamine receptors in rat striatum. *Brain Research. Molecular Brain Research, 14*(3), 186-195.

Fischli, W., Goldstein, A., Hunkapiller, M. W., & Hood, L. E. (1982). Isolation and amino acid sequence analysis of a 4,000-dalton dynorphin from porcine pituitary. *Proceedings of the National Academy of Sciences, United States of America, 79*(17), 5435-5437.

Fisone, G., Håkansson, K., Borgkvist, A., & Santini, E. (2007). Signaling in the basal ganglia: Postsynaptic and presynaptic mechanisms. *Physiology & Behavior, 92*(1-2), 8-14.

Fog, R. (1972). On stereotypy and catalepsy: studies on the effect of amphetamines and neuroleptics in rats. *Acta Neurologica Scandinavica, 50 (Suppl.)*, 3-66.

Fonnum, F., Gottesfeld, Z., & Grofova, I. (1978). Distribution of glutamate decarboxylase, choline acetyl-transferase and aromatic amino acid decarboxylase in the basal ganglia of normal and operated rats. Evidence for striatopallidal, striatoentopeduncular and striatonigral GABAergic fibres. *Brain Research, 143*(1), 125-138.

Frantz, K. J., & Van Hartesveldt, C. (1995). Sulpiride antagonizes the biphasic locomotor effects of quinpirole in weanling rats. *Psychopharmacology, 119*(3), 299-304.

Fremeau, R. T., Jr., Duncan, G. E., Fornaretto, M. G., Dearry, A., Gingrich, J. A., Breese, G. R., & Caron, M. G. (1991). Localization of D1 dopamine receptor mRNA in brain supports a role in cognitive, affective, and neuroendocrine aspects of dopaminergic neurotransmission. *Proceedings of the National Academy of Sciences, United States of America, 88*(9), 3772-3776.

Friederich, M. W., Friederich, D. P., & Walker, J. M. (1987). Effects of dynorphin (1-8) on movement: non-opiate effects and structure-activity relationship. *Peptides, 8*(5), 837-840.

Friedman, H. J., Jen, M. F., Chang, J. K., Lee, N. M., & Loh, H. H. (1981). Dynorphin: a possible modulatory peptide on morphine or beta-endorphin analgesia in mouse. *European Journal of Pharmacology, 69*(3), 357-360.

Frohna, P. A., Neal-Beliveau, B. S., & Joyce, J. N. (1995). Neonatal 6-hydroxydopamine lesions lead to opposing changes in the levels of dopamine receptors and their messenger RNAs. *Neuroscience, 68*(2), 505-518.

Fujimoto, K., & Kita, H. (1993). Response characteristics of subthalamic neurons to the stimulation of the sensorimotor cortex in the rat. *Brain Research, 609*(1-2), 185-192.

Fukuda, K., Kato, S., Mori, K., Nishi, M., & Takeshima, H. (1993). Primary structures and expression from cDNAs of rat opioid receptor delta- and mu-subtypes. *FEBS Letters, 327*(3), 311-314.

Funada, M., Suzuki, T., Narita, M., Misawa, M., & Nagase, H. (1993). Blockade of morphine reward through the activation of kappa-opioid receptors in mice. *Neuropharmacology, 32*(12), 1315-1323.

Fuxe, K., Li, X. M., Tanganelli, S., Hedlund, P., O'Connor, W. T., Ferraro, L., Ungerstedt, U., & Agnati, L. F. (1995). Receptor-receptor interactions and their relevance for receptor diversity. Focus on neuropeptide/dopamine interactions. *Annals of the New York Academy of Sciences, 757*, 365-376.

Gairin, J. E., Mazarguil, H., Alvinerie, P., Botanch, C., Cros, J., & Meunier, J. C. (1988). N,N-diallyl-tyrosyl substitution confers antagonist properties on the kappa-selective opioid peptide [D-Pro10]dynorphin A(1-11). *British Journal of Pharmacology, 95*(4), 1023-1030.

Galarraga, E., Hernandez-Lopez, S., Reyes, A., Miranda, I., Bermudez-Rattoni, F., Vilchis, C., & Bargas, J. (1999). Cholinergic modulation of neostriatal output: a functional antagonism between different types of muscarinic receptors. *Journal of Neuroscience, 19*(9), 3629-3638.

Gates, M. A., Coupe, V. M., Torres, E. M., Fricker-Gates, R. A., & Dunnett, S. B. (2004). Spatially and temporally restricted chemoattractive and chemorepulsive cues direct the formation of the nigro-striatal circuit. *European Journal of Neuroscience, 19*(4), 831-844.

Gelbard, H. A., Teicher, M. H., Baldessarini, R. J., Gallitano, A., Marsh, E. R., Zorc, J., & Faedda, G. (1990). Dopamine D1 receptor development depends on endogenous dopamine. *Developmental Brain Research, 56*(1), 137-140.

Gelbard, H. A., Teicher, M. H., Faedda, G., & Baldessarini, R. J. (1989). Postnatal development of dopamine D1 and D2 receptor sites in rat striatum. *Developmental Brain Research, 49*(1), 123-130.

Gerfen, C. R. (1992). The neostriatal mosaic: multiple levels of compartmental organization in the basal ganglia. *Annual Review of Neuroscience, 15*, 285-320.

Gerfen, C. R., & Engber, T. M. (1992). Molecular neuroanatomic mechanisms of Parkinson's disease: a proposed therapeutic approach. *Neurologic Clinics, 10*(2), 435-449.

Gerfen, C. R., Engber, T. M., Mahan, L. C., Susel, Z., Chase, T. N., Monsma, F. J., Jr., & Sibley, D. R. (1990). D1 and D2 dopamine receptor-regulated gene expression of striatonigral and striatopallidal neurons. *Science, 250*(4986), 1429-1432.

Gerfen, C. R., & Keefe, K. A. (1994). Neostriatal dopamine receptors. *Trends in Neurosciences, 17*(1), 2-3; author reply 4-5.

Gerfen, C. R., Staines, W. A., Arbuthnott, G. W., & Fibiger, H. C. (1982). Crossed connections of the substantia nigra in the rat. *Journal of Comparative Neurology, 207*(3), 283-303.

Gerhardt, S., Gerber, R., & Liebman, J. M. (1985). SCH 23390 dissociated from conventional neuroleptics in apomorphine climbing and primate acute dyskinesia models. *Life Sciences, 37*(25), 2355-2363.

Gessa, G. L., Porceddu, M. L., Collu, M., Mereu, G., Serra, M., Ongini, E., & Biggio, G. (1985). Sedation and sleep induced by high doses of apomorphine after blockade of D-1 receptors by SCH 23390. *European Journal of Pharmacology, 109*(2), 269-274.

Gilbert, P. E., & Martin, W. R. (1976). The effects of morphine and nalorphine-like drugs in the nondependent, morphine-dependent and cyclazocine-dependent chronic spinal dog. *Journal of Pharmacology and Experimental Therapeutics, 198*(1), 66-82.

Giorgi, O., & Biggio, G. (1990a). Selective unilateral inactivation of striatal D1 and D2 dopamine receptor subtypes by EEDQ: turning behavior elicited by D2 dopamine receptor agonists. *Brain Research, 533*(1), 53-59.

Giorgi, O., & Biggio, G. (1990b). Unilateral inactivation of dopamine receptors after intrastriatal injection of N-ethoxy-carbonyl-2-ethoxy-1,2-dihydroquinoline (EEDQ): a novel rotational model to investigate dopamine receptor interactions. *Pharmacology, Biochemistry and Behavior, 35*(4), 877-884.

Giorgi, O., De Montis, G., Porceddu, M. L., Mele, S., Calderini, G., Toffano, G., & Biggio, G. (1987). Developmental and age-related changes in D1-dopamine receptors and dopamine content in the rat striatum. *Brain Research, 432*(2), 283-290.

Giorgi, O., Porceddu, M. L., Pepitoni, S., Serra, G. P., Toffano, G., & Biggio, G. (1990). Differential effect of aging on ^{3}H-SCH 23390 binding sites in the retina and in distinct areas of the rat brain. *Journal of Neural Transmission. General Section, 82*(3), 157-166.

Glick, S. D., Maisonneuve, I. M., Raucci, J., & Archer, S. (1995). Kappa opioid inhibition of morphine and cocaine self-administration in rats. *Brain Research, 681*(1-2), 147-152.

Gogas, K. R., Levine, J. D., & Basbaum, A. I. (1996). Differential contribution of descending controls to the antinociceptive actions of *kappa* and *mu* opioids: an analysis of formalin-evoked C-Fos expression. *Journal of Pharmacology and Experimental Therapeutics, 276*(2), 801-809.

