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FUNCTIONAL CHANGES IN NEURONS AND GLIA FOLLOWING
AMPHETAMINE-INDUCED BEHAVIORAL SENSITIZATION

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

by

Victoria Diane Armstrong


March 2003

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Approved by:




Sanders McDougall, Chair, Psychology

2/28/03
Date



Cynthia Crawford



Frederick Newton

ABSTRACT

Amphetamine abuse is increasing worldwide. To understand the mechanisms underlying addiction, as well as the psychosis that may develop with amphetamine use, animal models of behavioral sensitization are often employed. In the present study, markers of neuronal and glial toxicity (i.e., GFAP, DAT, GLT-1) were used to assess cellular changes following amphetamine-induced behavioral sensitization. As expected, repeated amphetamine treatment induced behavioral sensitization and conditioned activity in adult rats. Amphetamine pretreatment resulted in increased GFAP levels within the basal ganglia thalamocortical "motor" pathway. Additionally, enhanced DAT levels were evident in the basal ganglia thalamocortical "limbic" pathway, while GLT-1 levels were unchanged. The presence of gliosis (i.e., increased GFAP levels) supports the possibility that behavioral sensitization may be due, in part, to neurotoxicity. However, the lack of change in GLT-1 (a marker of glial cell toxicity) and an increase, rather than a decrease, in DAT levels (an indirect measure of DA neurotoxicity) is not consistent with a toxicity hypothesis of behavioral

sensitization. Instead, the latter results suggest the presence of neuroprotective and/or homeostatic mechanisms that may mediate both the development of behavioral sensitization and addiction.

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DEDICATION

To my mother, Eleanor, my aunt, Lorraine, and my children, Trevor, Jessica, Rachel, and Cassie without whose support and encouragement this manuscript would not have been possible.

TABLE OF CONTENTS

ABSTRACT	iii
ACKNOWLEDGMENTS	v
LIST OF FIGURES	x
CHAPTER ONE: THE CLINICAL RELEVANCE OF AMPHETAMINE STUDIES	
Prevalence of Abuse	1
Historical Background	2
Evolution of Clinical Usage and Utility	2
Amphetamine-Type Substance Addiction Controversy	4
High-Risk and Limited Therapeutic Application Determine Amphetamine-Type Substance Placement Under the Controlled Substances Act	5
Societal Impact of Amphetamine-Type Substance Abuse	7
Amphetamine-Type Substance Use for Both Medical and Non-Medical Purposes Remains High	7
Economic Costs	9
Summary	11
CHAPTER TWO: BEHAVIORAL SENSITIZATION: AN OVERVIEW	
Behavioral Sensitization Defined	12
Sensitization: A Model for Addiction, Psychosis and Neural Plasticity	13
Behavioral Sensitization and Addiction ...	13

Sensitization and Psychosis	14
CHAPTER THREE: BEHAVIORAL MANIFESTATIONS	
Factors Important for Behavioral Sensitization	18
Stimuli Known to Induce Behavioral Sensitization	19
Dosage Levels	20
Subject Age and Gender	21
Drug Administration and Testing Schedules	21
The Role of Environmental Context in Behavioral Sensitization	23
CHAPTER FOUR: NEURAL SUBSTRATES OF BEHAVIORAL SENSITIZATION	
The Two Components of Behavioral Sensitization: Induction and Expression	25
The Neural Basis of Behavioral Sensitization: Induction	25
The Neural Basis of Behavioral Sensitization: Expression	30
CHAPTER FIVE: GLUTAMATE AND BEHAVIORAL SENSITIZATION	
The Widespread Influence of Glutamate	37
Behavioral Sensitization, Learning, and N-methyl-D-aspartate Receptors	40
Behavioral Sensitization and Neurotoxicity	42
CHAPTER SIX: SENSITIZATION, GLUTAMATE, AND GLIAL CELLS	
The Toxic Effects of Glutamate	44

Predictions	46
CHAPTER SEVEN: METHODS	
Behavioral Methods	48
Subjects	48
Drugs	48
Apparatus	48
Procedure	49
Statistics	50
Immunohistochemistry Methods	50
Antibodies and Supplies	50
Procedure	51
Statistics	52
CHAPTER EIGHT: RESULTS AND DISCUSSION	
Behavioral Results	53
Pretreatment Phase	53
Test Day	53
Discussion of Behavioral Results	56
Immunohistochemistry Results	57
Glial Fibrillary Acidic Protein Assay	57
Dopamine Transporter Assay	60
Glutamate Transporter Assay	60
Discussion of Immunohistochemistry Results	64

CHAPTER NINE: GENERAL DISCUSSION

Rationale	66
Evidence for Amphetamine-Induced Behavioral Sensitization	68
Assays: Findings and Interpretations	69
Acute and Repeated Amphetamine Exposure Results in Gliosis	69
Glutamate Transporter and Dopamine Transporter Assays Yield Counterintuitive Findings	71
Dopamine Transporters and Augmented Dopamine Release in Sensitized Rats	72
Cellular Changes and Addiction	75
Summary	77
REFERENCES	79

LIST OF FIGURES

Figure 1. Illustration of the mesolimbic DA pathway projecting from the VTA and NAc. GABA is released by the NAc, which directly stimulates GABA_A receptors located on GABA interneurons and indirectly stimulating GABA_B receptors located on VTA DA neurons (see inset). 28

Figure 2. Illustration of the mesocortical and mesolimbic DA pathways showing the location of presynaptic DA D₁-like receptors. During the induction of behavioral sensitization, these receptors become "supersensitive" serving to enhance DA release in the NAc by inhibiting GABA in the VTA and reducing glutamatergic stimulation of the DA neurons that project back to the PFC. 31

Figure 3. Glutamatergic pathways originating in the PFC mediate accumbal activity via a direct pathway between the PFC and the NAc and via an indirect pathway that provides stimulation of the VTA by way of the PPTg. 34

Figure 4. Schematic representation illustrating the widespread presence of glutamate (dashed lines) within the mesocortical and mesolimbic pathways. The location of DA D₁-like receptors on glutamate pathways, as well as GABA (dotted lines) and DA (solid lines) projections are also shown. The PFC regulates the VTA indirectly via the PPTg, as direct PFC glutamatergic input to the VTA synapses only on DA projections that form a feedback loop to the PFC. The reciprocal relationship between the VTA and the NAc can also be seen. 38

Figure 5. Mean (\pm SEM) distance traveled (cm) of rats ($n = 20$ per group) receiving either

a daily i.p. injection of saline or 2.0 mg/kg amphetamine over seven pretreatment days. Measurement was taken during the 60 min period immediately following injection. 54

Figure 6. Mean (\pm SEM) distance traveled (cm) of saline- or amphetamine-pretreated rats ($n = 10$ per group) on test day (these are the same rats as described in Figure 1). Measurement was conducted for 120 min immediately following a challenge injection of either saline or 0.5 mg/kg amphetamine. 55

Figure 7. Mean level (\pm SEM) of anti-glial fibrillary acidic protein (GFAP) immunoreactive cells found in the dorsal caudate-putamen, ventral caudate-putamen, nucleus accumbens core, and nucleus accumbens shell for both saline- and amphetamine-pretreated rats ($n = 10$ per group). Open bars represent saline challenge; hatched bars indicate amphetamine challenge. ^aSignificantly different from saline-challenged rats ($p < 0.05$). ^bSignificantly different from saline-saline group ($p < 0.05$). ^cSignificantly different from saline-pretreated rats ($p < 0.05$). 58

Figure 8. Mean level (\pm SEM) of anti-glial fibrillary acidic protein (GFAP) immunoreactive cells found in hippocampal CA₁, hippocampal CA₃, dentate gyrus, and cingulate cortex for both saline- and amphetamine-pretreated rats ($n = 10$ per group). Open bars represent saline challenge; hatched bars indicate amphetamine challenge. ^aSignificantly different from saline-challenged rats ($p < 0.05$). ^bSignificantly different from saline-saline group ($p < 0.05$). 59

Figure 9. Mean level (\pm SEM) of dopamine transporter (DAT) immunoreactive cells found in hippocampal CA₁, hippocampal CA₃, dentate gyrus, and basolateral amygdala for both saline- and amphetamine-pretreated rats ($n = 10$ per group). Open bars represent saline challenge; hatched bars indicate amphetamine challenge. ^aSignificantly different from saline-challenged rats ($p < 0.05$). ^bSignificantly different from saline-saline group ($p < 0.05$). ^cSignificantly different from saline-pretreated rats ($p < 0.05$). 61

Figure 10. Mean level (\pm SEM) of dopamine transporter (DAT) immunoreactive cells found in the dorsal caudate-putamen, ventral caudate-putamen, nucleus accumbens core, and cingulate cortex for both saline- and amphetamine-pretreated rats ($n = 10$ per group). Open bars represent saline challenge; hatched bars indicate amphetamine challenge. ^aSignificantly different from saline-challenged rats ($p < 0.05$). 62

Figure 11. Mean level (\pm SEM) of glutamate transporter (GLT-1) immunoreactive cells found in the hippocampal CA₁, hippocampal CA₃, nucleus accumbens core, cingulate cortex, dorsal and ventral caudate-putamen for both saline- and amphetamine-pretreated rats ($n = 10$ per group). 63

CHAPTER ONE
THE CLINICAL RELEVANCE OF
AMPHETAMINE STUDIES

Prevalence of Abuse

Amphetamine abuse is on the rise. In a 9-year period from 1985 to 1994, the number of countries reporting abuse of amphetamine-type substances (ATS; e.g., d-amphetamine, methamphetamine, ephedrine, pseudoephedrine, etc.) tripled (United Nations Drug Control Programme [UNDCP], 1996). In addition, 35 countries providing ATS statistics revealed a 49% net increase in the abuse of ATS. This increase was higher than that documented for either cocaine or heroin (39% and 30% respectively; UNDCP, 1996). Not exempt from the ATS problem, the United States experienced a particularly sharp rise in the number of individuals misusing ATS, with levels peaking at an estimated 2.4 million persons in 1993 (UNDCP, 1996). It is clear that the ATS epidemic continues to spread, as data provided by the United States (1993-1999) show ATS treatment admissions increasing 131% nationwide, with 14 states claiming increases of 250% or more (SAMHSA, 2001).

Historical Background

Evolution of Clinical Usage and Utility

The role of ATS in clinical practice has changed significantly over the past 60 years. Originally synthesized in 1887, amphetamine was first made available to the public as a nasal inhaler in 1932, followed five years later by tablet form (Grinspoon & Bakalar, 1979; Keltner & Folks, 1997; LeBlanc, Kalant, & Kalant, 1973; Perrone, 1998; UNDCP, 1996). For many years after its introduction, amphetamine was considered a cure-all for everything from head injuries and irritable colon to anhedonia and difficulty in concentrating (Bett, 1946; Seymour & Smith, 1987; UNDCP, 1996). It was even listed as a facilitator for psychotherapy in a 1954 psychiatric text (Connell, 1958). Since the Controlled Substances Act convention in 1971, the limited therapeutic use of ATS has been recognized (Benet, 1996; UNDCP, 1996). Presently, ATS are prescribed mainly for the treatment of attention deficit/hyperactivity disorder, obesity, and narcolepsy (DEA, 2000; Hoffman & Lefkowitz, 1996; Keltner & Folks, 1997; Logan, 2001; Perrone, 1998; UNDCP, 1996).

Initially, lack of appreciation for ATS addiction potential, coupled with overconfidence in the therapeutic

efficacy of ATS drugs, precipitated lax prescription policies and abuse. It was not until the 1950s that governmental controls existed for ATS (Babayan, Astahova, Lepakin, & Lopatin, 1984; Connell, 1958; Konuma, 1994). Even then, the risk connected with ATS use was thought to be minimal. This was evident by its Schedule IV placement (indicating minimal risk and high therapeutic value) and its continued wide availability as an over-the-counter drug (Connell, 1958).

Unfortunately, the favorable view of ATS belied their dangers. Problems stemming from ATS usage were observed shortly after their appearance on the market. In fact, in 1938, Young and Scoville reported three incidences of psychosis related to amphetamine use (Young & Scoville, 1938). Sporadic reports of psychosis by other clinicians followed (Connell, 1958). However, physicians were hesitant to attribute psychosis directly to ATS use, and instead felt that these psychoses were rare occurrences in individuals already predisposed to psychiatric illness (Bett, 1946; Connell, 1958). Further, the apparent lack of classic withdrawal symptoms caused many clinicians to argue that addiction to an ATS was not possible (Bett, 1946; LeBlanc et al., 1973), even though information detailing

widespread ATS abuse in Japan was available following that country's inundation with the drug after WWII (Kalant, 1973; Konuma, 1994; Tatetsu, 1972; UNDCP, 1996).

Reluctance to acknowledge the possible hazards of ATS use, coupled with their presumed therapeutic benefits, precipitated generous and lax prescribing of these drugs and their general overuse (Kalant, 1973; UNDCP, 1996).

Amphetamine-Type Substance Addiction Controversy

By the 1960s, ATS abuse had spread throughout various European countries as well as North America (Kalant, 1973; Pickering & Stimson, 1994). Although ATS abuse was quickly becoming a global problem, experts disagreed as to whether ATS were addictive. The main point of contention was whether or not withdrawal symptoms accompanied ATS abstinence (Kalant, 1973). Many experts were using the characteristics of opiate withdrawal to define the symptomology of physical dependence. Using this frame of reference, these professionals determined that psychological depression, prolonged sleep, and increased appetite following the cessation of ATS use was simply a result of the fatigue that follows heightened physical alertness and exertion (LeBlanc et al., 1973). Those professionals who disagreed felt that these behavioral

manifestations constituted withdrawal symptoms, thus indicating that ATS produced a physical dependence and were potentially addictive (LeBlanc et al., 1973). The latter position was subsequently supported by sleep studies showing that changes in REM cycling were dependent upon previous ATS history and level of current exposure (Caldwell & Caldwell, 1997; Lin et al., 2000; Nicholson & Stone, 1981; Oswald & Thacore, 1963; Radulovacki & Zak, 1981; Watson, Hartmann, & Schildkraut, 1972).

In response to the continuing disagreement over the definition of addiction, the World Health Organization (WHO) revised its conceptualization of addiction to reflect a continuum of addictive symptomology. WHO changed their terminology to reflect this paradigm shift, implementing the term "drug dependence" followed by a qualifier (the drug of abuse) and specifying the dependence characteristics for that particular substance (Kalant, 1973).