Golden, G. S. (1973). Prenatal development of the biogenic amine systems of the mouse brain. *Developmental Biology, 33*(2), 300-311.

Goldstein, A., Tachibana, S., Lowney, L. I., Hunkapiller, M., & Hood, L. (1979). Dynorphin-(1-13), an extraordinarily potent opioid peptide. *Proceedings of the National Academy of Sciences, United States of America, 76*(12), 6666-6670.

Gower, A. J., & Marriott, A. S. (1982). Pharmacological evidence for the subclassification of central dopamine receptors in the rat. *British Journal of Pharmacology, 77*(1), 185-193.

Graybiel, A. M., Aosaki, T., Flaherty, A. W., & Kimura, M. (1994). The basal ganglia and adaptive motor control. *Science, 265*(5180), 1826-1831.

Gross, R. A., & Macdonald, R. L. (1987). Dynorphin A selectively reduces a large transient (N-type) calcium current of mouse dorsal root ganglion neurons in cell culture. *Proceedings of the National Academy of Sciences, United States of America, 84*(15), 5469-5473.

Gulland, J. M., & Robinson, R. (1923). The Morphine Group. Part I. A Discussion of the Constitutional Problem. *Journal of the Chemical Society*(23), 980-998.

Hakansson, K., Pozzi, L., Usiello, A., Haycock, J., Borrelli, E., & Fisone, G. (2004). Regulation of striatal tyrosine hydroxylase phosphorylation by acute and chronic haloperidol. *European Journal of Neuroscience, 20*(4), 1108-1112.

Hamblin, M. W., & Creese, I. (1983). Behavioral and radioligand binding evidence for irreversible dopamine receptor blockade by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline. *Life Sciences, 32*(19), 2247-2255.

Hammond, C., Deniau, J. M., Rizk, A., & Feger, J. (1978). Electrophysiological demonstration of an excitatory subthalamonigral pathway in the rat. *Brain Research, 151*(2), 235-244.

Harsing, L. G., Jr., & Zigmond, M. J. (1998). Postsynaptic integration of cholinergic and dopaminergic signals on medium-sized GABAergic projection neurons in the neostriatum. *Brain Research Bulletin, 45*(6), 607-613.

Hartley, E. J., & Seeman, P. (1983). Development of receptors for dopamine and noradrenaline in rat brain. *European Journal of Pharmacology, 91*(4), 391-397.

Hassani, O. K., Francois, C., Yelnik, J., & Feger, J. (1997). Evidence for a dopaminergic innervation of the subthalamic nucleus in the rat. *Brain Research, 749*(1), 88-94.

Hauber, W. (1998). Involvement of basal ganglia transmitter systems in movement initiation. *Progress in Neurobiology, 56*(5), 507-540.

Hedner, T., & Lundborg, P. (1985). Development of dopamine autoreceptors in the postnatal rat brain. *Journal of Neural Transmission, 62*(1-2), 53-63.

Heimer, L., Zahm, D. S., & Alheid, G. F. (1995). Basal Ganglia. In G. Paxinos (Ed.), *The Rat Nervous System* (Second ed., pp. 579-628). San Diego: Academic Press.

Henry, J. M., Joseph, J. A., Kochman, K., & Roth, G. S. (1987). Effect of aging on striatal dopamine receptor subtype recovery following N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline blockade and relation to motor function in Wistar rats. *Brain Research, 418*(2), 334-342.

Herman, B. H., & Goldstein, A. (1985). Antinociception and paralysis induced by intrathecal dynorphin A. *Journal of Pharmacology and Experimental Therapeutics, 232*(1), 27-32.

Herman, B. H., & Panksepp, J. (1978). Effects of morphine and naloxone on separation distress and approach attachment: evidence for opiate mediation of social affect. *Pharmacology, Biochemistry and Behavior, 9*(2), 213-220.

Herrera-Marschitz, M., Christensson-Nylander, I., Sharp, T., Staines, W., Reid, M., Hokfelt, T., Terenius, L., & Ungerstedt, U. (1986). Striato-nigral dynorphin and substance P pathways in the rat. II. Functional analysis. *Experimental Brain Research, 64*(1), 193-207.

Herrera-Marschitz, M., Hokfelt, T., Ungerstedt, U., & Terenius, L. (1983). Functional studies with the opioid peptide dynorphin: acute effects of injections into the substantia nigra reticulata of naive rats. *Life Sciences, 33 Suppl 1*, 555-558.

Herrera-Marschitz, M., Hokfelt, T., Ungerstedt, U., Terenius, L., & Goldstein, M. (1984). Effect of intranigral injections of dynorphin, dynorphin fragments and alpha-neoendorphin on rotational behaviour in the rat. *European Journal of Pharmacology, 102*(2), 213-227.

Hersch, S. M., Ciliax, B. J., Gutekunst, C. A., Rees, H. D., Heilman, C. J., Yung, K. K., Bolam, J. P., Ince, E., Yi, H., & Levey, A. I. (1995a). Electron microscopic analysis of D1 and D2 dopamine receptor proteins in the dorsal striatum and their synaptic relationships with motor corticostriatal afferents. *J. Neurosci., 15*(7), 5222-5237.

Hersch, S. M., Ciliax, B. J., Gutekunst, C. A., Rees, H. D., Heilman, C. J., Yung, K. K., Bolam, J. P., Ince, E., Yi, H., & Levey, A. I. (1995b). Electron microscopic analysis of D1 and D2 dopamine receptor proteins in the dorsal striatum and their synaptic relationships with motor corticostriatal afferents. *The Journal of Neuroscience, 15*(7), 5222-5237.

Hess, S. M., Connamacher, R. H., Ozaki, M., & Udenfriend, S. (1961). The effects of α-methyl-DOPA and α-methyl-metatyrosine on the metabolism of norepinephrine and serotonin *in vivo*. *Journal of Pharmacology and Experimental Therapeutics, 134*, 129-138.

Hollt, V., Sanchez-Blazquez, P., & Garzon, J. (1985). Multiple opioid ligands and receptors in the control of nociception. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences, 308*(1136), 299-312.

Huang, Q., Zhou, D., Chase, K., Gusella, J. F., Aronin, N., & DiFiglia, M. (1992). Immunohistochemical localization of the D1 dopamine receptor in rat brain reveals its axonal transport, pre- and postsynaptic localization, and prevalence in the basal ganglia, limbic system, and thalamic reticular nucleus. *Proceedings of the National Academy of Sciences, United States of America, 89*(24), 11988-11992.

Huntley, G. W., Morrison, J. H., Prikhozhan, A., & Sealfon, S. C. (1992). Localization of multiple dopamine receptor subtype mRNAs in human and monkey motor cortex and striatum. *Molecular Brain Research, 15*(3-4), 181-188.

Imai, H., Steindler, D. A., & Kitai, S. T. (1986). The organization of divergent axonal projections from the midbrain raphe nuclei in the rat. *Journal of Comparative Neurology, 243*(3), 363-380.

Iversen, S. D., & Koob, G. F. (1977). Behavioral implications of dopaminergic neurons in the mesolimbic system. *Advances in Biochemical Psychopharmacology, 16*, 209-214.

Jackson, A., & Cooper, S. J. (1988). Observational analysis of the effects of kappa opioid agonists an open field behaviour in the rat. *Psychopharmacology, 94*(2), 248-253.

Jackson, D. M., Anden, N. E., & Dahlstrom, A. (1975). A functional effect of dopamine in the nucleus accumbens and in some other dopamine-rich parts of the rat brain. *Psychopharmacologia, 45*(2), 139-149.

Jackson, H. C., & Sewell, R. D. (1984). The involvement of mu- and kappa- but not delta-opioid receptors in the body weight gain of suckling rats. *Psychopharmacology, 84*(1), 143-144.

Janecka, A., Fichna, J., & Janecki, T. (2004). Opioid receptors and their ligands. *Current Topics in Medicinal Chemistry, 4*(1), 1-17.

Joel, D., Ayalon, L., Tarrasch, R., Veenman, L., Feldon, J., & Weiner, I. (1998). Electrolytic lesion of globus pallidus ameliorates the behavioral and neurodegenerative effects of quinolinic acid lesion of the striatum: a potential novel treatment in a rat model of Huntington's disease. *Brain Research, 787*(1), 143-148.

Jones, R. M., Hjorth, S. A., Schwartz, T. W., & Portoghese, P. S. (1998). Mutational evidence for a common kappa antagonist binding pocket in the wild-type kappa and mutant mu[K303E] opioid receptors. *Journal of Medicinal Chemistry, 41*(25), 4911-4914.