High-Risk and Limited Therapeutic Application

Determine Amphetamine-Type Substance Placement

Under the Controlled Substances Act

Following the 1971 Convention on Psychotropic Drugs, ATS were reclassified as Schedule II substances as defined

by the Controlled Substances Act. Under this act, drugs are classified under one of four schedules based upon therapeutic utility and level of health risk with lower schedule numbers denoting less utility and higher risk (Benet, 1996; UNDCP, 1996). As Schedule II drugs, ATS are considered drugs of limited clinical use that carry a high risk of dependence, both physical and psychological, and abuse (Benet, 1996; DEA, 2000). This change in Schedule placement, from level IV to level II, brought about stricter controls of ATS and a decrease in indiscriminate prescribing practices (Benet, 1996). However, a curious discrepancy still remains as ATS continue to be readily available in many over-the-counter preparations (Keltner & Folks, 1997; Perrone, 1998; Soutullo, Cottingham, & Keck, 1999; UNDCP, 1996). The stricter control of ATS has also resulted in a decline in regulated manufacturers as well as a substantial reduction in the amount of ATS being diverted from licit to illicit markets (DEA, 2000; UNDCP, 1996). Even so, the paradoxical Schedule IV placement of ATS precursors, the relative simplicity of ATS synthesis, and the ability of small clandestine laboratories to produce ATS virtually anywhere, has allowed the illicit manufacture

of ATS to flourish (Logan, 2001; Mayrhauser, Brecht, & Anglin, 2002; Rawson, Anglin, & Ling, 2002; UNDCP, 1996).

Societal Impact of Amphetamine-Type Substance Abuse

Amphetamine-Type Substance Use for Both Medical and Non-Medical Purposes Remains High

ATS are now routinely prescribed for only a limited number of clinical indications, namely attention deficit/hyperactivity disorder, obesity, and narcolepsy (Logan, 2001; Hartman, 1995; Hoffman & Lefkowitz, 1996; Mitler, 1994; Perrone, 1998). Even though there are only three medically approved reasons for ATS use, the number of persons receiving this pharmacotherapy is substantial. It has been reported that 3% of children worldwide are diagnosed with attention deficit/hyperactivity disorder, with 0.2%-100% (depending on geographic region) receiving medication for this disorder (Safer & Krager, 1988; Simeon, Wiggins, & Williams, 1995; UNDCP, 1996). Further, it is estimated that 30%-50% of middle-aged adults in industrialized nations suffer from obesity, and that the prevalence rate of narcolepsy is 0.1% globally (UNDCP, 1996). With the long-term treatment of these conditions

often necessary, the potential for an escalation in ATS addiction and abuse seems great.

The use of ATS for non-medicinal purposes has also increased. The rise in the occupational and recreational use of ATS has been attributed to both their CNS effects as well as commonly held misconceptions regarding their presumed safety (DEA, 2000; Hando, Topp, & Hall, 1997; Pickering & Stimson, 1994; Rawson et al., 2002). ATS are sympathomimetics that induce subjective feelings of increased energy, mental acuity, concentration, and alertness, as well as an elevation in mood (Hoffman & Lefkowitz, 1996; Keltner & Folks, 1997; UNDCP, 1996; Wesson & Smith, 1979). These properties have made ATS attractive for those seeking greater endurance and mental performance (such as truck drivers, construction workers, athletes, and students), in addition to those seeking an overall feeling of well-being, euphoria, and greater self-confidence (Babcock & Byrne, 2000; Seymour & Smith, 1987; Pickering & Stimson, 1994; Rawson et al., 2002; UNDCP, 1996). Popularity of ATS are further enhanced by their public image as a relatively harmless drug, their ease of availability, as well as their longevity of effect and cheaper cost relative to cocaine (Mayrhauser et al., 2002;

Rawson et al., 2002; UNDCP, 1996). The proliferation of ATS usage is reflected not only by increases in the illegal manufacture and trafficking of these drugs, but also by increases in the number of ATS-related emergency room and rehabilitation clinic admissions (Baberg, Nelesen, & Dimsdale, 1996; DEA, 2000, 2002; SAMHSA, 2001; UNDCP, 1996).

Economic Costs

Chronic ATS use results in increased financial costs both to individuals who use ATS and to society at large. Individuals who engage in chronic ATS use can experience medical complications of both a physical and psychological nature. Possible physical consequences include: cerebral hemorrhage, stroke, cardiac arrhythmias, seizures, and liver damage (Babayan et al., 1984; Hoffman & Lefkowitz, 1996; Keltner & Folks, 1997; Logan, 2001; Seymour & Smith, 1987). Depending upon the method of ingestion, nasal ulcers and hepatitis may also occur (Perrone, 1998; Seymour & Smith, 1987; UNDCP, 1996). Psychological consequences of ATS use include aggressive behavior, anxiety, and psychosis (Asnis & Smith, 1979; Ellinwood, 1972; Hando, et al., 1997; Hartman, 1995; Logan, 2001; UNDCP, 1996). For society, ATS abuse results in greater economic costs due to loss of

worker productivity, criminality, and increased health care costs (Hando et al., 1997; Rawson et al., 2002; UNDCP, 1996).

Over the long term, economic costs resulting from ATS use can be profound. Decreased business revenues due to loss of worker productivity can result in increased consumer costs for goods and services (UNDCP, 1996). This decrement in worker productivity stems from memory and fine motor skill impairment, general hyperactivity that is unfocused and nonproductive, as well as an overall increase in workplace accidents (UNDCP, 1996, p. 123; see also Cox & Smart, 1970; Hando et al., 1997; Rawson et al., 2002; Simon et al., 2002). Publicly supported governmental expenditures are also required to provide for increased law enforcement and judicial costs associated with ATS related policing, litigation, and detention expenses. In fact, since 1964 it has been recognized that there is a causal relationship between ATS use and violent crime (Asnis & Smith, 1979; Ellinwood, 1972; Kalant, 1973; Kramer, 1972). Moreover, there is growing involvement of organized crime syndicates as well as continuing increases in manufacture and trafficking activities that necessitate greater law enforcement resources (DEA, 2000; Rawson et al., 2002;

UNDCP, 1996). ATS use also places a greater burden on health care systems because of medical costs related to physical, psychological, and rehabilitative treatment (Rawson et al., 2002; UNDCP, 1996). The possibility of greater elderly care costs exist as well, as it has been suggested that aged individuals with a prior history of ATS use may develop a unique dementia-type symptomology (Schuster & Hartel, 1994).

Summary

The use of ATS for medical conditions that require long-term treatment remains high. This is especially true in cases of attention deficit/hyperactivity disorder. In addition, occupational and recreational use of these drugs is on the rise. Considering the global extent of ATS manufacture, trafficking, abuse, and related economic costs, it is clear that further experimental research is needed to more fully understand the long-term impact of ATS on individuals and societies worldwide.

CHAPTER TWO
BEHAVIORAL SENSITIZATION:
AN OVERVIEW

Behavioral Sensitization Defined

Behavioral sensitization is the enduring augmentation of behavior following repeated intermittent exposure to psychostimulants (e.g., cocaine or amphetamine) as well as stressors (Antelman, Eichler, Black, & Kocan, 1980; Badiani, Cabib, & Puglisi-Allegra, 1992; Díaz-Otañez, Capriles, & Cancela, 1997; Kalivas & Stewart, 1991; Kozell & Meshul, 2001; Piazza, Deminiere, le Moal, & Simon, 1990; Post, Weiss, & Pert, 1988, 1992). This behavioral augmentation is most often manifested as increased locomotor activity and/or stereotypy and varies in degree of expression depending upon both the prior level of stimulant exposure and dose of the challenge drug (Segal & Kuczenski, 1987; Wolf, Dahlin, Hu, Xue, & White, 1995). Sensitization has been observed in various species (Machiyama, 1992; Robinson & Becker, 1986), and is thought to be a useful paradigm for the study of addiction, psychosis, and neural plasticity (Aizenstein, Segal, & Kuczenski, 1990; Post et al., 1988; Robinson & Becker,

1986; Segal & Schuckit, 1983; Strakowski, Sax, Setter, & Keck, 1996; Wolf, 1998).

Sensitization: A Model for Addiction, Psychosis
and Neural Plasticity

Behavioral Sensitization and Addiction

The intermittent consumption of psychomotor stimulants by humans, often referred to as "runs", resembles the intermittent administration schedules that are known to reliably induce behavioral sensitization in animals (Kramer, 1972; Post & Weiss, 1988; Segal & Kuczenski, 1999). As with animals, humans experiencing psychostimulant-induced sensitization often show both stereotypy, in the form of jaw grinding, picking of the skin, and pundning (a preoccupation with objects involving repetitive analyzation, categorization, and polishing), as well as post-stereotypy locomotion manifested as periods of sustained hyperactivity (Brady, Lydiard, Malcolm, & Ballenger, 1991; de Leon, Antelo, & Simpson, 1992; Ellinwood, 1972; Elpern, 1988; Kramer, 1972; Satel, Southwick, & Gawin, 1991b; Schiørring, 1981). These behaviors are analogous to the gnawing, grooming, and increased locomotor activity exhibited by sensitized rats (Machiyama, 1992; Schiørring, 1981; Segal & Schuckit, 1983).

In addition to these behavioral changes, repeated psychostimulant exposure modifies a variety of neuronal mechanisms underlying reward and motivational processes (Grace, 1995; Kalivas & Duffy, 1990; Robinson & Berridge, 1993; White & Wolf, 1991; Wolf et al., 1995). For example, repeated cocaine exposure causes postsynaptic dopamine (DA) receptors to become increasingly more sensitive (Henry & White, 1991). When this occurs, doses of the drug that would not normally be rewarding become gratifying, resulting in continued self-administration (White & Wolf, 1991). Moreover, sensitization-induced changes in neuronal functioning often are manifested as drug craving, which further precipitates ongoing drug-seeking and is an important component in drug relapse (Bartlett, Hallin, Chapman, & Angrist, 1997; Ciccocioppo, Sanna, & Weiss, 2001; De Vries, Schoffelmeer, Binnekade, Mulder, & Vanderschuren, 1998; De Vries, Schoffelmeer, Binnekade, & Vanderschuren, 1999; Robinson & Berridge, 1993; Weiss et al., 2001).

Sensitization and Psychosis

The symptomology of psychostimulant-induced psychosis closely mimics that of paranoid schizophrenia (Brady et al., 1991; Connell, 1958; Janowsky & Risch, 1979; Mitchell

& Vierkant, 1991; Snyder, 1973; Yui, Ikemoto, Ishiguro, & Goto, 2000). Presentation includes hallucinations involving one or more modalities, delusions of persecution and/or ideas of reference, and logorrhea (continuous, repetitive speech), accompanied by clear consciousness (Brady et al., 1991; Connell, 1958; Ellinwood, 1967, 1972; Mitchell & Vierkant, 1991; Satel et al., 1991b; Schiørring, 1981). Although there are instances of pseudo-psychosis, in which psychostimulant use precipitates the "break" that signals the onset of schizophrenia, most individuals suffering from psychostimulant-induced psychosis experience spontaneous remission of psychotic symptomology upon cessation of drug intake (Angrist, 1994; Kalant, 1973; Satel, Seibyl, & Charney, 1991a; Satel et al., 1991b; Seymour & Smith, 1987).

Animal models of behavioral sensitization have long been thought to be a useful paradigm for stimulant-induced psychosis (Robinson & Becker, 1986; Schiørring, 1981). This is because animals show robust behavioral sensitization when exposed to a drug regimen similar to that which reliably produces psychotic symptoms in humans (Griffith, Fann, & Oates, 1972; Kramer, 1972; Robinson & Becker, 1986; Segal & Kuczenski, 1987; Segal & Schuckit, 1983).

Furthermore, just as sensitization can be induced in animals by a single acute exposure, or multiple low-dose exposures, to a psychostimulant (Browne & Segal, 1977; Kuczenski & Segal, 1999, 2001; Kuczenski, Segal, & Todd, 1997; Robinson, 1984; Ushijima, Carino, & Horita, 1995; Vanderschuren et al., 1999; Wiaderna & Tomas, 2000), psychotic symptomology can occur in humans following a single exposure or multiple low-dose exposures (Connell, 1958; Hando et al., 1997; Kalant, 1973; Gold & Bowers, 1978).

Additional parallels can be drawn between behavioral sensitization in animals and psychostimulant-induced psychosis in humans. Specifically, four major characteristics of sensitization, namely: persistence, decreased latency to expression, increase in response magnitude, and hypersensitivity of DA receptors are also discernable in psychostimulant-induced psychosis (Li et al., 1999; Post & Weiss, 1988; Wolf, 1998). In psychostimulant-induced psychosis, the persistent quality of sensitization is apparent because individuals remain highly susceptible to recurrent episodes of psychosis when exposed to the same psychostimulant again, even after years of abstinence (Sato, 1992; Sato, Chen, Akiyama, & Otsuki,

1983; Sato, Numachi, & Hamamura, 1992). The sensitization qualities of decreased latency and increased response magnitude are also evident in psychostimulant-induced psychosis, because each subsequent psychotic experience is marked by acceleration in symptom onset and an increase in symptom intensity (Bartlett et al., 1997; Brady et al., 1991; Satel et al., 1991b). Moreover, DA receptor hypersensitivity is characteristic of both behavioral sensitization and psychostimulant-induced psychosis (Sato et al., 1983; see also Yui, Goto, Ikemoto, & Ishiguro, 1997, 2000).

CHAPTER THREE

BEHAVIORAL MANIFESTATIONS

Factors Important for Behavioral Sensitization

Behavioral sensitization, once induced, may be detectable for weeks, months, or longer (Post & Contel, 1983; Post & Weiss, 1988; Strakowski et al., 1996). However, the robustness of the sensitized response is influenced by several factors. These include: type of drug and dosage (Browman, Badiani, & Robinson, 1998; Kuczenski & Segal, 2001; Vanderschuren et al., 1997; Võikar et al., 1999; Wiaderna & Tomas, 2000), subject age and gender (Kuhn, Walker, Kaplan, & Li, 2001; Laviola, Wood, Kuhn, Francis, & Spear, 1995; Melnick & Dow-Edwards, 2001; Sircar & Kim, 1999; Zavala, Nazarian, Crawford, & McDougall, 2000), administration and testing schedules (Kuczenski & Segal, 1988; Partridge & Schenk, 1999; Robinson, 1984; Schenk & Partridge, 2000; Segal & Kuczenski, 1987), as well as contextual cues (Anagnostaras & Robinson, 1996; Battisti, Uretsky, & Wallace, 2000; Crombag, Badiani, Maren, & Robinson, 2000; Post et al., 1988; White & Wolf, 1991).

Stimuli Known to Induce Behavioral Sensitization

Although opioids and related drugs will induce behavioral sensitization (Vanderschuren, De Vries, Wardeh, Hogenboom, & Schoffelmeer, 2001; Võikar et al., 1999), sensitization is most often induced through exposure to psychostimulant drugs (Kalivas & Stewart, 1991; Segal & Schuckit, 1983; White & Wolf, 1991). Of these, cocaine, amphetamine, and methamphetamine are the most commonly used (Aizenstein et al., 1990; Kuczenski & Segal, 2001; Schenk & Partridge, 2000; Shimosato & Ohkuma, 2000).

Psychostimulants are thought to have enduring effects on behavior because of their similarity to stressors in their physiological consequence, and cross-sensitization between these two stimuli is well documented (Antelman et al., 1980; Díaz-Otañez et al., 1997; Piazza et al., 1990; Suzuki, Ishigooka, Watanabe, & Miyaoka, 2002; for reviews see Antelman & Chiodo, 1983; Robinson, 1988; Stam, Bruijnzeel, & Wiegant, 2000). The reciprocity between psychostimulants and stressors appears to lie not only in their shared ability to activate the sympathetic nervous system, but also in their ability to alter the sensitivity

of monoamine systems (Cole et al., 1990; Stam et al., 2000).

Dosage Levels

Behavioral sensitization can be induced using either low or high doses of psychostimulants (Robinson & Becker, 1986). However, behavioral manifestations vary according to dosage level (Post & Weiss, 1988). When low dosage levels are used, subjects primarily exhibit a state of general hyperactivity that can be quantitatively measured by their locomotor activity (Kuczenski & Segal, 1999; Post & Contel, 1983; White & Wolf, 1991). At moderate doses, a multiphasic pattern is routinely observed. This pattern is characterized by initial increases in locomotion that transition into a period of pronounced stereotypic behaviors and conclude with post-stereotypy locomotion (Kuczenski & Segal, 1999). As drug dosage levels increase, behaviors become increasingly restricted with stereotypic behaviors predominating (Kuczenski & Segal, 1988; Segal & Kuczenski, 1987; Segal, Kuczenski, & Florin, 1995). In addition to affecting the strength of expression, drug dosage and number of exposures impacts the type of behavioral sensitization expressed (i.e., context-dependent

versus context-independent) as well as resistance to extinction (Battisti et al., 2000; but see Anagnostaras, Schallert, & Robinson, 2002).

Subject Age and Gender

Subject age and gender affect both the speed of onset and intensity of the sensitized response. Adult subjects demonstrate a more robust sensitized response that develops more quickly than in younger animals (Laviola et al., 1995; Zavala et al., 2000). Similarly, females are more readily sensitized and exhibit a more pronounced behavioral response to psychostimulant challenge than do males (Kuhn et al., 2001; Melnick & Dow-Edwards, 2001; Robinson, Becker, & Presty, 1982; Sircar & Kim, 1999). This gender difference is likely due to hormones that modulate pituitary activity (Becker, Molenda, & Hummer, 2001; Chiu, Kalant, & Lê, 1998; Perrotti et al., 2001; Post, Contel, & Gold, 1982).

Drug Administration and Testing Schedules

Drug administration and testing intervals are critically important to the sensitization phenomenon (Robinson & Becker, 1986). Although behavioral

sensitization has been demonstrated following a single acute injection of a psychostimulant, stereotypy and perseverative effects are most often observed following repeated drug exposure (Battisti et al., 2000; Kashihara, Sato, Kazahaya, & Otsuki, 1986; Post & Weiss, 1988; Robinson et al., 1982). When using a repeated exposure paradigm, the time between treatments is an important factor in determining whether sensitization or tolerance will develop, with intermittent administration resulting in sensitization and continuous exposure inducing tolerance (Blanchet et al., 1995; Kalivas & Duffy, 1993; Nelson & Ellison, 1978; Stewart & Badiani, 1993; Strakowski et al., 1996). Similarly, administration schedules may also determine whether, and to what extent, neurotoxicity will develop, with shorter intervals between exposures generally having more deleterious effects (Huang, Tsai, Su, & Sim, 1999; Nelson & Ellison, 1978; Segal & Schuckit, 1983). Therefore, when using a repeated administration paradigm to induce behavioral sensitization, an intermittent schedule consisting of administration intervals spanning one or more days is preferable (Emmett-Oglesby, 1995; Kashihara et al., 1986; Post & Contel, 1983; Robinson & Becker, 1986; Strakowski et al., 1996; Tadokoro & Kuribara, 1990).

Likewise, an abstinence period between drug pretreatment and drug challenge lasting one or more days will result in a more robust sensitized response (Post & Weiss, 1988; Robinson & Becker, 1986; Robinson & Berridge, 1993). The importance of these time constraints indicates that the neurophysiological changes underlying behavioral sensitization require an extended period of time to fully develop (Antelman & Chiodo, 1983; Kalivas, 1995; Kashihara et al., 1986).

The Role of Environmental Context in Behavioral Sensitization

A number of studies have shown that sensitized responding is more robust when drug administrations are given in a novel environment (Crombag et al., 2000; Fraioli, Crombag, Badiani, & Robinson, 1999; Robinson, Browman, Crombag, & Badiani, 1998; Tirelli & Terry, 1998). This suggests that Pavlovian associations formed between the drug and environmental cues (e.g., visual cues related to the drug taking environment and drug paraphernalia, tactile cues related to administration, etc.) influence the development and expression of behavioral sensitization. Additionally, stimulus generalization (a phenomenon in which a stimulus that is similar in characteristic to the

cue also comes to elicit the response) may also play a role in behavioral sensitization (Post & Weiss, 1988). The influence of Pavlovian cues appears to be particularly important for young animals, or when adults are sensitized using a single drug exposure paradigm (Battisti et al., 2000; Post & Contel, 1983; Robinson et al., 1982; Zavala et al., 2000).

In paradigms involving multiple drug administrations and/or greater dosage levels, the importance of Pavlovian associations for the development of behavioral sensitization is of dispute. Some researchers argue that Pavlovian processes and stimulus generalization principles govern behavioral sensitization and do not diminish in importance with an increased number of drug administrations or larger drug dosages (Anagnostaras & Robinson, 1996; Post & Weiss, 1988; Post et al., 1988; Tirelli & Terry, 1998). Conversely, other researchers suggest that the importance of environmental cues for behavioral sensitization diminishes or becomes inconsequential as the number of drug exposures increase or higher doses of psychostimulants are used (Battisti et al., 2000; Browman et al., 1998; Robinson et al., 1998; Segal & Schuckit, 1983; Vezina & Stewart, 1990).

CHAPTER FOUR

NEURAL SUBSTRATES OF BEHAVIORAL SENSITIZATION

The Two Components of Behavioral Sensitization: Induction and Expression

Behavioral sensitization is the physical manifestation of complex neural changes within the CNS. Behavioral sensitization is comprised of two distinct phases: induction and expression (Karler, Chaudhry, Calder, & Turkanis, 1990; Leith & Kuczenski, 1982; Stewart & Druhan, 1993; Vezina & Stewart, 1990). Moreover, each of these two phases involves a different primary neural substrate. The ventral tegmental area (VTA) is predominantly involved in the induction of behavioral sensitization; whereas, the nucleus accumbens (NAc) is important for expression (Cador, Bjijou, & Stinus, 1995; Cornish & Kalivas, 2001a, 2001b; Karler, Bedingfield, Thai, & Calder, 1997; Li & Wolf, 1997; Pierce & Kalivas, 1997).

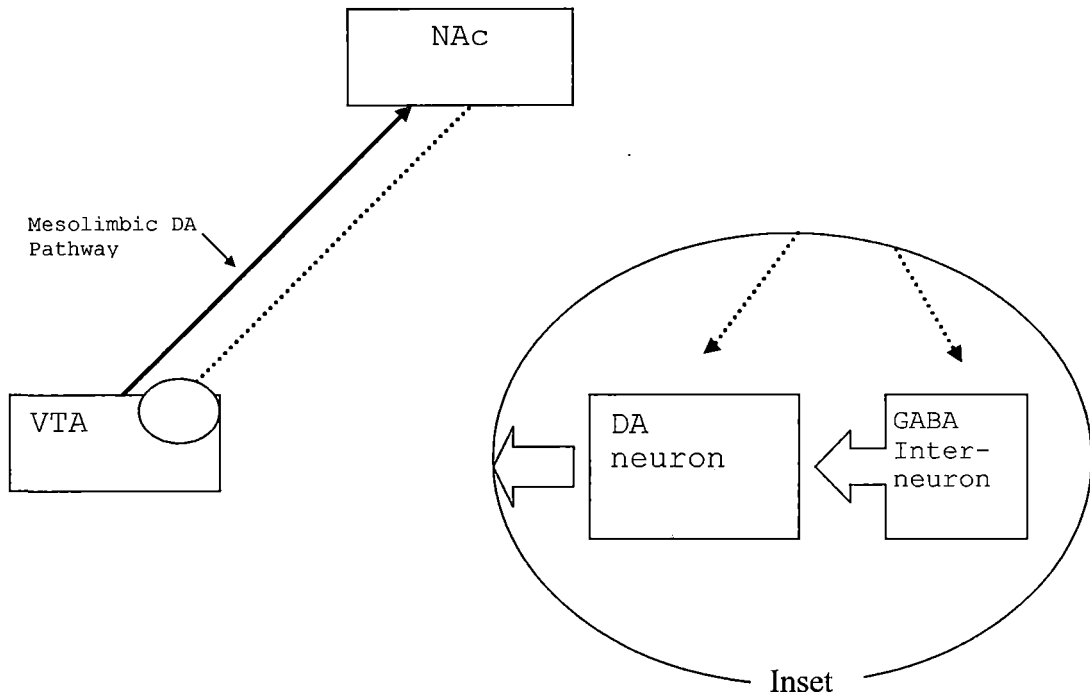
The Neural Basis of Behavioral Sensitization: Induction

Induction is the first phase of the sensitization process (Wolf, 1998). Induction involves a transient change in neuronal activity within the VTA caused by the

actions of monoamines and amino acids (Bjijou, De Deurwaerdere, Spampinato, Stinus & Cador, 2002; Cador, Bjijou, Cailhol, & Stinus, 1999; Cornish & Kalivas, 2001b; Kalivas, 1995a; Kalivas & Alesdatter, 1993; Vezina & Queen, 2000). Psychostimulants increase the extracellular concentrations of DA in the VTA (Fawcett & Busch, 1998). High levels of extracellular DA activate presynaptic D₁-like receptors on glutamate pathways that project to the VTA (Cador et al., 1999; Pierce, Bell, Duffy, & Kalivas, 1996). Under basal conditions, the activation of these D₁-like receptors inhibits the release of glutamate (Cador et al., 1995; Kalivas & Duffy, 1995). However, when high levels of DA are released following psychostimulant activation, D₁-like receptors paradoxically stimulate the release of glutamate (Kalivas & Duffy, 1995), thus activating N-methyl-D-aspartate (NMDA) receptors located on DA cell bodies in the VTA (Gnegy, 2000; Kalivas & Duffy, 1995, 1998). Stimulation of these NMDA receptors increases extracellular levels of glutamate and γ -amino butyric acid (GABA) in the VTA, which ultimately results in burst firing by DA neurons of the mesolimbic pathway (Kalivas, 1995a; Suaud-Chagny, Chergui, Chouvet, & Gonon, 1992; Timmerman &

Westerink, 1995). More precisely, glutamate (an excitatory amino acid) stimulates DA neurons resulting in: (a) increased somatodendritic DA release in the VTA, and (b) a temporary change in the responsiveness of VTA DA neurons to glutamate (Grace & Bunney, 1984; Kretschmer, 1999; Mereu, Costa, Armstrong, & Vicini, 1991; White, Hu, Zhang, & Wolf, 1995).

The NMDA receptor stimulation associated with induction also increases extracellular GABA (an inhibitory amino acid) in the VTA (Timmerman & Westerink, 1995). Stimulation of GABA_A receptors, located on GABAergic interneurons, normally acts to depress the firing rate of DA neurons in the VTA. Therefore, activation of the GABA_A receptors disinhibits DA neurons, resulting in enhanced somatodendritic DA release in the VTA (Klitenick, DeWitte, & Kalivas, 1992). The increased extracellular DA in the VTA then stimulates presynaptic D₁-like receptors located on terminals of a separate set of descending GABA_B neurons (see Fig. 1) (Klitenick et al., 1992). Stimulation of these D₁-like receptors reduces GABA activity, further potentiating somatodendritic DA release in the VTA (Bonci & Williams, 1996; Kalivas, 1995a; Klitenick et al., 1992; Walaas & Fonnum, 1980). To summarize, psychostimulants modulate



..... Dotted lines denote GABA projections
 ——— Solid line denotes DA projection

Figure 1. Illustration of the mesolimbic DA pathway projecting from the VTA to the NAc. GABA is released in the NAc, which directly stimulates GABA_A receptors located on GABA interneurons and indirectly stimulates GABA_B receptors located on VTA DA neurons (see inset).

glutamate and GABA levels by indirectly stimulating NMDA receptors. By altering glutamate and GABA levels, psychostimulants increase extracellular concentrations of DA in the VTA.

The importance of these mechanisms for the induction of behavioral sensitization is supported by studies showing that: (1) Repeated administration of amphetamine into the VTA (where DA cell bodies are located) results in behavioral sensitization (Cador et al., 1995, 1999; Perugini & Vezina, 1994; Vezina & Stewart, 1990); (2) Repeated administration of amphetamine into the NAC (where DA terminals are located) does not induce behavioral sensitization (Cador et al., 1995; Kalivas & Weber, 1988; Swanson, 1982; Vezina & Stewart, 1990); (3) Robustness of the sensitized response is directly related to the amount of initial VTA stimulation (Cador et al., 1995; see also Stewart & Vezina, 1989); and (4) Blocking NMDA receptors inhibits the induction, but not the expression, of behavioral sensitization (Druhan & Wilent, 1999; Karler et al., 1990; Li et al., 1999; Johnson, Eodice, Winterbottom, & Mokler, 2000; Vezina & Queen, 2000; but see Battisti, Shreffler, Uretsky, & Wallace, 2000). Taken together, these findings suggest that the induction of behavioral

sensitization results from a complex interplay between modulatory amino acid neurons (both glutamate and GABA) and DA projection neurons.

The Neural Basis of Behavioral Sensitization: Expression

The NAC mediates the expression of behavioral sensitization (Cornish & Kalivas, 2001a; Delfs, Schreiber, & Kelley, 1990; Essman, McGonigle, & Lucki, 1993; Franklin & Druhan, 2000; Kalivas & Duffy, 1990). The expression phase is characterized by an augmentation of locomotion and/or stereotypy after a drug abstinence period (Wolf, 1998). For expression of behavioral sensitization to occur, the physiological processes that underlie sensitization must, in effect, "transfer" from the VTA to the NAC (Wolf, 1998, p. 681).