Joyce, E. M., Stinus, L., & Iversen, S. D. (1983). Effect of injections of 6-OHDA into either nucleus accumbens septi or frontal cortex on spontaneous and drug-induced activity. *Neuropharmacology, 22*(9), 1141-1145.

Kalivas, P. W. (1993). Neurotransmitter regulation of dopamine neurons in the ventral tegmental area. *Brain Research Review, 18*(1), 75-113.

Kalsbeek, A., Voorn, P., Buijs, R. M., Pool, C. W., & Uylings, H. B. (1988). Development of the dopaminergic innervation in the prefrontal cortex of the rat. *Journal of Comparative Neurology, 269*(1), 58-72.

Kandel, E. R., Schwartz, J. H., & Jessell, T. M. (2000). *Priniciples of Neural Sciene* (4th ed.): McGraw-Hill.

Karper, P. E., Nazarian, A., Crawford, C. A., Drago, J., & McDougall, S. A. (2000). Role of dopamine D(1) receptors for kappa-opioid-mediated locomotor activity and antinociception during the preweanling period: a study using D(1) receptor knockout mice. *Physiology and Behavior, 68*(4), 585-590.

Kaufman, S., & Friedman, S. (1965). Dopamine-β-Hydroxylase. *Pharmacological Reviews, 17*, 71-100.

Kawasaki, A. M., Knapp, R. J., Walton, A., Wire, W. S., Zalewska, T., Yamamura, H. I., Porreca, F., Burks, T. F., & Hruby, V. J. (1993). Syntheses, opioid binding affinities, and potencies of dynorphin A analogues substituted in positions, 1, 6, 7, 8 and 10. *International Journal of Peptide and Protein Research, 42*(5), 411-419.

Kehoe, P., & Boylan, C. B. (1994). Behavioral effects of kappa-opioid-receptor stimulation on neonatal rats. *Behavioral Neuroscience, 108*(2), 418-423.

Kelly, P. H., Seviour, P. W., & Iversen, S. D. (1975). Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. *Brain Research, 94*(3), 507-522.

Kent, J. L., Pert, C. B., & Herkenham, M. (1981). Ontogeny of opiate receptors in rat forebrain: visualization by in vitro autoradiography. *Brain Research, 254*(4), 487-504.

Kieffer, B. L., Befort, K., Gaveriaux-Ruff, C., & Hirth, C. G. (1992). The delta-opioid receptor: isolation of a cDNA by expression cloning and pharmacological characterization. *Proceedings of the National Academy of Sciences, United States of America, 89*(24), 12048-12052.

Kimura, M. (1995). Role of basal ganglia in behavioral learning. *Neuroscience Research, 22*(4), 353-358.

Kita, H., & Kitai, S. T. (1987). Efferent projections of the subthalamic nucleus in the rat: light and electron microscopic analysis with the PHA-L method. *Journal of Comparative Neurology, 260*(3), 435-452.

Kitchen, I., Kelly, M., & Viveros, M. P. (1990). Ontogenesis of kappa-opioid receptors in rat brain using [^{3}H]U-69593 as a binding ligand. *European Journal of Pharmacology, 175*(1), 93-96.

Knowlton, B. J., Mangels, J. A., & Squire, L. R. (1996). A neostriatal habit learning system in humans. *Science, 273*(5280), 1399-1402.

Koller, W. C., & Herbster, G. (1988). D1 and D2 dopamine receptor mechanisms in dopaminergic behaviors. *Clinical Neuropharmacology, 11*(3), 221-231.

Kornblum, H. I., Hurlbut, D. E., & Leslie, F. M. (1987). Postnatal development of multiple opioid receptors in rat brain. *Brain Research, 465*(1-2), 21-41.

Kostrzewa, R. M., & Saleh, M. I. (1989). Impaired ontogeny of striatal dopamine D1 and D2 binding sites after postnatal treatment of rats with SCH-23390 and spiroperidol. *Developmental Brain Research, 45*(1), 95-101.

Kuzmin, A., Sandin, J., Terenius, L., & Ogren, S. O. (2000). Dose- and time-dependent bimodal effects of kappa-opioid agonists on locomotor activity in mice. *Journal of Pharmacology and Experimental Therapeutics, 295*(3), 1031-1042.

Kuzmin, A. V., Semenova, S., Gerrits, M. A., Zvartau, E. E., & Van Ree, J. M. (1997). Kappa-opioid receptor agonist U50,488H modulates cocaine and morphine self-administration in drug-naive rats and mice. *European Journal of Pharmacology, 321*(3), 265-271.

Lacey, M. G., Mercuri, N. B., & North, R. A. (1987). Dopamine acts on D2 receptors to increase potassium conductance in neurones of the rat substantia nigra zona compacta. *Journal of Physiology, 392*, 397-416.

Lal, S., & Sourkes, T. L. (1973). Ontogeny of stereotyped behaviour induced by apomorphine and amphetamine in the rat. *Archives Internationales de Pharmacodynamie et de Therapie, 202*(1), 171-182.

Larson, D. L., Jones, R. M., Hjorth, S. A., Schwartz, T. W., & Portoghese, P. S. (2000). Binding of norbinaltorphimine (*norBNI*) congeners to wild-type and mutant mu and kappa opioid receptors: molecular recognition loci for the pharmacophore and address components of kappa antagonists. *Journal of Medicinal Chemistry, 43*(8), 1573-1576.

Lauder, J. M., & Bloom, F. E. (1974). Ontogeny of monoamine neurons in the locus coeruleus, raphe nuclei and substantia nigra of the rat. I. Cell differentiation. *Journal of Comparative Neurology, 155*(4), 469-481.

Lazarus, L. H., Bryant, S. D., Cooper, P. S., & Salvadori, S. (1999). What peptides these deltorphins be. *Progress in Neurobiology, 57*(4), 377-420.

Le Moine, C., & Bloch, B. (1995). D1 and D2 dopamine receptor gene expression in the rat striatum: sensitive cRNA probes demonstrate prominent segregation of D1 and D2 mRNAs in distinct neuronal populations of the dorsal and ventral striatum. *Journal of Comparative Neurology, 355*(3), 418-426.

Le Moine, C., Normand, E., & Bloch, B. (1991). Phenotypical characterization of the rat striatal neurons expressing the D1 dopamine receptor gene. *Proceedings of the National Academy of Sciences, United States of America, 88*(10), 4205-4209.

Le Moine, C., Normand, E., Guitteny, A. F., Fouque, B., Teoule, R., & Bloch, B. (1990). Dopamine receptor gene expression by enkephalin neurons in rat forebrain. *Proceedings of the National Academy of Sciences, United States of America, 87*(1), 230-234.

Leander, J. D., Zerbe, R. L., & Hart, J. C. (1985). Diuresis and suppression of vasopressin by kappa opioids: comparison with mu and delta opioids and clonidine. *Journal of Pharmacology and Experimental Therapeutics, 234*(2), 463-469.

Lemaire, S., Chouinard, L., Denis, D., Panico, M., & Morris, H. R. (1982). Mass spectrometric identification of various molecular forms of dynorphin in bovine adrenal medulla. *Biochemical and Biophysical Research Communications, 108*(1), 51-58.

Lemaire, S., & Turcotte, A. (1986). Synthesis and biological activity of analogs of dynorphin-A(1-13) substituted in positions 2 and 4: design of [Ala2,Trp4]-Dyn-A(1-13) as a putative selective opioid antagonist. *Canadian Journal of Physiology and Pharmacology, 64*(6), 673-678.

Lepekhina, L. M., & Tsitsurina, E. A. (2007). Stereotyped behavior in the ontogeny of rats. *Bulletin of Experimental Biology and Medicine, 144*(3), 349-351.

Leslie, F. M. (1987). Methods used for the study of opioid receptors. *Pharmacological Reviews, 39*(3), 197-249.

Leslie, F. M., & Loughlin, S. E. (1993). Ontogeny and plasticity of opioid systems. In R. P. Hammer (Ed.), *The Neurobiology of Opiates* (pp. 85-123): CRC Press, Boca Raton, FL.

Lester, J., Fink, S., Aronin, N., & DiFiglia, M. (1993). Colocalization of D1 and D2 dopamine receptor mRNAs in striatal neurons. *Brain Research, 621*(1), 106-110.