The shift from the VTA to the NAC is initiated by increased somatodendritic DA release in the VTA (see previous section) (Kalivas, 1995a; Kimelberg, Goderie, Higman, Pang, & Waniewski, 1990; Pierce & Kalivas, 1997; White & Wolf, 1991). Specifically, the transient change in D₁-like receptors that occurs during induction becomes long lasting, as the presynaptic D₁-like receptors located in the VTA (see Fig. 2) change from a temporary state of

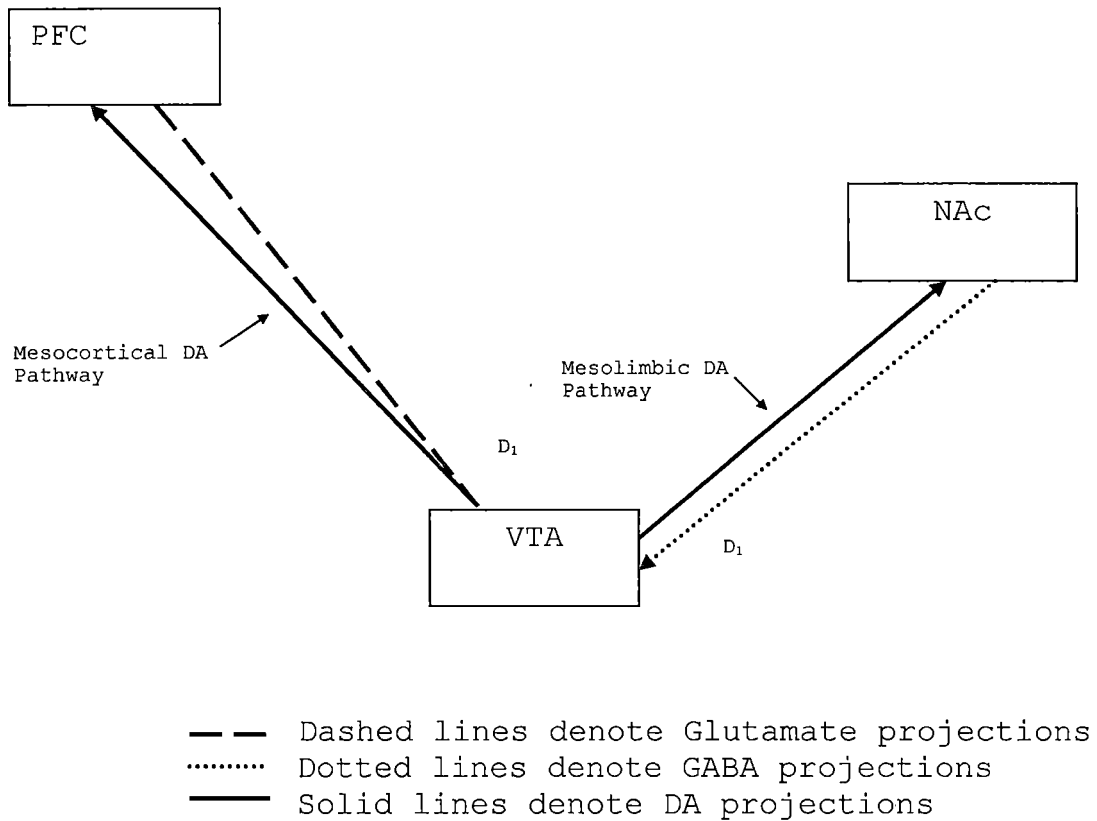


Figure 2. Illustration of the mesocortical and mesolimbic DA pathways showing the location of presynaptic DA D₁-like receptors. During the induction of behavioral sensitization, these receptors become "supersensitive" serving to enhance DA release in the NAc by inhibiting GABA in the VTA and reducing glutamatergic stimulation of the DA neurons that project back to the PFC.

subsensitivity to an enduring state of supersensitivity (Hu, Brooderson, & White, 1992; Kalivas, 1995a; Sesack, Deutch, Roth, & Bunney, 1989; White & Wolf, 1991; Wolf, White, & Hu, 1994). This D₁-like receptor supersensitivity modulates NAc functioning in two main ways, both of which appear to be important for the expression of behavioral sensitization.

First, D₁-like receptor supersensitivity directly alters the functioning of mesolimbic DA neurons projecting from the VTA to the NAc. Specifically, stimulation of supersensitive D₁-like receptors attenuates GABAergic functioning in the VTA (Bonci & Williams, 1996; Klitenick et al., 1992). These changes in amino acid neurotransmission act to enhance the firing rate of DA neurons projecting from the VTA to the NAc (Grace & Bunney, 1998). Thus, through this direct mechanism repeated psychostimulant treatment results in augmented DA release in the NAc.

Second, D₁-like receptor supersensitivity serves to potentiate DA release in the NAc by modulating glutamate via two indirect pathways involving the prefrontal cortex (PFC). Both pathways involve the stimulation of presynaptic D₁-like receptors located on glutamatergic

neurons projecting from the PFC to the VTA. These glutamate neurons synapse with mesocortical DA neurons that project from the VTA to the PFC (see Fig. 3) (Takahata & Moghaddam, 2000). Thus, stimulation of these D₁-like receptors causes a reduction in glutamatergic stimulation and, consequently, induces sustained hypoactivity in DA neurons (Grace & Bunney, 1998).

The lack of tonic inhibition by the mesocortical DA neurons affects two distinct glutamatergic pathways that originate at the PFC (see Fig. 3). One pathway projects directly from the PFC to the NAc (PFC → NAc), and provides glutamatergic excitation to the NAc (Berendse, Galis-DE Graaf, & Groenewegen, 1992; Christie, Summers, Stephenson, Cook, & Beart, 1987; Montaron, Deniau, Menetrey, Glowinski, & Thierry, 1996). The other glutamate pathway projects from the PFC to the VTA via the pedunculopontine tegmental nucleus (PPTg; PFC → PPTg → VTA) (Lokwan, Overton, Berry, & Clark, 1999; Sesack et al., 1989). When stimulated, glutamate neurons projecting to the PPTg activate a second glutamate pathway going from the PPTg to the VTA (Lokwan, et al., 1999). This excess glutamate activity results in further stimulation of DA neurons, which are already supersensitive to glutamate because of the induction

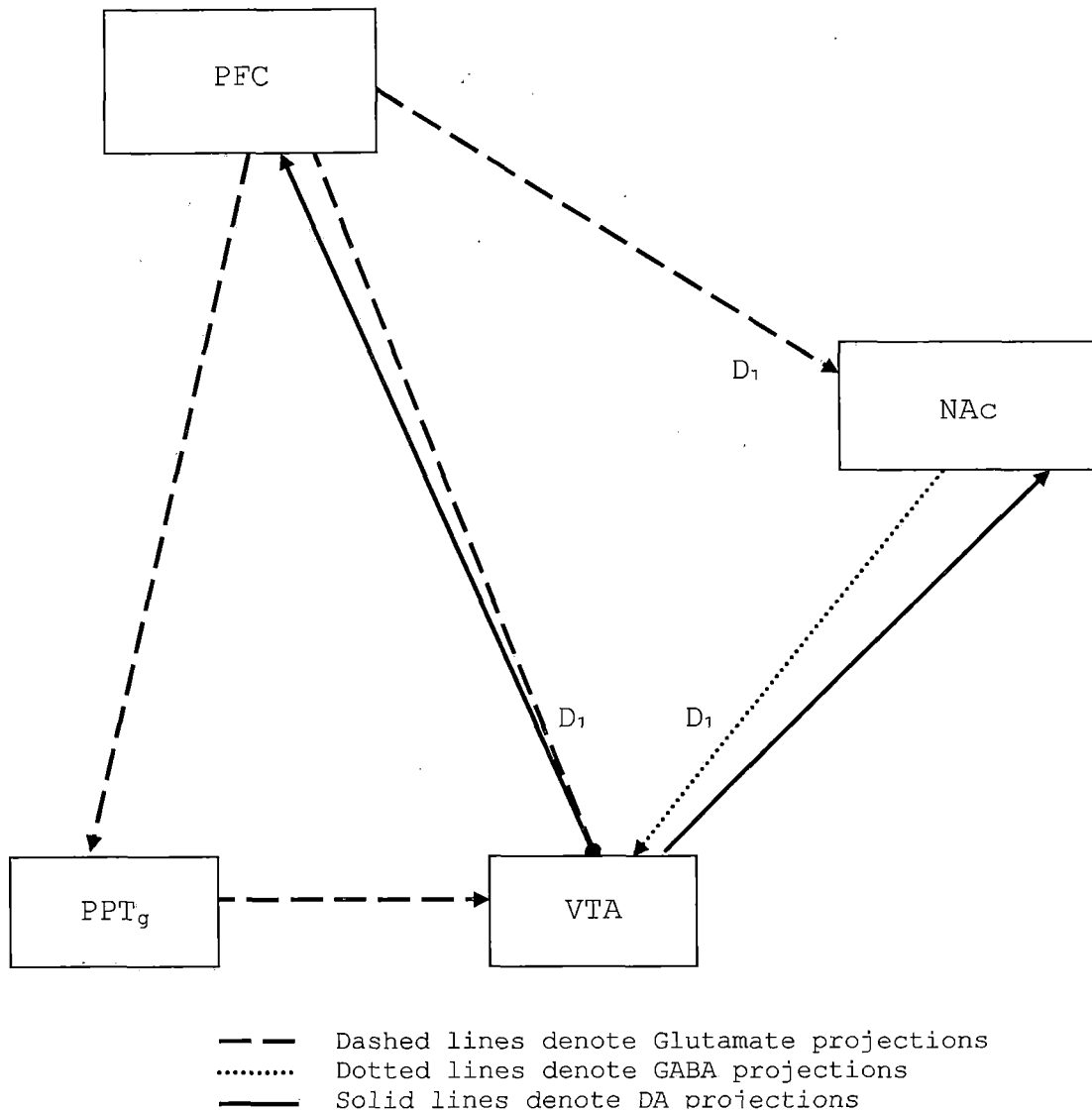


Figure 3. Glutamatergic pathways originating in the PFC mediate accumbal activity via a direct pathway between the PFC and the NAc and via an indirect pathway that provides stimulation of the VTA by way of the PPT_g.

process (Youngren, Daly, & Moghaddam, 1993). Therefore, changes in D₁-like receptor sensitivity in the VTA, brought about by the induction phase of sensitization, causes changes in the NAc, the structure responsible for the expression of behavioral sensitization. These changes include increased DA release and D₁-like receptor supersensitivity, which both result from psychostimulant-induced alterations of these direct and indirect pathways.

In conclusion, D₁-like receptors modulate the release of DA from the VTA and glutamate from the PFC (see Fig. 3) (Higashi, Inanaga, Nishi, & Uchimura, 1989; Kalivas & Duffy, 1995, 1998; Vanderschuren & Kalivas, 2000). Stimulation of D₁-like receptors causes a decrease in GABA at the VTA, as well as an increase in glutamate at both the VTA and the NAc (Bonci & Williams, 1996; Kalivas, 1995a; Kalivas & Duffy, 1995, 1998; Pierce & Kalivas, 1997; Takahata & Moghaddam, 2000; Youngren et al., 1993). The action of these amino acids increases DA release in the NAc. This increase in excitatory, and decrease in inhibitory, impulses produces a positive feedback loop to the VTA resulting in burst firing of dopamine neurons (Kalivas & Duffy, 1995; Takahata & Moghaddam, 2000). Burst firing of DA neurons increases DA release and,

consequently, glutamate release (Bockstaele & Pickel, 1995; Bonci & Williams, 1996; Kalivas & Duffy, 1998; Mereu et al., 1991; Pierce & Kalivas, 1997). Therefore, it is the summation of amino acid impulses combined with inhibitory dopaminergic input that modulates NAc activity and, thus, the behavioral manifestations of sensitization (Kalivas, 1995a; Kretschmer, 1999; Vanderschuren & Kalivas, 2000).

CHAPTER FIVE

GLUTAMATE AND BEHAVIORAL SENSITIZATION

The Widespread Influence of Glutamate

Glutamate neurons are located extensively throughout the basal ganglia and related structures. For example, glutamate neurons project bi-directionally between the PFC and the medial dorsal thalamus (MD_{Thal}), as well as descending from the PFC to the NAc, VTA, and PPTg (Berendse et al., 1992; Christie et al., 1987; Montaron et al., 1996; Pierce & Kalivas, 1997; Sesack et al., 1989; Takahata & Moghaddam, 2000; Tzschentke & Schmidt, 2000). The PFC projection to the NAc is a direct one. However, the PFC projection to the VTA is indirect, as the PFC innervates the PPTg which, in turn, sends a glutamatergic projection to the VTA (see Fig. 4) (Lokwan et al., 1999; Sesack et al., 1989; Tzschentke & Schmidt, 2000).