Levesque, D., Diaz, J., Pilon, C., Martres, M. P., Giros, B., Souil, E., Schott, D., Morgat, J. L., Schwartz, J. C., & Sokoloff, P. (1992). Identification, characterization, and localization of the dopamine D_3 receptor in rat brain using 7-[^{3}H]hydroxy-*N*,*N*-di-*n*-propyl-2-aminotetralin. *Proceedings of the National Academy of Sciences, United States of America, 89*(17), 8155-8159.

Levey, A. I., Hersch, S. M., Rye, D. B., Sunahara, R. K., Niznik, H. B., Kitt, C. A., Price, D. L., Maggio, R., Brann, M. R., Ciliax, B. J., & et al. (1993). Localization of D1 and D2 dopamine receptors in brain with subtype-specific antibodies. *Proceedings of the National Academy of Sciences, United States of America, 90*(19), 8861-8865.

Levin, E. Y., Levenberg, B., & Kaufman, S. (1960). The enzymatic conversion of 3,4-dihydroxyphenylethylamine to norepinephrine. *Journal of Biological Chemistry, 235*, 2080-2086.

Levitt, M., Spector, S., Sjoerdsma, A., & Udenfriend, S. (1965). Elucidation of the rate-limiting step in norepinephrine biosynthesis in the perfused guinea-pig heart. *Journal of Pharmacology and Experimental Therapeutics, 148*, 1-8.

Leyton, M., & Stewart, J. (1992). The stimulation of central kappa opioid receptors decreases male sexual behavior and locomotor activity. *Brain Res, 594*(1), 56-74.

Li, S., Zhu, J., Chen, C., Chen, Y. W., Deriel, J. K., Ashby, B., & Liu-Chen, L. Y. (1993). Molecular cloning and expression of a rat kappa opioid receptor. *Biochemical Journal, 295 (Pt 3)*, 629-633.

Lin, C. E., Takemori, A. E., & Portoghese, P. S. (1993). Synthesis and kappa-opioid antagonist selectivity of a norbinaltorphimine congener. Identification of the address moiety required for kappa-antagonist activity. *Journal of Medicinal Chemistry, 36*(16), 2412-2415.

Lin, M. Y., & Walters, D. E. (1994). Dopamine D2 autoreceptors in rats are behaviorally functional at 21 but not 10 days of age. *Psychopharmacology, 114*(2), 262-268.

Lindvall, O., & Bjorklund, A. (1979). Dopaminergic innervation of the globus pallidus by collaterals from the nigrostriatal pathway. *Brain Research, 172*(1), 169-173.

Ljungberg, T. (1986). Locomotion and stereotyped behaviours induced by 1-amino-3,5-dimethyladamantane (D 145) and apomorphine in the rat: a comparison. *Journal of Pharmacy and Pharmacology, 38*(7), 520-525.

Lu, Y., Nguyen, T. M., Weltrowska, G., Berezowska, I., Lemieux, C., Chung, N. N., & Schiller, P. W. (2001). [2',6'-Dimethyltyrosine]dynorphin A(1-11)-NH2 analogues lacking an N-terminal amino group: potent and selective kappa opioid antagonists. *Journal of Medicinal Chemistry, 44*(19), 3048-3053.

Magnan, J., Paterson, S. J., Tavani, A., & Kosterlitz, H. W. (1982). The binding spectrum of narcotic analgesic drugs with different agonist and antagonist properties. *Naunyn-Schmiedeberg's Archives of Pharmacology, 319*(3), 197-205.

Maisonneuve, I. M., Archer, S., & Glick, S. D. (1994). U50,488, a kappa opioid receptor agonist, attenuates cocaine-induced increases in extracellular dopamine in the nucleus accumbens of rats. *Neuroscience Letters, 181*(1-2), 57-60.

Mansour, A., Fox, C. A., Meng, F., Akil, H., & Watson, S. J. (1994). κ_1 Receptor mRNA distribution in the rat CNS: comparison to kappa receptor binding and prodynorphin mRNA. *Molecular and Cellular Neurosciences, 5*(2), 124-144.

Mansour, A., Hoversten, M. T., Taylor, L. P., Watson, S. J., & Akil, H. (1995). The cloned mu, delta and kappa receptors and their endogenous ligands: evidence for two opioid peptide recognition cores. *Brain Research, 700*(1-2), 89-98.

Mansour, A., Khachaturian, H., Lewis, M. E., Akil, H., & Watson, S. J. (1987). Autoradiographic differentiation of mu, delta, and kappa opioid receptors in the rat forebrain and midbrain. *Journal of Neuroscience,* 7(8), 2445-2464.

Mansour, A., Khachaturian, H., Lewis, M. E., Akil, H., & Watson, S. J. (1988). Anatomy of CNS opioid receptors. *Trends in Neurosciences, 11*(7), 308-309.

Marchese, A., Docherty, J. M., Nguyen, T., Heiber, M., Cheng, R., Heng, H. H. Q., Tsui, L.-C., Shi, X., George, S. R., & O'Dowd, B. F. (1994). Cloning of Human Genes Encoding Novel G Protein-Coupled Receptors. *Genomics, 23*(3), 609-618.

Marshall, J. F., & Ungerstedt, U. (1977). Supersensitivity to apomorphine following destruction of the ascending dopamine neurons: quantification using the rotational model. *European Journal of Pharmacology, 41*(4), 361-367.

Marti, M., Paganini, F., Stocchi, S., Mela, F., Beani, L., Bianchi, C., & Morari, M. (2003). Plasticity of glutamatergic control of striatal acetylcholine release in experimental parkinsonism: opposite changes at group-II metabotropic and NMDA receptors. *Journal of Neurochemistry, 84*(4), 792-802.

Martin, W. R., Eades, C. G., Thompson, J. A., Huppler, R. E., & Gilbert, P. E. (1976). The effects of morphine- and nalorphine- like drugs in the nondependent and morphine-dependent chronic spinal dog. *Journal of Pharmacology and Experimental Therapeutics, 197*(3), 517-532.

Matsumoto, R. R., Brinsfield, K. H., Patrick, R. L., & Walker, J. M. (1988). Rotational behavior mediated by dopaminergic and nondopaminergic mechanisms after intranigral microinjection of specific mu, delta and kappa opioid agonists. *Journal of Pharmacology and Experimental Therapeutics, 246*(1), 196-203.

Mattson, M. P. (1988). Neurotransmitters in the regulation of neuronal cytoarchitecture. *Brain Research, 472*(2), 179-212.

McDevitt, J. T., & Setler, P. E. (1981). Differential effects of dopamine agonists in mature and immature rats. *European Journal of Pharmacology, 72*(1), 69-75.

McDougall, S. A., Arnold, T. F., & Nonneman, A. J. (1990). Ontogeny of locomotor activity and grooming in the young rat: role of dopamine D1 and D2 receptors. *European Journal of Pharmacology, 186*(2-3), 223-230.

McDougall, S. A., Crawford, C. A., & Nonneman, A. J. (1993). Behavioral effects of selective and nonselective dopamine agonists on young rats after irreversible antagonism of D1 and/or D2 receptors. *Psychopharmacology, 111*(2), 225-232.

McDougall, S. A., Garmsen, G. M., Meier, T. L., & Crawford, C. A. (1997). Kappa opioid mediated locomotor activity in the preweanling rat: role of pre- and postsynaptic dopamine receptors. *Psychopharmacology, 133*(1), 62-68.

McDougall, S. A., Rodarte-Freeman, A. L., & Nazarian, A. (1999). Indirect dopamine agonists augment the locomotor activating effects of the kappa-opioid receptor agonist U-50,488 in preweanling rats. *Developmental Psychobiology, 34*(3), 183-193.

McGeorge, A. J., & Faull, R. L. (1989). The organization of the projection from the cerebral cortex to the striatum in the rat. *Neuroscience, 29*(3), 503-537.

McLean, S., Rothman, R. B., & Herkenham, M. (1986). Autoradiographic localization of mu- and delta-opiate receptors in the forebrain of the rat. *Brain Research, 378*(1), 49-60.

Meador-Woodruff, J. H., Mansour, A., Grandy, D. K., Damask, S. P., Civelli, O., & Watson, S. J., Jr. (1992). Distribution of D5 dopamine receptor mRNA in rat brain. *Neuroscience Letters, 145*(2), 209-212.

Meador-Woodruff, J. H., Mansour, A., Healy, D. J., Kuehn, R., Zhou, Q. Y., Bunzow, J. R., Akil, H., Civelli, O., & Watson, S. J., Jr. (1991). Comparison of the distributions of D1 and D2 dopamine receptor mRNAs in rat brain. *Neuropsychopharmacology, 5*(4), 231-242.