As described in Chapter Four, glutamate projections are critical for the induction of behavioral sensitization. Induction is prevented by either co-administering an NMDA antagonist (glutamate stimulates NMDA receptors) or by lesioning the PFC (the PFC sends glutamate projections to

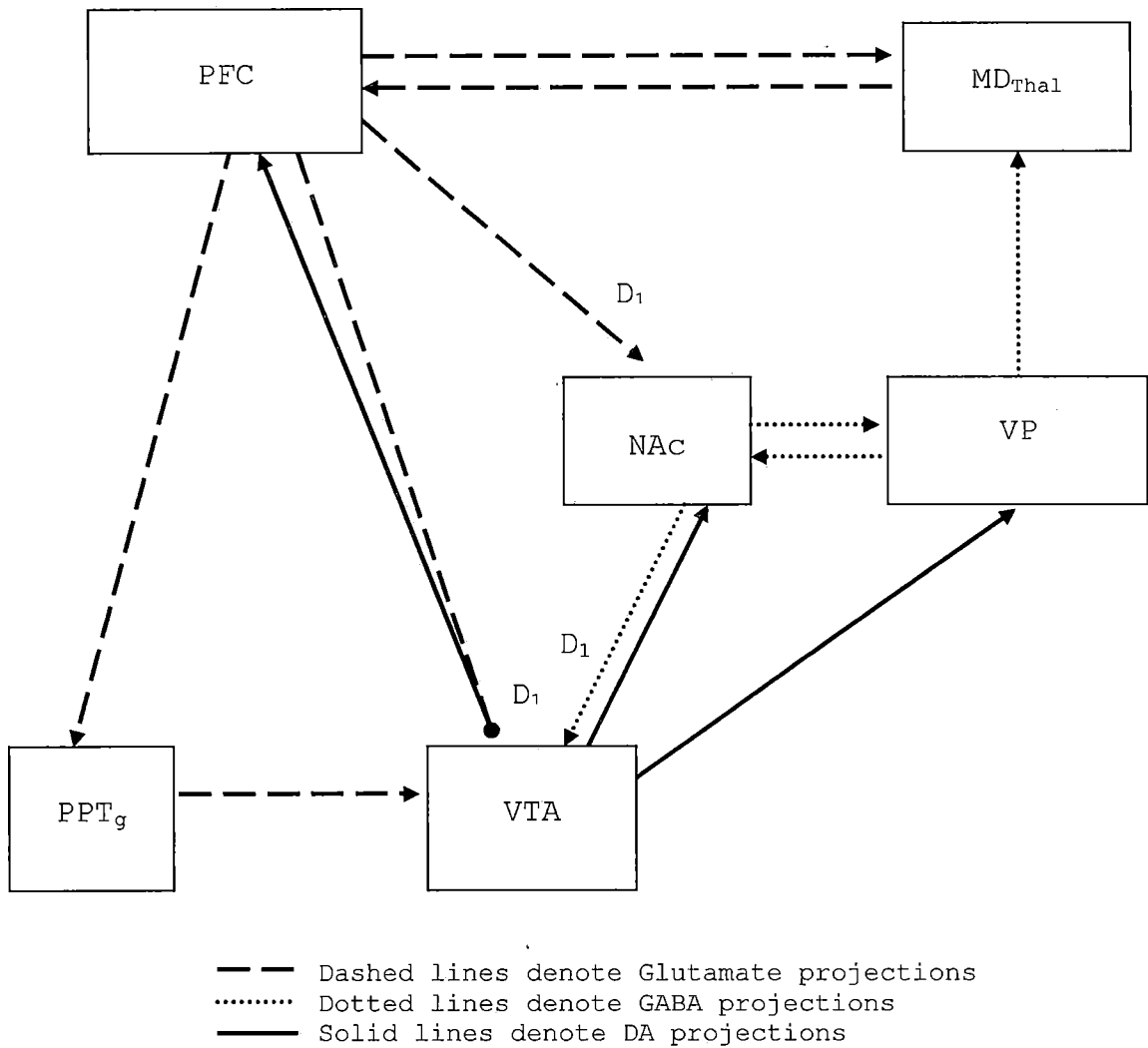


Figure 4. Schematic representation illustrating the widespread presence of glutamate (dashed lines) within the mesocortical and mesolimbic pathways. The location of DA D_1 -like receptors on glutamate pathways, as well as GABA (dotted lines) and DA (solid lines) projections are also shown. The PFC regulates the VTA indirectly via the PPT_g, as direct PFC glutamatergic input to the VTA synapses on DA projections that form a feedback loop to the PFC. The reciprocal relationship between the VTA and The NAC can also be seen.

both the VTA and the PPTg) (Cador et al., 1999; Karler, Calder, Chaudhry, & Turkanis, 1989; Li et al., 1999; Stewart & Druhan, 1993; Wolf et al., 1995). Glutamate neurons are also fundamentally involved in the expression of behavioral sensitization (Edley & Graybiel, 1983; Gnegy, 2000; Kozell & Meshul, 2001; Li et al., 1999; Montaron et al., 1986; Pierce & Kalivas, 1997). Specifically, glutamate increases DA release in the NAc by altering the firing rate of DA neurons in the mesolimbic pathway (Cornish & Kalivas, 2001a; Kalivas, 1995a; Kalivas & Stewart, 1991; Kretschmer, 1999; Lokwan et al., 1999). The altered firing rate results from: (a) glutamatergic stimulation of NMDA receptors located on DA cell bodies in the VTA (Gnegy, 2000; Kalivas, 1995a), (b) an NMDA-induced subsensitivity of DA autoreceptors in the VTA (Grace, 1995; Li et al., 1999; White & Wolf, 1991; Wolf, 1998), and (c) an NMDA-induced hypersensitivity of D₁-like receptors located on GABA pathways that project bi-directionally between the NAc and the ventral pallidum (VP) and unidirectionally from the NAc to the VTA (see Fig. 4) (Bonci & Williams, 1996; Gnegy, 2000; Kalivas, 1995b; Li et al., 1999; Walaas & Fonnum, 1980; White et al., 1995; Wolf, 1998). The pervasive presence of glutamate throughout the

neural circuit underlying behavioral sensitization has lead some authors to refer to glutamate as the "ubiquitous regulator" (Li et al., 1999, p. 177; see also Danbolt, 2001; Karler et al., 1997; Laming, 1998; Wolf, 1998).

Behavioral Sensitization, Learning, and N-methyl-D-aspartate Receptors

As discussed in Chapter Three, the strength of the sensitized response is at least partially dependent on Pavlovian associations formed between the drug and environmental context (Kuczenski & Segal, 2001; Tirelli & Terry, 1998). Specifically, it has been argued that expression is context-dependent (Tirelli & Terry, 1998; but see Vezina & Stewart, 1990), particularly when younger animals or lower doses of psychostimulants are used (Battisti et al., 2000; Zavala et al., 2000). Moreover, even when context-independent sensitization occurs, interoceptive feedback may serve as a discriminative stimulus providing associative learning cues (Lienau & Kuschinsky, 1997).

Learning is the result of enduring changes in neuronal sensitivity due to the activation of both ionotropic (i.e., NMDA, AMPA, and kinate) and metabotropic (mGluR) glutamate receptor subtypes in the hippocampus (Morris, Anderson,

Lynch, & Baudry, 1986; Rickard & Ng, 1995; Riedel, 1996; Vezina & Kim, 1999). A specific mGluR subtype, namely mGluR₁, has been implicated in hippocampus-based context-dependent learning (Aiba et al., 1994). The hippocampus provides glutamatergic input directly to the PFC, NAc, and VTA (the same structures responsible for sensitization) (Christie et al., 1987; Groenewegen, Becker, & Lohman, 1980; Mulder, Hodenpijl, & Lopes da Silva, 1998; Pierce & Kalivas, 1997; Tzschentke & Schmidt, 2000). Evidence supporting the idea that the hippocampus is important is becoming more abundant. For example, blocking glutamatergic input from the hippocampus prevents the expression of behavioral sensitization (Aiba et al., 1994; Kalivas, 1995a; but see Wolf, 1998). Moreover, a relationship between hippocampal stimulation (which occurs during learning) and glutamate content in the NAc has been reported, with increased levels of glutamate found only in rats given repeated drug exposures (Pierce et al., 1996). Consistent with this finding, efforts to extinguish a sensitized response are successful only when induction involves a single psychostimulant exposure (Battisti et al., 2000).

Behavioral Sensitization and Neurotoxicity

DA is catabolized through oxidation (Mansour, Meador-Woodruff, López, & Watson, 1998), with high levels of DA producing oxidative stress resulting in neurotoxicity (Cohen, 1984; Yamamoto, Gudelsky, & Stephans, 1998). Additionally, free radicals produced during oxidation increase glutamate release that, in turn, produces more free radicals (Pellegrini-Giampietro, 1994; Pellegrini-Giampietro, Cherici, Alesiani, Carla, & Moroni, 1988, 1990; Sonsalla, 1995; Yamamoto et al., 1998).

Excess extracellular glutamate has been implicated in various neurological disorders and neurodegenerative diseases (Choi, 1988; Lipton & Rosenberg, 1994). It has been suggested that neuronal death caused by excess glutamate (also known as excitotoxicity) (for a review see Pellegrini-Giampietro, 1994) operates like a "domino effect" (Choi, 1988; Lipton & Rosenberg, 1994). Excitotoxicity has been characterized in this way because the excessive amounts of intracellular glutamate released by a dying cell threaten the viability of all other cells in close proximity. Therefore, the death of a cell via excitotoxicity can perpetuate further neurotoxicity in an

exponential fashion (Lipton & Rosenberg, 1994). Additionally, elevated levels of extracellular glutamate potentiate the neurotoxic effects of DA oxidation (Hoyt, Reynolds, & Hastings, 1997; Yamamoto et al., 1998). Because sustained increases in DA and glutamate occur in behavioral sensitization (Pierce & Kalivas, 1997), and because NMDA antagonists not only block induction (Calder et al., 1989; Li et al., 1999; Stewart & Druhan, 1993; Vezina & Queen, 2000), but protect against neuronal assault (Choi, 1988; Finnegan, Skratt, Irwin, & Langston, 1990; Sonsalla, 1995; Sonsalla, Riordan, & Heikkila, 1991), it is possible that sensitization may be a by-product of neuronal damage (Peterson et al., 1997; Wolf, 1998; see also Itzhak, Martin, & Ali, 2000; Wallace, Gudelsky, & Vorhees, 2001). More specifically, glutamate excitotoxicity triggered by repeated psychostimulant exposure may be a critical mechanism underlying behavioral sensitization. Not only is excitotoxicity potentially important for understanding the sensitization process, it also has implications for human ATS abuse.

CHAPTER SIX
SENSITIZATION, GLUTAMATE, AND
GLIAL CELLS


The Toxic Effects of
Glutamate

It is possible that the expression of behavioral sensitization is a manifestation of neuronal injury (Peterson et al., 1997; Wolf, 1998; see also Itzhak et al., 2000; Wallace et al., 2001). This is because sensitization involves extracellular increases in both DA and glutamate concentrations (Kalivas & Duffy, 1998; Kuczenski & Segal, 2001; Pierce & Kalivas, 1997). Increases in extracellular DA cause oxidative stress that can lead to neurotoxicity, particularly when followed by neuronal exposure to glutamate (Cohen, 1984; Hoyt et al., 1997; Yamamoto et al., 1998). Additionally, a positive feedback loop exists between free radicals (produced through DA degradation) and glutamate, whereby each increases the production of the other (Pellegrini-Giampietro, 1994; Pellegrini-Giampietro et al., 1990; Sonsalla, 1995).

The reciprocal action of the free-radical/glutamate feedback loop produces a sustained increase in glutamate that depletes the adenosine triphosphate (ATP) required to

transport and metabolize extracellular glutamate (Yamamoto et al., 1998). This action further increases the extracellular concentrations of glutamate due to lack of uptake, reversal of transporters, or via leakage from swollen cells (Danbolt, 2001; Kimelberg et al., 1990, Kimelberg, Rutledge, Goderie, & Charniga, 1995; Lipton & Rosenberg, 1994; Syková, Hansson, Rönnbäck & Nicholson, 1998; Yamamoto et al., 1998). When high levels of extracellular glutamate accumulate, the self-perpetuating process of excitotoxicity begins, spreading at an exponential rate as destroyed cells release their intracellular stores of glutamate (Lipton & Rosenberg, 1994; Pellegrini-Giampietro, 1994).

The release of glutamate that occurs during excitotoxicity bathes all proximal cells. This means that both neurons and glial cells (i.e., astrocytes and oligodendrocytes) are vulnerable to the excitotoxic effects of glutamate. There are several findings that support this position. First, widespread neuronal damage occurs due to the synergistic combination of DA and glutamate. Second, glial cells, like neurons, uptake glutamate through transporters (Danbolt, 2001; Pellegrini-Giampietro, 1994). Third, glial cells, like neurons, contain glutamate and



dopamine receptors (Cull-Candy & Wyllie, 1991; Pearce, 1991). And finally, glial cells have the ability to engage in cross-communication with, as well as modulate the activity of, neurons (Araque, Sanzgiri, Parpura, & Haydon, 1998; Carmignoto, 2000; Cull-Candy & Wyllie, 1991; Laming, 1998; Pearce, 1991).

Predictions

Despite a substantial body of evidence indicating that glutamate toxicity affects both neurons and glia, few studies have examined the effects of repeated psychostimulant exposure on glial cell functioning. Therefore, the current investigation examined changes in glial and DA cell toxicity in amphetamine-sensitized rats. Specifically, it was predicted that: (1) rats pretreated with amphetamine would show a sensitized response after acute amphetamine challenge; (2) rats pretreated with amphetamine and challenged with saline, would show greater locomotor activity (i.e., conditioned activity) than saline controls; (3) rats pretreated with amphetamine would exhibit increased gliosis (i.e., an increase in the number of glial fibrillary protein [GFAP] immunoreactive cells), indicating cellular neurotoxicity; (4) DA neurotoxicity

would be evident in amphetamine-pretreated rats, with a loss of DA transporters (DAT) being used as a marker of DA neurotoxicity (i.e., a decrease in the number of DAT immunoreactive cells); and (5) Glial cell toxicity would also occur, as shown by a loss of glutamate transporter subtype 1 (GLT-1) (i.e., a decrease in the number of GLT-1 immunoreactive cells).

CHAPTER SEVEN

METHODS

Behavioral Methods

Subjects

Subjects were 40 ($n = 10$ per group) adult male Sprague-Dawley rats (Harlan, Indianapolis, IN). Rats weighed between 225-249 g on arrival and were housed singly in a colony room maintained on a 12:12 light:dark cycle at 22°-24°C. Food and water were provided *ad lib* and rats were treated in accordance with National Institute of Health guidelines ("Principles of Laboratory Animal Care", NIH Publication #85-23).

Drugs

d-Amphetamine was purchased from Sigma (St. Louis, MO), dissolved in saline, and injected intraperitoneally (i.p.) at a volume of 1 ml/kg.

Apparatus

Locomotor activity was monitored using commercially available Coulbourn activity chambers (Coulbourn Instruments, Allentown, PA). Chambers measured 25.5 × 25.5 × 41 cm and were constructed of Plexiglas. Chambers contained a removable plastic bottom and had an open top.

Each chamber utilized an X-Y photobeam array with 16 photocells and detectors to determine the total distance traveled (horizontal locomotor activity).

Procedure

Prior to any experimental manipulation, animals were allowed to acclimate to the California State University vivarium for a period of not less than 14 days. During this time, the rats were handled daily. Rats were randomly assigned to one of four treatment conditions:

saline/saline, amphetamine/saline, saline/amphetamine, or amphetamine/amphetamine. Following assignment, the 7-day pretreatment phase began. During pretreatment, rats received a single daily injection of saline or amphetamine (2.0 mg/kg, i.p.) at approximately the same time each day. Immediately following injections, rats were individually placed in activity chambers for a period of 60 min, with distance traveled measured in 5 min increments.

A single test day occurred after a 10-day abstinence period. On test day, rats were given a challenge injection of either saline or amphetamine (0.5 mg/kg, i.p.).