Meller, E., Bohmaker, K., Goldstein, M., & Friedhoff, A. J. (1985). Inactivation of D1 and D2 dopamine receptors by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline in vivo: selective protection by neuroleptics. *Journal of Pharmacology and Experimental Therapeutics, 233*(3), 656-662.

Meller, E., Bordi, F., & Bohmaker, K. (1988). Enhancement by the D1 dopamine agonist SKF 38393 of specific components of stereotypy elicited by the D2 agonists LY 171555 and RU 24213. *Life Sciences, 42*(25), 2561-2567.

Mello, L. E., & Villares, J. (1997). Neuroanatomy of the basal ganglia. *Psychiatric Clinics of North America, 20*(4), 691-704.

Meng, F., Xie, G. X., Thompson, R. C., Mansour, A., Goldstein, A., Watson, S. J., & Akil, H. (1993). Cloning and pharmacological characterization of a rat kappa opioid receptor. *Proceedings of the National Academy of Sciences, United States of America, 90*(21), 9954-9958.

Meriney, S. D., Gray, D. B., & Pilar, G. (1985). Morphine-induced delay of normal cell death in the avian ciliary ganglion. *Science, 228*(4706), 1451-1453.

Mestlin, M., & McDougall, S. A. (1993). Ontogenetic differences in the effects of EEDQ on dopamine-mediated behaviors. *Pharmacology, Biochemistry and Behavior, 45*(4), 797-802.

Millan, M. J., Czlonkowski, A., Lipkowski, A., & Herz, A. (1989). Kappa-opioid receptor-mediated antinociception in the rat. II. Supraspinal in addition to spinal sites of action. *Journal of Pharmacology and Experimental Therapeutics, 251*(1), 342-350.

Miller, L. G., Lumpkin, M., Galpern, W. R., Greenblatt, D. J., & Shader, R. I. (1991). Modification of gamma-aminobutyric acidA receptor binding and function by N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline in vitro and in vivo: effects of aging. *Journal of Neurochemistry, 56*(4), 1241-1247.

Minami, M., Hosoi, Y., Toya, T., Katao, Y., Maekawa, K., Katsumata, S., Yabuuchi, K., Onogi, T., & Satoh, M. (1993). In situ hybridization study of kappa-opioid receptor mRNA in the rat brain. *Neuroscience Letters, 162*(1-2), 161-164.

Mogenson, G. J., & Wu, M. (1991a). Effects of administration of dopamine D2 agonist quinpirole on exploratory locomotion. *Brain Research, 551*(1-2), 216-220.

Mogenson, G. J., & Wu, M. (1991b). Quinpirole to the accumbens reduces exploratory and amphetamine-elicited locomotion. *Brain Research Bulletin, 27*(5), 743-746.

Mollereau, C., Parmentier, M., Mailleux, P., Butour, J.-L., Moisand, C., Chalon, P., Caput, D., Vassart, G., & Meunier, J.-C. (1994). ORL1, a novel member of the opioid receptor family : Cloning, functional expression and localization. *FEBS Letters, 341*(1), 33-38.

Molloy, A. G., & Waddington, J. L. (1984). Dopaminergic behaviour stereospecific promoted by the D1 agonist R-SK & F 38393 and selectively blocked by the D1 antagonist SCH 23390. *Psychopharmacology, 82*(4), 409-410.

Montecucchi, P. C., de Castiglione, R., Piani, S., Gozzini, L., & Erspamer, V. (1981). Amino acid composition and sequence of dermorphin, a novel opiate-like peptide from the skin of Phyllomedusa sauvagei. *International Journal of Peptide and Protein Research, 17*(3), 275-283.

Montmayeur, J. P., Guiramand, J., & Borrelli, E. (1993). Preferential coupling between dopamine D2 receptors and G-proteins. *Molecular Endocrinology, 7*(2), 161-170.

Moody, C. A., & Spear, L. P. (1992). Ontogenetic differences in the psychopharmacological responses to separate and combined stimulation of D1 and D2 dopamine receptors during the neonatal to weanling age period. *Psychopharmacology, 106*(2), 161-168.

Morelli, M., & Di Chiara, G. (1985). Non-dopaminergic mechanisms in the turning behavior evoked by intranigral opiates. *Brain Research, 341*(2), 350-359.

Mottola, D. M., Kilts, J. D., Lewis, M. M., Connery, H. S., Walker, Q. D., Jones, S. R., Booth, R. G., Hyslop, D. K., Piercey, M., Wightman, R. M., Lawler, C. P., Nichols, D. E., & Mailman, R. B. (2002). Functional selectivity of dopamine receptor agonists. I. Selective activation of postsynaptic dopamine D2 receptors linked to adenylate cyclase. *Journal of Pharmacology and Experimental Therapeutics, 301*(3), 1166-1178.

Mrabet, O., Messier, C., & Destrade, C. (1989). [Circling behavior produced by the unilateral intra-accumbens injection of dopaminergic agonist and two dopaminergic antagonists in mice]. *Comptes Rendus de l'Academie des Sciences. Serie III, Sciences de la Vie, 309*(3), 77-82.

Mrzljak, L., Bergson, C., Pappy, M., Huff, R., Levenson, R., & Goldman-Rakic, P. S. (1996). Localization of dopamine D4 receptors in GABAergic neurons of the primate brain. *Nature, 381*(6579), 245-248.

Mulder, A. H., Wardeh, G., Hogenboom, F., & Frankhuyzen, A. L. (1989). Selectivity of various opioid peptides towards delta-, kappa; and mu-opioid receptors mediating presynaptic inhibition of neurotransmitter release in the brain. *Neuropeptides, 14*(2), 99-104.

Murrin, L. C., & Zeng, W. Y. (1990). Ontogeny of dopamine D1 receptors in rat forebrain: a quantitative autoradiographic study. *Developmental Brain Research, 57*(1), 7-13.

Myslivecek, J., & Hassmannova, J. (1979). Ontogeny of active avoidance in the rat: learning and memory. *Developmental Psychobiology, 12*(2), 169-186.

Nagatsu, T., Levitt, M., & Udenfriend, S. (1964). Conversion of L-tyrosine to 3,4-dihydroxyphenylalanine by cell-free preparations of brain and sympathetically innervated tissues. *Biochemical and Biophysical Research Communications, 14*, 543-549.

Nagy, J. I., Carter, D. A., Lehmann, J., & Fibiger, H. C. (1978). Evidence for a GABA-containing projection from the entopeduncular nucleus to the lateral habenula in the rat. *Brain Research, 145*(2), 360-364.

Nakamura, S., Ito, Y., Shirasaki, R., & Murakami, F. (2000). Local directional cues control growth polarity of dopaminergic axons along the rostrocaudal axis. *Journal of Neuroscience, 20*(11), 4112-4119.

Nakanishi, H., Kita, H., & Kitai, S. T. (1987). Intracellular study of rat substantia nigra pars reticulata neurons in an in vitro slice preparation: electrical membrane properties and response characteristics to subthalamic stimulation. *Brain Research, 437*(1), 45-55.

Nauta, H. J. (1979). Projections of the pallidal complex: an autoradiographic study in the cat. *Neuroscience, 4*(12), 1853-1873.

Nazarian, A., Rodarte-Freeman, A. L., & McDougall, S. A. (1999). Dopaminergic modulation of kappa opioid-mediated ultrasonic vocalization, antinociception, and locomotor activity in the preweanling rat. *Behavioral Neuroscience, 113*(4), 816-825.

Neal, B. S., & Joyce, J. N. (1992). Neonatal 6-OHDA lesions differentially affect striatal D1 and D2 receptors. *Synapse, 11*(1), 35-46.

Neisewander, J. L., Lucki, I., & McGonigle, P. (1991). Behavioral and neurochemical effects of chronic administration of reserpine and SKF-38393 in rats. *Journal of Pharmacology and Experimental Therapeutics, 257*(2), 850-860.

Nishi, M., Takeshima, H., Fukuda, K., Kato, S., & Mori, K. (1993). cDNA cloning and pharmacological characterization of an opioid receptor with high affinities for kappa-subtype-selective ligands. *FEBS Letters, 330*(1), 77-80.

Nock, B., Rajpara, A., O'Connor, L. H., & Cicero, T. J. (1988). Autoradiography of [^{3}H]U-69593 binding sites in rat brain: evidence for kappa opioid receptor subtypes. *European Journal of Pharmacology, 154*(1), 27-34.

Norman, A. B., & Creese, I. (1986). Effects of in vivo and in vitro treatments with N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline on putative muscarinic receptor subtypes in rat brain. *Molecular Pharmacology, 30*(2), 96-103.