Immediately following injections, rats were individually placed in activity chambers for 120 min, with distance traveled measured in 5 min increments.

Statistics

Distance traveled data from the drug pretreatment phase was analyzed using a 2×7 (Pretreatment \times Day) repeated measures analysis of variance (ANOVA). Test day data was analyzed using a $2 \times 2 \times 24$ (Pretreatment \times Test Treatment \times Time [5 min blocks]) repeated measures ANOVA. Post hoc analysis of data from the drug pretreatment phase and test day was made using Tukey tests ($p < .05$).

Immunohistochemistry Methods

Antibodies and Supplies

Primary antibodies for three different proteins (glial fibrillary acidic protein [GFAP], dopamine transporter [DAT], and glutamate transporter [GLT-1]) were used. Anti-glial fibrillary acidic protein, anti-dopamine transporter antibody, and anti-glial transporter antibody was purchased from Chemicon (Temecula, CA). Secondary antibodies consisted of either biotinylated rabbit (for GFAP and DAT) or biotinylated guinea pig (for GLT-1) antiserum (Vector Laboratories, Burlingame, CA). An avidin-biotin-horseradish peroxidase conjugate kit (ABC Vectastain Kit; Vector Laboratories, Burlingame, CA) was also required.

Procedure

Rats were anesthetized with phenobarbital and rapidly perfused with 4% paraformaldehyde after completion of behavioral assessment on the test day. Following a postfixation period, 75 μ l coronal sections were taken from each brain using a cryostat (Mikron, Nussloch, Germany) maintained at -25°C ($\pm 1^{\circ}\text{C}$).

To control for variability between assays, all assay procedures were done in sets of four, so that each treatment condition was represented. Sections were incubated in peroxidase solution (3% hydrogen peroxide and 10% methanol), followed by three washes in 0.1 M phosphate buffer (PB). All washes lasted 5 min. Sections were then incubated in goat serum solution (GSS; 1% goat serum and 0.1% Triton X-100 in PB) for 1 hr, followed by one wash in PB. Control sections were placed in GSS void of any primary antibody. All other sections were incubated for 48-72 hr with one of three primary antibodies (i.e., GFAP [1:2000 in GSS]; DAT [1:3750 in GSS]; GLT-1 [1:5000 in GSS]). After completion of the primary antibody incubation, sections were washed in PB three more times. Sections were then transferred into either rabbit (GFAP and

DAT [1:200 in GSS]) or guinea pig (GLT-1 [1:5000 in GSS]) antiserum and allowed to incubate 1 hr. Sections then received three more washes in PB followed by 1 hr incubation in ABC solution (1:200 in GSS). After this final incubation, sections were washed three times in PB. Sections were then stained using a DAB/hydrogen peroxide solution followed by three final washes in PB. Sections were then mounted on Superfrost Plus slides (Fisher, Philadelphia, PA), air-dried, dehydrated, and coverslipped with Depex.

Sections were then examined for GFAP, DAT, and GLT-1 immunoreactivity. Quantification was conducted manually at a magnification of $\times 40$ by researchers blind to treatment condition. The brain regions assessed included cingulate cortex, CA₁ and CA₃ regions of the hippocampus, NAc core and shell, and the ventral and dorsal caudate-putamen.

Statistics

GFAP, DAT, and GLT-1 immunoreactivity was analyzed using separate 2×2 (Pretreatment \times Test Treatment) ANOVAs for each brain region. Post hoc analysis of the immunohistochemistry data was made using Tukey tests ($p < .05$).

CHAPTER EIGHT
RESULTS AND DISCUSSION

Behavioral Results

Pretreatment Phase

During the pretreatment phase, rats given 2.0 mg/kg amphetamine displayed more horizontal locomotor activity than did saline controls (see Figure 5) (Pretreatment Drug main effect, $F_{1,38}=232.95$, $p < 0.01$). In addition, amphetamine-pretreated rats showed a general increase in distance traveled over the pretreatment phase, while saline controls showed a general decline (Pretreatment Drug \times Day interaction, $F_{6, 228}=12.24$, $p < 0.01$).

Test Day

Overall, rats given 2 mg/kg amphetamine during the pretreatment phase showed more test day locomotor activity than rats pretreated with saline (see Figure 6) (Pretreatment Drug main effect, $F_{1, 36}=25.53$, $p < 0.01$; Pretreatment Drug \times Time interaction, $F_{23, 828}=1.69$, $p < 0.05$). In addition, rats receiving a challenge injection of 0.5 mg/kg amphetamine on the test day exhibited more horizontal locomotor activity than rats receiving a

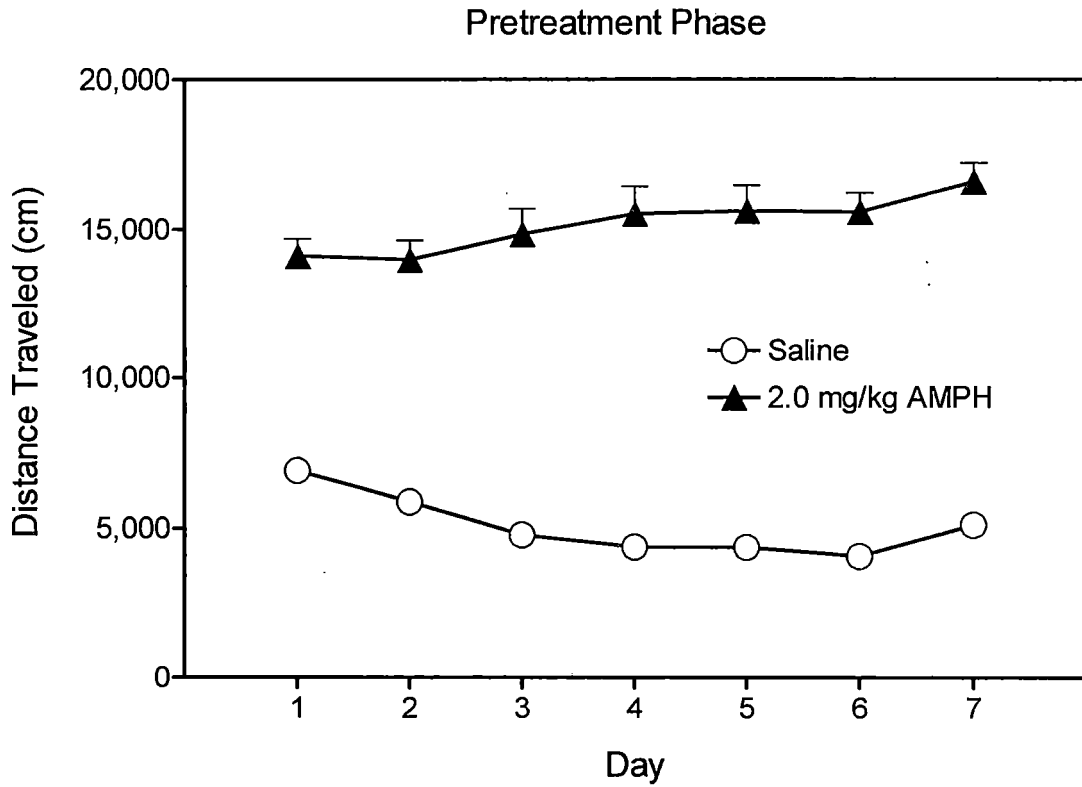


Figure 5. Mean (\pm SEM) distance traveled (cm) of rats ($n = 20$ per group) receiving either a daily i.p. injection of saline or 2.0 mg/kg amphetamine over seven pretreatment days. Measurement was taken during the 60 min period immediately following injection.

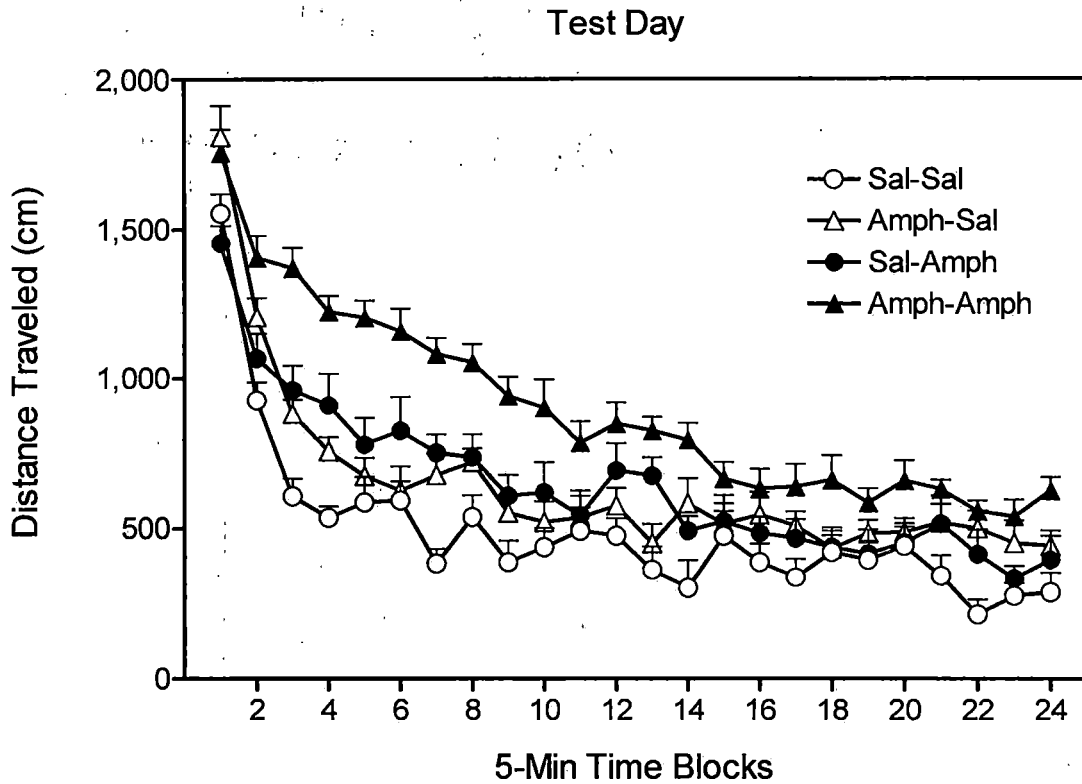


Figure 6. Mean (\pm SEM) distance traveled (cm) of saline- or amphetamine-pretreated rats ($n = 10$ per group) on test day (these are the same rats as described in Figure 1). Measurement was conducted for 120 min immediately following a challenge injection of either saline or 0.5 mg/kg amphetamine.

challenge injection of saline (Challenge Drug main effect, $F_{1,36}=26.61$, $p < 0.01$; Challenge Drug \times Time interaction, $F_{23,828}=5.59$, $p < 0.01$). Separate ANOVAs indicated that amphetamine pretreatment resulted in a sensitized locomotor response on the test day. More specifically, amphetamine-pretreated rats given a challenge injection of amphetamine (filled triangles) exhibited more test day locomotor activity than rats given amphetamine for the first time on the test day (filled circles) (Pretreatment Drug main effect, $F_{1,18}=17.75$, $p < 0.01$). Conditioned activity was also apparent, as rats pretreated with amphetamine and challenged with saline (open triangles) were more active than saline controls (open circles) (Pretreatment Drug main effect, $F_{1,18}=8.25$, $p < 0.05$).

Discussion of Behavioral Results

In terms of the behavioral data, two original predictions were made regarding behavioral sensitization and conditioned activity. Specifically, it was hypothesized that rats pretreated with amphetamine would show a sensitized locomotor response after acute amphetamine challenge. This hypothesis was supported. The

AMPH/AMPH group demonstrated greater horizontal locomotion than did the SAL/AMPH group. This indicates a sensitized response to the sympathomimetic properties of amphetamine. It was also predicted that rats pretreated with amphetamine and challenged with saline would demonstrate conditioned activity. This prediction was also supported as the AMPH/SAL group exhibited greater locomotion than did the SAL/SAL group. This finding indicates the presence of a conditioning component operating upon the sensitized animals.

Immunohistochemistry Results

Glial Fibrillary Acidic Protein Assay

Rats pretreated with 2 mg/kg amphetamine sustained neurotoxicity in the ventral and dorsal caudate-putamen (CP) (see Figure 7) as well as the CA₃ region of the hippocampus (see Figure 8). In the ventral CP, pretreatment with amphetamine resulted in an increase in GFAP irrespective of challenge injection (Pretreatment Drug main effect, $F_{1,27}=10.20$, $p < 0.01$). Similarly, pretreatment with amphetamine enhanced gliosis (i.e., the number of GFAP-immunoreactive cells) in both the dorsal CP and CA₃ of saline-challenged rats (Pretreatment Drug \times Test Drug

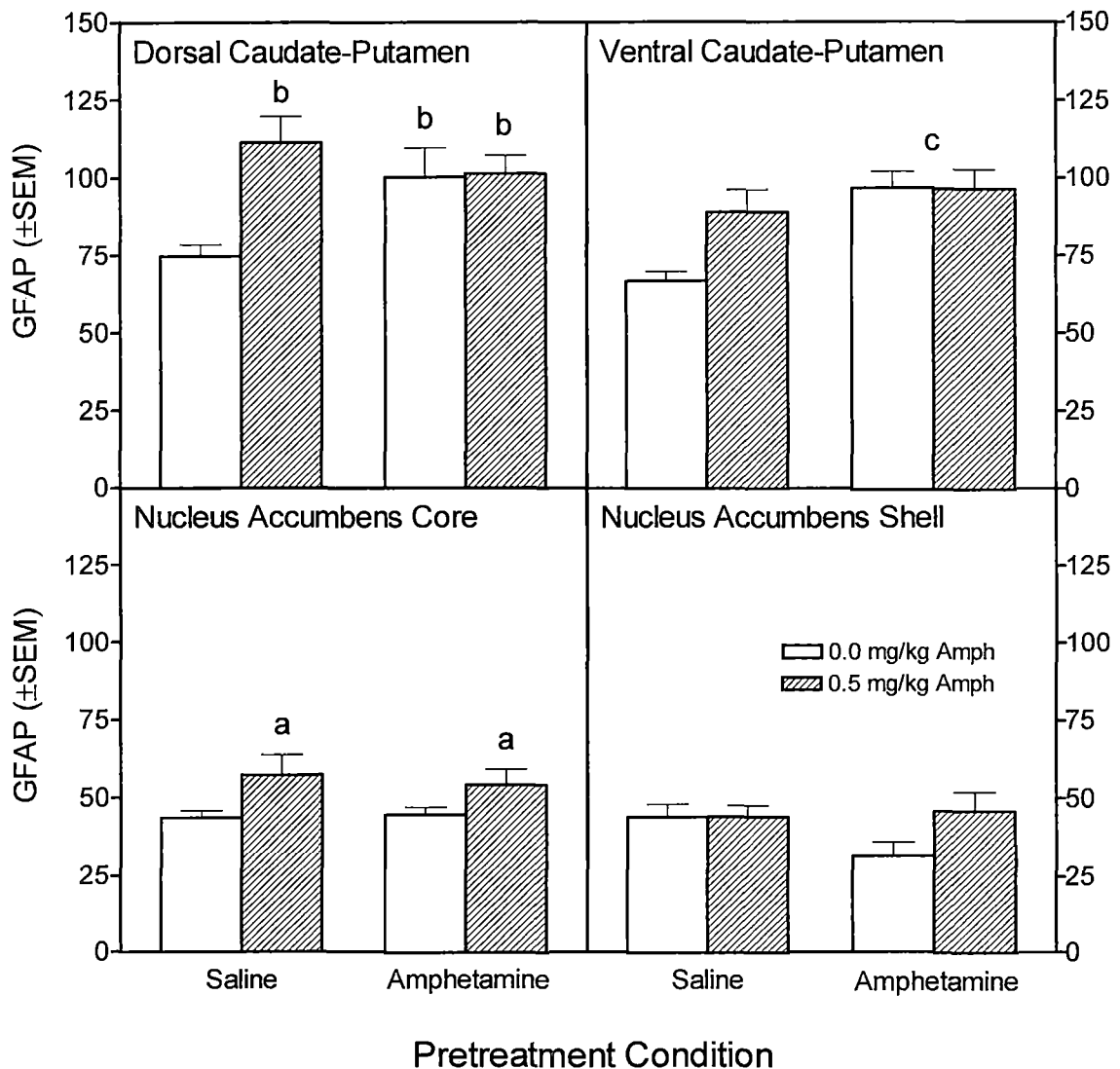


Figure 7. Mean number (\pm SEM) of anti-gial fibrillary acidic protein (GFAP) immunoreactive cells found in the dorsal caudate-putamen, ventral caudate-putamen, nucleus accumbens core, and nucleus accumbens shell for both saline- and amphetamine-pretreated rats ($n = 10$ per group). Open bars represent saline challenge; hatched bars indicate amphetamine challenge. ^aSignificantly different from saline-challenged rats ($p < 0.05$). ^bSignificantly different from saline-saline group ($p < 0.05$). ^cSignificantly different from saline-pretreated rats ($p < 0.05$).

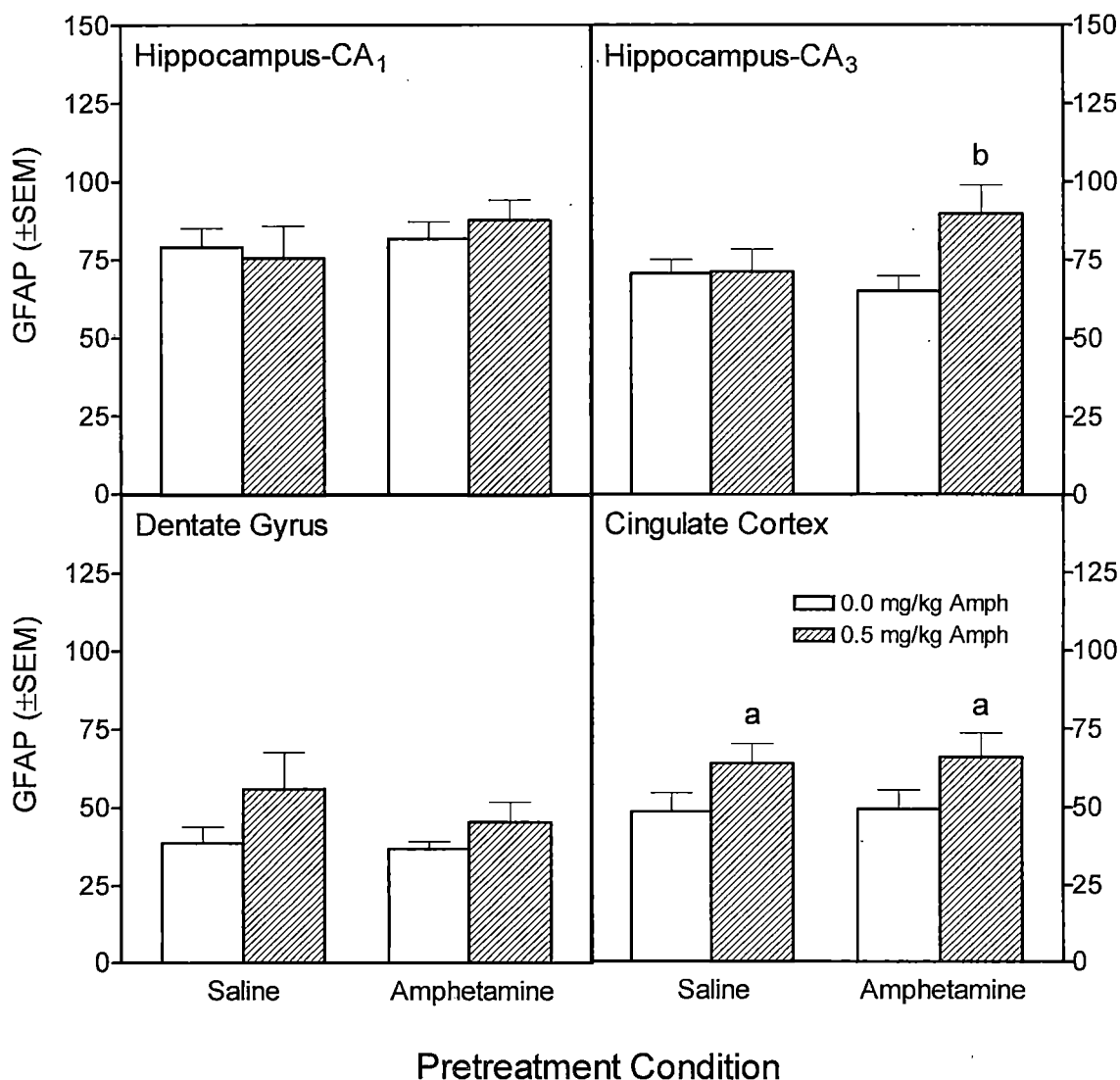


Figure 8. Mean number (\pm SEM) of anti-glial fibrillary acidic protein (GFAP) immunoreactive cells found in hippocampal CA₁, hippocampal CA₃, dentate gyrus, and cingulate cortex for both saline- and amphetamine-pretreated rats ($n = 10$ per group). Open bars represent saline challenge; hatched bars indicate amphetamine challenge. ^aSignificantly different from saline-challenged rats ($p < 0.05$). ^bSignificantly different from saline-saline group ($p < 0.05$).

interaction, $F_{1,27}=7.72$, $p = 0.01$; $F_{1,27}=4.46$, $p < 0.05$, respectively).

In addition, a challenge injection of 0.5 mg/kg amphetamine resulted in higher levels of GFAP in the dorsal CP, as well as the NAc core and cingulate cortex (Test Drug main effect, $F_{1,27}=4.57$, $p < 0.05$; $F_{1,27}=8.66$, $p < 0.01$; $F_{1,27}=18.55$, $p < 0.001$, respectively).

Dopamine Transporter Assay

Examination of the CA₁ region of the hippocampus revealed increased numbers of DAT-immunoreactive cells in those rats repeatedly exposed to amphetamine during the pretreatment phase (Pretreatment Drug main effect, $F_{1,27}=4.42$, $p < 0.05$; see Figure 9). Acute effects were also evident, as an increase in DAT was found in the amygdala, dentate gyrus, dorsal CP, and cingulate cortex of those rats given a challenge injection of amphetamine on test day (Test Drug main effect, $F_{1,27}=4.57$, $p < 0.05$; $F_{1,27}=8.76$, $p < 0.01$, respectively; see Figures 9 and 10).

Glutamate Transporter Assay

Neither amphetamine pretreatment nor challenge caused a significant decrease in the number of GLT-1 immunoreactive cells in any of the brain areas examined

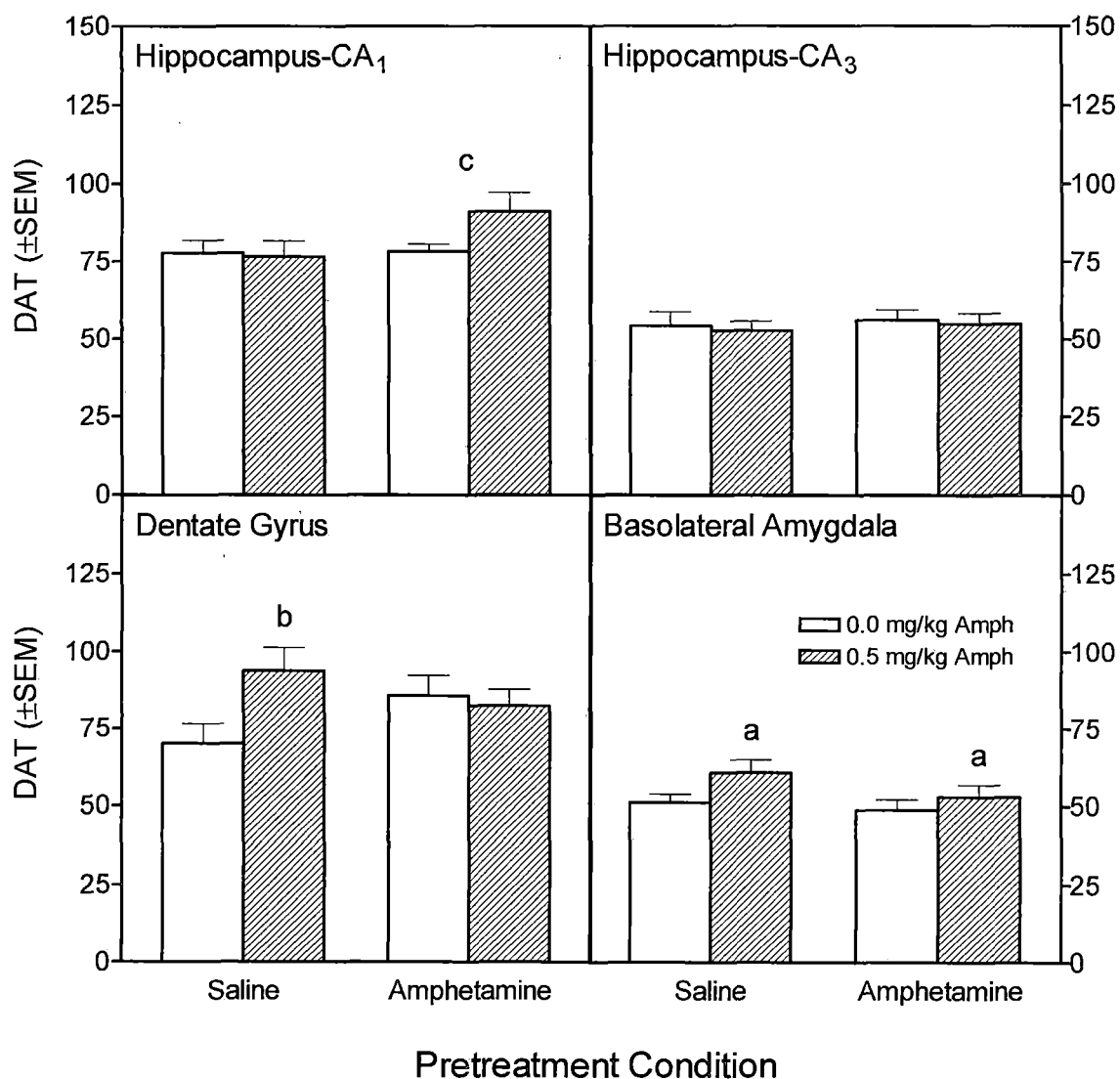


Figure 9. Mean number (\pm SEM) of dopamine transporter (DAT) immunoreactive cells found in hippocampal CA₁, hippocampal CA₃, dentate gyrus, and basolateral amygdala for both saline- and amphetamine-pretreated rats ($n = 10$ per group). Open bars represent saline challenge; hatched bars indicate amphetamine challenge. ^aSignificantly different from saline-challenged rats ($p < 0.05$). ^bSignificantly different from saline-saline group ($p < 0.05$). ^cSignificantly different from saline-pretreated rats ($p < 0.05$).

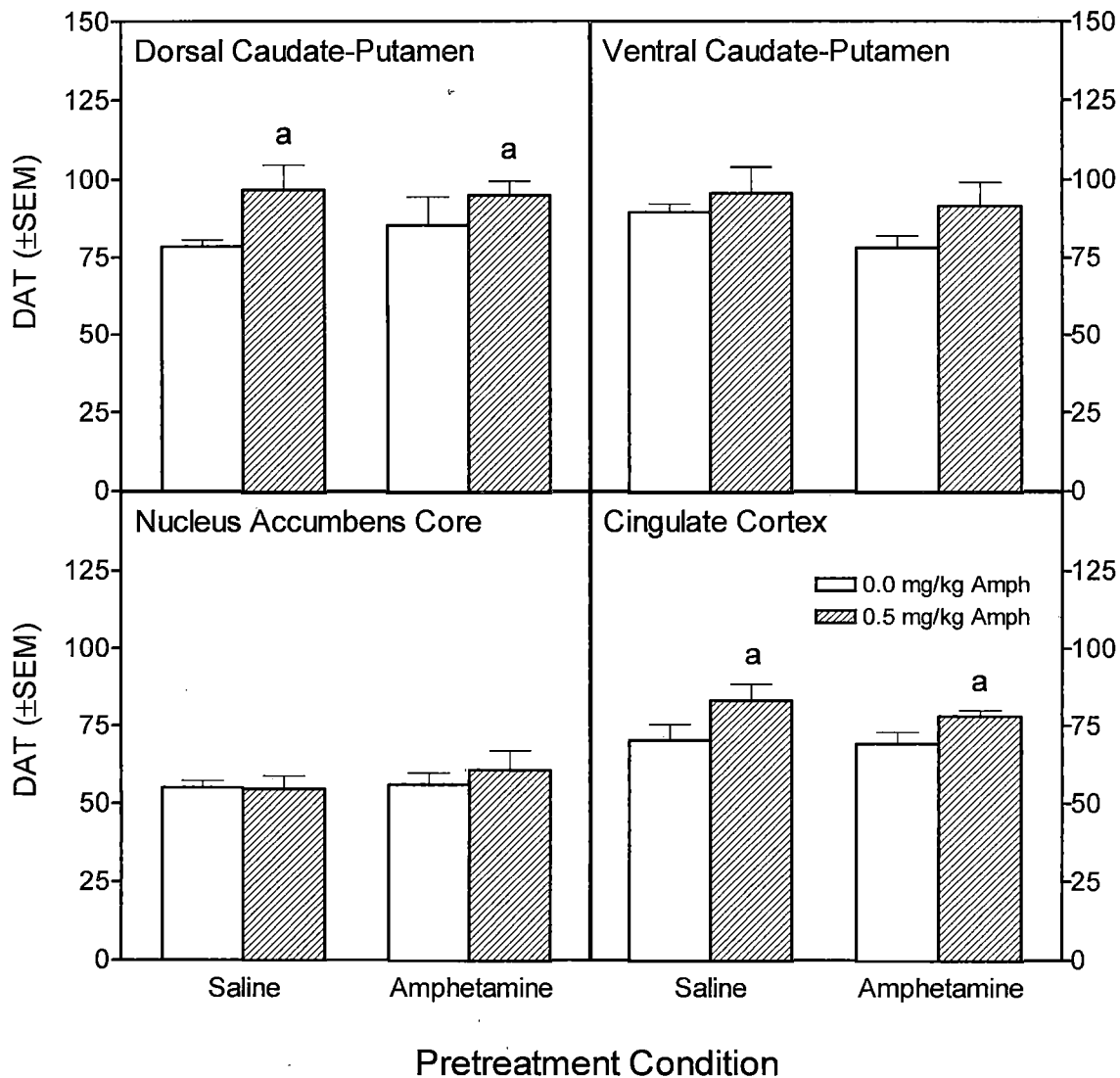


Figure 10. Mean number (\pm SEM) of dopamine transporter (DAT) immunoreactive cells found in the dorsal caudate-putamen, ventral caudate-putamen, nucleus accumbens core, and cingulate cortex for both saline- and amphetamine-pretreated rats ($n = 10$ per group). Open bars represent saline challenge; hatched bars indicate amphetamine challenge. ^aSignificantly different from saline-challenged rats ($p < 0.05$).