Norman, A. B., Eubanks, J. H., & Creese, I. (1989). Irreversible and quaternary muscarinic antagonists discriminate multiple muscarinic receptor binding sites in rat brain. *Journal of Pharmacology and Experimental Therapeutics, 248*(3), 1116-1122.

North, R. A. (1993). Opioid actions on membrane ion channels. In A. Herz (Ed.), *Opioids I* (Vol. 104, pp. 773-796). New York: Springer-Verlag.

Nowak, G., Arnt, J., & Hyttel, J. (1988). EEDQ, a tool for ex vivo measurement of occupancy of D-1 and D-2 dopamine receptors. *European Journal of Pharmacology, 153*(2-3), 309-311.

Nyberg, F., Sanderson, K., & Glamsta, E. L. (1997). The hemorphins: a new class of opioid peptides derived from the blood protein hemoglobin. *Biopolymers, 43*(2), 147-156.

O'Connor, W. T. (2001). Functional neuroanatomy of the ventral striopallidal GABA pathway. New sites of intervention in the treatment of schizophrenia. *Journal of Neuroscience Methods, 109*(1), 31-39.

O'Malley, K. L., Harmon, S., Tang, L., & Todd, R. D. (1992). The rat dopamine D4 receptor: sequence, gene structure, and demonstration of expression in the cardiovascular system. *New Biologist, 4*(2), 137-146.

Olson, G. A., Olson, R. D., & Kastin, A. J. (1992). Endogenous opiates: 1991. *Peptides, 13*(6), 1247-1287.

Panksepp, J., Siviy, S., Normansell, L., White, K., & Bishop, P. (1982). Effects of beta-chlornaltrexamine on separation distress in chicks. *Life Sciences, 31*(20-21), 2387-2390.

Pardo, J. V., Creese, I., Burt, D. R., & Snyder, S. H. (1977). Ontogenesis of dopamine receptor binding in the corpus striatum of the rat. *Brain Research, 125*(2), 376-382.

Parent, A., & Hazrati, L. N. (1994). Multiple striatal representation in primate substantia nigra. *Journal of Comparative Neurology, 344*(2), 305-320.

Parent, A., & Hazrati, L. N. (1995). Functional anatomy of the basal ganglia. II. The place of subthalamic nucleus and external pallidum in basal ganglia circuitry. *Brain Research Review, 20*(1), 128-154.

Paxinos, G., & Watson, C. (1998). *The rat brain: in stereotaxic coordinates* (4th ed.). San Diego: Academic Press.

Pereda, A., Triller, A., Korn, H., & Faber, D. S. (1992). Dopamine enhances both electrotonic coupling and chemical excitatory postsynaptic potentials at mixed synapses. *Proceedings of the National Academy of Sciences, United States of America, 89*(24), 12088-12092.

Petrillo, P., Tavani, A., Verotta, D., Robson, L. E., & Kosterlitz, H. W. (1987). Differential postnatal development of mu-, delta- and kappa-opioid binding sites in rat brain. *Brain Research, 428*(1), 53-58.

Pijnenburg, A. J., Honig, W. M., Van der Heyden, J. A., & Van Rossum, J. M. (1976). Effects of chemical stimulation of the mesolimbic dopamine system upon locomotor activity. *European Journal of Pharmacology, 35*(1), 45-58.

Plaznik, A., Stefanski, R., & Kostowski, W. (1989). Interaction between accumbens D1 and D2 receptors regulating rat locomotor activity. *Psychopharmacology, 99*(4), 558-562.

Pugh, M. T., O'Boyle, K. M., Molloy, A. G., & Waddington, J. L. (1985). Effects of the putative D-1 antagonist SCH 23390 on stereotyped behaviour induced by the D-2 agonist RU24213. *Psychopharmacology, 87*(3), 308-312.

Quirion, R., Pilapil, C., & Magnan, J. (1987). Localization of kappa opioid receptor binding sites in human forebrain using [^{3}H]U69,593: comparison with [^{3}H]bremazocine. *Cellular and Molecular Neurobiology, 7*(3), 303-307.

Ramarao, P., Jablonski, H. I., Jr., Rehder, K. R., & Bhargava, H. N. (1988). Effect of kappa-opioid receptor agonists on morphine analgesia in morphine-naive and morphine-tolerant rats. *European Journal of Pharmacology, 156*(2), 239-246.

Rao, P. A., Molinoff, P. B., & Joyce, J. N. (1991). Ontogeny of dopamine D1 and D2 receptor subtypes in rat basal ganglia: a quantitative autoradiographic study. *Developmental Brain Research, 60*(2), 161-177.

Rappaport, M. S., Sealfon, S. C., Prikhozhan, A., Huntley, G. W., & Morrison, J. H. (1993). Heterogeneous distribution of D1, D2 and D5 receptor mRNAs in monkey striatum. *Brain Research, 616*(1-2), 242-250.

Reisine, T., & Bell, G. I. (1993). Molecular biology of opioid receptors. *Trends in Neurosciences, 16*(12), 506-510.

Richfield, E. K., Young, A. B., & Penney, J. B. (1987). Comparative distribution of dopamine D-1 and D-2 receptors in the basal ganglia of turtles, pigeons, rats, cats, and monkeys. *Journal of Comparative Neurology, 262*(3), 446-463.

Rius, R. A., Barg, J., Bem, W. T., Coscia, C. J., & Loh, Y. P. (1991). The prenatal development profile of expression of opioid peptides and receptors in the mouse brain. *Developmental Brain Research, 58*(2), 237-241.

Robertson, G. S., Vincent, S. R., & Fibiger, H. C. (1992). D1 and D2 dopamine receptors differentially regulate c-fos expression in striatonigral and striatopallidal neurons. *Neuroscience, 49*(2), 285-296.

Ryan, L. J., & Clark, K. B. (1991). The role of the subthalamic nucleus in the response of globus pallidus neurons to stimulation of the prelimbic and agranular frontal cortices in rats. *Experimental Brain Research, 86*(3), 641-651.

Schambra, U. B., Duncan, G. E., Breese, G. R., Fornaretto, M. G., Caron, M. G., & Fremeau, R. T., Jr. (1994). Ontogeny of D_{1A} and D_2 dopamine receptor subtypes in rat brain using in situ hybridization and receptor binding. *Neuroscience, 62*(1), 65-85.

Schiffmann, S. N., Jacobs, O., & Vanderhaeghen, J. J. (1991). Striatal restricted adenosine A2 receptor (RDC8) is expressed by enkephalin but not by substance P neurons: an in situ hybridization histochemistry study. *Journal of Neurochemistry, 57*(3), 1062-1067.

Schiorring, E. (1971). Amphetamine induced selective stimulation of certain behaviour items with concurrent inhibition of others in an open-field test with rats. *Behaviour, 39*(1), 1-17.

Schoffelmeer, A. N., Warden, G., Hogenboom, F., & Mulder, A. H. (1991). Beta-endorphin: a highly selective endogenous opioid agonist for presynaptic mu opioid receptors. *Journal of Pharmacology and Experimental Therapeutics, 258*(1), 237-242.

Schultz, W. (1994). Behavior-related activity of primate dopamine neurons. *Revue Neurologique, 150*(8-9), 634-639.

Schultz, W., & Ungerstedt, U. (1978). Striatal cell supersensitivity to apomorphine in dopamine-lesioned rats correlated to behaviour. *Neuropharmacology, 17*(6), 349-353.

Schwarcz, R., Fuxe, K., Agnati, L. F., Hokfelt, T., & Coyle, J. T. (1979). Rotational behaviour in rats with unilateral striatal kainic acid lesions: a behavioural model for studies on intact dopamine receptors. *Brain Research, 170*(3), 485-495.

Seamans, J. K., Durstewitz, D., Christie, B. R., Stevens, C. F., & Sejnowski, T. J. (2001). Dopamine D1/D5 receptor modulation of excitatory synaptic inputs to layer V prefrontal cortex neurons. *Proceedings of the National Academy of Sciences, United States of America, 98*(1), 301-306.

Seeman, P., & Van Tol, H. H. (1994). Dopamine receptor pharmacology. *Trends in Pharmacological Sciences, 15*(7), 264-270.

Seroogy, K., Ceccatelli, S., Schalling, M., Hokfelt, T., Frey, P., Walsh, J., Dockray, G., Brown, J., Buchan, A., & Goldstein, M. (1988). A subpopulation of dopaminergic neurons in rat ventral mesencephalon contains both neurotensin and cholecystokinin. *Brain Research, 455*(1), 88-98.

Shalaby, I. A., & Spear, L. P. (1980). Psychopharmacological effects of low and high doses of apomorphine during ontogeny. *European Journal of Pharmacology, 67*(4), 451-459.

Sherwood, N. M., & Timiras, P. (1970). *A Stereotaxic Atlas of the Developing Rat Brain*: University of California Press, Berkley.

Simon, E. R. (1971). *Narcotic Drugs: Biochemical Pharmacology*. New York: Plenum.

Slotkin, T. A., Seidler, F. J., & Whitmore, W. L. (1980). Effects of maternal methadone administration on ornithine decarboxylase in brain and heart of the offspring: relationships of enzyme activity to dose and to growth impairment in the rat. *Life Sciences, 26*(11), 861-867.

Smidt, M. P., & Burbach, J. P. (2007). How to make a mesodiencephalic dopaminergic neuron. *Nature Reviews Neuroscience, 8*(1), 21-32.

Smiley, J. F., Levey, A. I., Ciliax, B. J., & Goldman-Rakic, P. S. (1994). D1 dopamine receptor immunoreactivity in human and monkey cerebral cortex: predominant and extrasynaptic localization in dendritic spines. *Proceedings of the National Academy of Sciences, United States of America, 91*(12), 5720-5724.

Smith, A. A., Hui, F. W., & Crofford, M. J. (1977). Inhibition of growth in young mice treated with d1-methadone. *European Journal of Pharmacology, 43*(4), 307-314.

Smith, Y., & Bolam, J. P. (1989). Neurons of the substantia nigra reticulata receive a dense GABA-containing input from the globus pallidus in the rat. *Brain Research, 493*(1), 160-167.

Snyder, L. A., Roberts, J. L., & Sealfon, S. C. (1991). Distribution of dopamine D2 receptor mRNA splice variants in the rat by solution hybridization/protection assay. *Neuroscience Letters, 122*(1), 37-40.

Soghomonian, J. J., Descarries, L., & Watkins, K. C. (1989). Serotonin innervation in adult rat neostriatum. II. Ultrastructural features: a radioautographic and immunocytochemical study. *Brain Research, 481*(1), 67-86.

Solomon, P. R., & Staton, D. M. (1982). Differential effects of microinjections of d-amphetamine into the nucleus accumbens or the caudate putamen on the rat's ability to ignore an irrelevant stimulus. *Biological Psychiatry, 17*(6), 743-756.

Spain, J. W., Roth, B. L., & Coscia, C. J. (1985). Differential ontogeny of multiple opioid receptors (mu, delta, and kappa). *Journal of Neuroscience, 5*(3), 584-588.

Spanagel, R., Herz, A., & Shippenberg, T. S. (1990). The effects of opioid peptides on dopamine release in the nucleus accumbens: an in vivo microdialysis study. *Journal of Neurochemistry, 55*(5), 1734-1740.

Spanagel, R., Herz, A., & Shippenberg, T. S. (1992). Opposing tonically active endogenous opioid systems modulate the mesolimbic dopaminergic pathway. *Proceedings of the National Academy of Sciences, United States of America, 89*(6), 2046-2050.

Spear, L. P., & Brick, J. (1979). Cocaine-induced behavior in the developing rat. *Behavioral and Neural Biology, 26*(4), 401-415.

Specht, L. A., Pickel, V. M., Joh, T. H., & Reis, D. J. (1981). Light-microscopic immunocytochemical localization of tyrosine hydroxylase in prenatal rat brain. II. Late ontogeny. *Journal of Comparative Neurology, 199*(2), 255-276.

Starr, B. S., Starr, M. S., & Kilpatrick, I. C. (1987). Behavioural role of dopamine D1 receptors in the reserpine-treated mouse. *Neuroscience, 22*(1), 179-188.

Steiner, H., & Gerfen, C. R. (1996). Dynorphin regulates D1 dopamine receptor-mediated responses in the striatum: relative contributions of pre- and postsynaptic mechanisms in dorsal and ventral striatum demonstrated by altered immediate-early gene induction. *Journal of Comparative Neurology, 376*(4), 530-541.

Stiene-Martin, A., Mattson, M. P., & Hauser, K. F. (1993). Opiates selectively increase intracellular calcium in developing type-1 astrocytes: role of calcium in morphine-induced morphologic differentiation. *Developmental Brain Research, 76*(2), 189-196.

Stoof, J. C., & Kebabian, J. W. (1981). Opposing roles for D-1 and D-2 dopamine receptors in efflux of cyclic AMP from rat neostriatum. *Nature, 294*(5839), 366-368.

Stoof, J. C., & Kebabian, J. W. (1984). Two dopamine receptors: biochemistry, physiology and pharmacology. *Life Sciences, 35*(23), 2281-2296.

Surmeier, D. J., Eberwine, J., Wilson, C. J., Cao, Y., Stefani, A., & Kitai, S. T. (1992). Dopamine receptor subtypes colocalize in rat striatonigral neurons. *Proc Natl Acad Sci U S A, 89*(21), 10178-10182.

Surmeier, D. J., Reiner, A., Levine, M. S., & Ariano, M. A. (1993). Are neostriatal dopamine receptors co-localized? *Trends in Neurosciences, 16*(8), 299-305.

Szechtman, H., Ornstein, K., Teitelbaum, P., & Golani, I. (1985). The morphogenesis of stereotyped behavior induced by the dopamine receptor agonist apomorphine in the laboratory rat. *Neuroscience, 14*(3), 783-798.

Takada, M., Tokuno, H., Ikai, Y., & Mizuno, N. (1994). Direct projections from the entopeduncular nucleus to the lower brainstem in the rat. *Journal of Comparative Neurology, 342*(3), 409-429.

Takemori, A. E., & Portoghese, P. S. (1987). Evidence for the interaction of morphine with *kappa* and *delta* opioid receptors to induce analgesia in β-funaltrexamine-treated mice. *Journal of Pharmacology and Experimental Therapeutics, 243*(1), 91-94.

Tallent, M., Dichter, M. A., Bell, G. I., & Reisine, T. (1994). The cloned kappa opioid receptor couples to an N-type calcium current in undifferentiated PC-12 cells. *Neuroscience, 63*(4), 1033-1040.

Tanganelli, S., Li, X. M., Ferraro, L., Von Euler, G., O'Connor, W. T., Bianchi, C., Beani, L., & Fuxe, K. (1993). Neurotensin and cholecystokinin octapeptide control synergistically dopamine release and dopamine D2 receptor affinity in rat neostriatum. *European Journal of Pharmacology, 230*(2), 159-166.

Tao, P. L., Hwang, C. L., & Chen, C. Y. (1994). U-50,488 blocks the development of morphine tolerance and dependence at a very low dose in guinea pigs. *European Journal of Pharmacology, 256*(3), 281-286.

Tarazi, F. I., Campbell, A., Yeghiayan, S. K., & Baldessarini, R. J. (1998). Localization of dopamine receptor subtypes in corpus striatum and nucleus accumbens septi of rat brain: comparison of D1-, D2-, and D4-like receptors. *Neuroscience, 83*(1), 169-176.

Tavani, A., Robson, L. E., & Kosterlitz, H. W. (1985). Differential postnatal development of mu-, delta- and chi-opioid binding sites in mouse brain. *Brain Research, 355*(2), 306-309.

Teicher, M. H., Gallitano, A. L., Gelbard, H. A., Evans, H. K., Marsh, E. R., Booth, R. G., & Baldessarini, R. J. (1991). Dopamine D1 autoreceptor function: possible expression in developing rat prefrontal cortex and striatum. *Developmental Brain Research, 63*(1-2), 229-235.

Teschemacher, H. (1993). Atypical opioid peptides. In A. Herz (Ed.), *Handbook of Experimental Pharmacology.* (Vol. 104, pp. 499-528). Berlin: Springer-Verlag.

Thomas, W. S., Neal-Beliveau, B. S., & Joyce, J. N. (1998). There is a limited critical period for dopamine's effects on D1 receptor expression in the developing rat neostriatum. *Developmental Brain Research, 111*(1), 99-106.

Thompson, L. A., & Walker, J. M. (1992). Involvement of the nigrotectal and nigrothalamic pathways in kappa opioid-induced circling. *Synapse, 12*(3), 189-194.

Thornburg, J. E., & Moore, K. E. (1975). Supersensitivity to dopamine agonists following unilateral, 6-hydroxydopamine-induced striatal lesions in mice. *Journal of Pharmacology and Experimental Therapeutics, 192*(1), 42-49.

Tiberi, M., Jarvie, K. R., Silvia, C., Falardeau, P., Gingrich, J. A., Godinot, N., Bertrand, L., Yang-Feng, T. L., Fremeau, R. T., Jr., & Caron, M. G. (1991). Cloning, molecular characterization, and chromosomal assignment of a gene encoding a second D1 dopamine receptor subtype: differential expression pattern in rat brain compared with the D1A receptor. *Proceedings of the National Academy of Sciences, United States of America, 88*(17), 7491-7495.

Tossman, U., Eriksson, S., Delin, A., Hagenfeldt, L., Law, D., & Ungerstedt, U. (1983). Brain amino acids measured by intracerebral dialysis in portacaval shunted rats. *Journal of Neurochemistry, 41*(4), 1046-1051.

Tulunay, F. C., Jen, M. F., Chang, J. K., Loh, H. H., & Lee, N. M. (1981). Possible regulatory role of dynorphin on morphine- and beta-endorphin-induced analgesia. *Journal of Pharmacology and Experimental Therapeutics, 219*(2), 296-298.

Ukai, M., & Kameyama, T. (1985). Multi-dimensional analyses of behavior in mice treated with U-50,488H, a purported kappa (non-mu) opioid agonist. *Brain Research, 337*(2), 352-356.

Unterwald, E. M., Knapp, C., & Zukin, R. S. (1991). Neuroanatomical localization of κ_1 and κ_2 opioid receptors in rat and guinea pig brain. *Brain Research, 562*(1), 57-65.

Vaccheri, A., Dall'Olio, R., Gandolfi, O., & Montanaro, N. (1986). Involvement of different dopamine receptors in rat diphasic motility response to apomorphine. *Psychopharmacology, 89*(3), 265-268.

van der Kooy, D., & Carter, D. A. (1981). The organization of the efferent projections and striatal afferents of the entopeduncular nucleus and adjacent areas in the rat. *Brain Research, 211*(1), 15-36.

Van Eden, C. G., Hoorneman, E. M., Buijs, R. M., Matthijssen, M. A., Geffard, M., & Uylings, H. B. (1987). Immunocytochemical localization of dopamine in the prefrontal cortex of the rat at the light and electron microscopical level. *Neuroscience, 22*(3), 849-862.

Van Hartesveldt, C., Cottrell, G. A., Potter, T., & Meyer, M. E. (1992). Effects of intracerebral quinpirole on locomotion in rats. *European Journal of Pharmacology, 214*(1), 27-32.

Van Hartesveldt, C., Meyer, M. E., & Potter, T. J. (1994). Ontogeny of biphasic locomotor effects of quinpirole. *Pharmacology, Biochemistry and Behavior, 48*(3), 781-786.

Van Tol, H. H., Bunzow, J. R., Guan, H. C., Sunahara, R. K., Seeman, P., Niznik, H. B., & Civelli, O. (1991). Cloning of the gene for a human dopamine D4 receptor with high affinity for the antipsychotic clozapine. *Nature, 350*(6319), 610-614.

Vertes, R. P. (1991). A PHA-L analysis of ascending projections of the dorsal raphe nucleus in the rat. *Journal of Comparative Neurology, 313*(4), 643-668.

Volterra, A., Brunello, N., Restani, P., Galli, C. L., & Racagni, G. (1986). Ontogenetic studies on mu, delta and kappa opioid receptors in rat brain. *Pharmacological Research Communications, 18*(10), 979-990.

Voorn, P., Kalsbeek, A., Jorritsma-Byham, B., & Groenewegen, H. J. (1988). The pre- and postnatal development of the dopaminergic cell groups in the ventral mesencephalon and the dopaminergic innervation of the striatum of the rat. *Neuroscience, 25*(3), 857-887.

Waddell, A. B., & Holtzman, S. G. (1998). Modulation of cocaine-induced motor activity in the rat by opioid receptor agonists. *Behavioural Pharmacology, 9*(5-6), 397-407.

Walker, J. M., Thompson, L. A., Frascella, J., & Friederich, M. W. (1987). Opposite effects of mu and kappa opiates on the firing-rate of dopamine cells in the substantia nigra of the rat. *European Journal of Pharmacology, 134*(1), 53-59.

Wan, Q., Murray, T. F., & Aldrich, J. V. (1999). A novel acetylated analogue of dynorphin A-(1-11) amide as a kappa-opioid receptor antagonist. *Journal of Medicinal Chemistry, 42*(16), 3011-3013.

Wang, J. B., Johnson, P. S., Imai, Y., Persico, A. M., Ozenberger, B. A., Eppler, C. M., & Uhl, G. R. (1994). cDNA cloning of an orphan opiate receptor gene family member and its splice variant. *FEBS Letters, 348*(1), 75-79.

Weiner, D. M., Levey, A. I., Sunahara, R. K., Niznik, H. B., O'Dowd, B. F., Seeman, P., & Brann, M. R. (1991). D1 and D2 dopamine receptor mRNA in rat brain. *Proceedings of the National Academy of Sciences, United States of America, 88*(5), 1859-1863.

Werling, L. L., Frattali, A., Portoghese, P. S., Takemori, A. E., & Cox, B. M. (1988). Kappa receptor regulation of dopamine release from striatum and cortex of rats and guinea pigs. *Journal of Pharmacology and Experimental Therapeutics, 246*(1), 282-286.

Worms, P., Gueudet, C., & Biziere, K. (1986). Induction of turning by direct intrastriatal injection of dopaminomimetic drugs in mice: pharmacological analysis of a simple screening model. *Life Sciences, 39*(23), 2199-2208.

Xie, G. X., Meng, F., Mansour, A., Thompson, R. C., Hoversten, M. T., Goldstein, A., Watson, S. J., & Akil, H. (1994). Primary structure and functional expression of a guinea pig kappa opioid (dynorphin) receptor. *Proceedings of the National Academy of Sciences, United States of America, 91*(9), 3779-3783.

Yasuda, K., Rens-Domiano, S., Breder, C. D., Law, S. F., Saper, C. B., Reisine, T., & Bell, G. I. (1992). Cloning of a novel somatostatin receptor, SSTR3, coupled to adenylylcyclase. *Journal of Biological Chemistry, 267*(28), 20422-20428.

Yung, K. K., Bolam, J. P., Smith, A. D., Hersch, S. M., Ciliax, B. J., & Levey, A. I. (1995). Immunocytochemical localization of D1 and D2 dopamine receptors in the basal ganglia of the rat: light and electron microscopy. *Neuroscience, 65*(3), 709-730.

Zagon, I. S., & McLaughlin, P. J. (1977). The effects of different schedules of methadone treatment on rat brain development. *Experimental Neurology, 56*(3), 538-552.

Zagon, I. S., & McLaughlin, P. J. (1983). Increased brain size and cellular content in infant rats treated with an opiate antagonist. *Science, 221*(4616), 1179-1180.

Zagon, I. S., & McLaughlin, P. J. (1987). Endogenous opioid systems regulate cell proliferation in the developing rat brain. *Brain Research, 412*(1), 68-72.

Zarrindast, M. R., & Eliassi, A. (1991). Differential effects of dopamine agonists on locomotion in intact and reserpine-treated mice. *General Pharmacology, 22*(6), 1027-1031.

Zarrindast, M. R., & Minaian, A. (1991). Different effects of direct and indirect dopamine receptor agonists on immobility time in reserpine-treated mice. *General Pharmacology, 22*(6), 1017-1021.

Zavala, A. R., Yoshida, S. T., Osburn, J. R., & McDougall, S. A. (2002). Paradoxical locomotor activating effects of k-opioid receptor stimulation in the preweanling rat: Role of the ventromedial thalamus and superior colliculus. *Developmental Brain Research, 139*(2), 301-306.

Zeng, W. Y., Hyttel, J., & Murrin, L. C. (1988). Ontogeny of dopamine D1 receptors in rat striatum. *Journal of Neurochemistry, 50*(3), 862-867.

Zhang, A. Z., & Pasternak, G. W. (1981). Ontogeny of opioid pharmacology and receptors: high and low affinity site differences. *European Journal of Pharmacology, 73*(1), 29-40.

Zhu, Y., Hsu, M. S., & Pintar, J. E. (1998). Developmental expression of the mu, kappa, and delta opioid receptor mRNAs in mouse. *Journal of Neuroscience, 18*(7), 2538-2549.

Zukin, R. S., Eghbali, M., Olive, D., Unterwald, E. M., & Tempel, A. (1988). Characterization and visualization of rat and guinea pig brain kappa opioid receptors: evidence for κ_1 and kappa κ_2 opioid receptors. *Proceedings of the National Academy of Sciences, United States of America, 85*(11), 4061-4065.