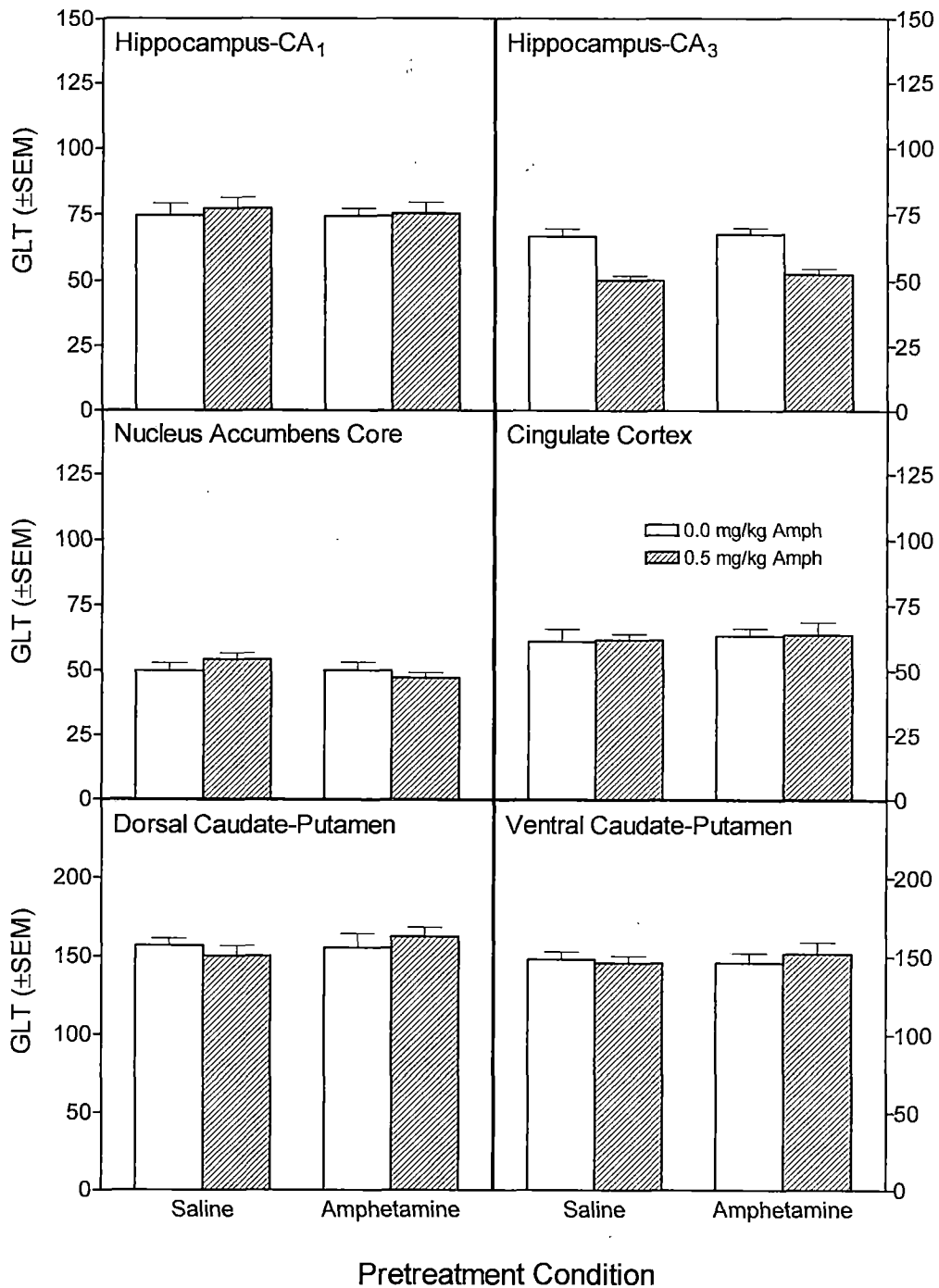


Figure 11. Mean number (\pm SEM) of glutamate transporter (GLT-1) immunoreactive cells found in the hippocampal CA₁, hippocampal CA₃, nucleus accumbens core, cingulate cortex, dorsal and ventral caudate-putamen for both saline- and amphetamine-pretreated rats ($n = 10$ per group).

(ventral and dorsal CP, NAc, hippocampus, cingulate cortex and prefrontal cortex; see Figure 11).

Discussion of Immunohistochemistry Results

Three original hypotheses were made regarding changes in neuronal and glial functioning. First, it was predicted that rats pretreated with amphetamine would exhibit increased gliosis. This prediction was supported because a significant increase in GFAP was observed in both ventral and dorsal CP of amphetamine-pretreated rats. This increase in GFAP suggests that amphetamine does induce gliosis in specific regions of the rat brain.

Second, it was hypothesized that amphetamine-pretreated rats would exhibit DA toxicity as indicated by a decrease in DAT. This hypothesis was not supported as DAT immunoreactive cells within the CA₁ region of the hippocampus *increased* rather than *decreased* following amphetamine pretreatment. Additionally, increases in DAT were also observed in the amygdala, dentate gyrus, dorsal CP and cingulate cortex following amphetamine challenge. This increase in DAT immunoreactive cells suggests that DAT transporters may exhibit compensatory changes after amphetamine treatment.

Lastly, it was predicted that amphetamine-pretreated rats would exhibit glial toxicity as indicated by a decrease in GLT-1. This prediction was not supported, as amphetamine pretreatment. The reason for this lack of effect is uncertain.

CHAPTER NINE

GENERAL DISCUSSION

Rationale

Behavioral sensitization is known to involve increases in both DA and glutamate in various brain regions (see Chapter 4). The current investigation was undertaken to determine whether the toxic interaction of these two neurotransmitters underlies behavioral sensitization. The importance of toxicity for behavioral sensitization has garnered support, as a feedback loop exists between DA and glutamate. Specifically, the stimulation of DA receptors increase glutamate release, and glutamate enhances DA release (Kalivas & Duffy, 1998; Mereu et al., 1991; Takahata & Moghaddam, 2000; for a fuller discussion see Chapter 4). The break down of DA produces cell-damaging ROS and stimulates glutamate release, while excess glutamate depletes cellular ATP (Pellegrini-Giampietro, 1994; Pellegrini-Giampietro et al., 1988, 1990; Wolf, Xue, Li, & Wavak, 2000; Yamamoto et al., 1998). ATP depletion, in turn, further increases extracellular glutamate (Anderson & Swanson, 2000; Lipton & Rosenberg, 1994). Thus, the escalation of DA and glutamate is synergistic,

because cells stressed by the DA oxidation process are more vulnerable to glutamate toxicity (Hoyt et al., 1997; Yamamoto et al., 1988). In sum, repeated exposure to amphetamine causes both neurotoxicity (through the synergistic effects of DA and glutamate) and behavioral sensitization. Determining whether this relationship is more than correlative was the purpose of this thesis.

In the present study, toxicity was measured using three immunohistochemistry assays. To provide an indice of general neurotoxicity, glial fibrillary protein (GFAP) was assessed. Due to the existence of a feedback loop between DA and glutamate, and previous findings that excitotoxicity can occur following increases in extracellular glutamate concentrations, it was expected that GFAP levels would increase following amphetamine exposure. Assessment of amphetamine-induced DA neurotoxicity was accomplished by measuring DA transporters (DAT). Neurotoxic doses of psychostimulants have been shown to decrease DAT levels (indicating DA neuron loss). Thus, it was predicted that an amphetamine regimen sufficient to induce behavioral sensitization would decrease DAT levels. Because excess DA and glutamate impact *all* proximal cells including glia,

glial glutamate transporter levels were examined as a measure of glial cell loss.

Evidence for Amphetamine-Induced Behavioral Sensitization

Behavioral sensitization was induced in amphetamine-pretreated rats, and both pharmacological and learning components were evident. Specifically, rats repeatedly exposed to amphetamine exhibited an increase in horizontal locomotion over pretreatment days. On test day, an enhanced response to the pharmacological effects of the drug were observed, because sensitized rats given an amphetamine challenge (the AMPH-AMPH group) displayed a significantly greater level of locomotor activity than did those rats experiencing acute amphetamine exposure (the SAL-AMPH group). Learning components (i.e., conditioned activity) were also evident, in that sensitized rats receiving a challenge injection of saline on test day (the AMPH-SAL group) exhibited significantly greater locomotor activity than did control rats that had never been exposed to the drug (the SAL-SAL group).

Assays: Findings and Interpretations

Acute and Repeated Amphetamine Exposure Results in

Gliosis

Amphetamine-exposed rats were expected to show gliosis. Acute exposure to amphetamine caused increased GFAP in three brain areas: the cingulate cortex, dorsal CP, and NAc core. More interesting, however, was the finding that amphetamine pretreatment caused gliosis in the CA₃ area of the hippocampus as well as both the ventral and dorsal CP. In the CA₃ region of the hippocampus, gliosis occurred after amphetamine challenge, but only in those rats chronically exposed to amphetamine during the pretreatment phase. Similarly, amphetamine pretreatment caused increased GFAP in the ventral and dorsal CP of both amphetamine- and saline-challenged rats.

Overall, GFAP findings were consistent with original expectations, and the increased number of GFAP immunoreactive cells suggests two possible interpretations. First, the anatomical pattern of gliosis along the basal ganglia-thalamocortical "motor" pathway is consistent with published assertions that neuronal injury is the basis for the expression of behavioral sensitization (Peterson et al., 1997; Wolf, 1998). The basal ganglia-thalamocortical

"motor" pathway extends from the cingulate cortex to the core of the NAc and the adjoining CP and projects to various motor cortices (Alexander & Crutcher, 1990; Zahm & Brog, 1992). The core of the NAc is particularly susceptible to neurotoxins and is thought to be the locus of stimulant-induced locomotion, as well as the area responsible for determining the saliency of response reward in associative learning (Boye, Grant, & Clarke, 2001; Broening, Pu, & Vorhees, 1997; Corbit, Muir, & Balleine, 2001). Second, it has been proposed that gliosis may indicate the activation of neuroprotective mechanisms as astrocytes contain antioxidants and have the ability to both synthesize and release neurotrophins (Deng, Ladenheim, Tsao, & Cadet, 1999). Therefore, GFAP concentrations may not simply reflect the degree of neurotoxicity, instead GFAP may serve as a neuroprotective mechanism depending on the level of environmental toxicity. In terms of the present study, it is possible that the amphetamine-induced increases in GFAP are more indicative of a neuroprotective response than actual cell loss.

Glutamate Transporter and Dopamine Transporter

Assays Yield Counterintuitive Findings

The GLT-1 and DAT findings were not consistent with initial predictions that repeated amphetamine exposure would induce behavioral sensitization via injury to DA neurons and glial cells. Specifically, amphetamine treatment did not cause significant changes in the number of GLT-1 immunoreactive cells, while there was an *increase*, rather than a *decrease*, in the number of DAT immunoreactive cells. Although the reasons for the null GLT-1 findings are unknown, it is possible that the GLT-1 marker may not be sufficiently sensitive to detect excitotoxic-induced changes in glial glutamate transporters within the present paradigm. In particular, there are disagreements regarding the cellular and regional specificity of the various glutamate transporter subtypes (e.g., GLT-1, GLAST, EAAC1), as well as contradictory results regarding their expression (Chen et al., 2002; Nakajima et al., 2001; Perego et al., 2000; Redecker & Pabst, 2000; Rothstein et al., 1994).

In contrast to the null GLT-1 findings, amphetamine treatment caused an increase in DAT within the CA₁ region of the hippocampus, the basolateral amygdala, the dentate gyrus, the dorsal portion of the CP, and the cingulate

cortex. DAT levels in CA₁ were enhanced only when rats received both amphetamine pretreatment and amphetamine challenge. Within the dentate gyrus, DAT increases were limited to the saline-pretreated rats administered a test-day amphetamine challenge; while amphetamine challenged rats (i.e., the SAL-AMPH and the AMPH-AMPH groups) showed increased DAT in the amygdala, the dorsal portion of the CP, and the cingulate cortex.

Dopamine Transporters and Augmented Dopamine

Release in Sensitized Rats

The increased DAT levels are surprising considering the large body of literature demonstrating DA neurotoxicity following amphetamine, methamphetamine, or ROS exposure (Fleckenstein et al., 1999; Fleckenstein, Metzger, Beyeler, Gibb, & Hanson, 1997; Gulley, Doolen & Zahniser, 2002; Nakayama, Koyama, & Yamashita, 1993; Ricaurte, Guillery, Seiden, Schuster, & Moore, 1982; Wagner et al., 1980). However, some researchers have shown that DAT levels within the VTA and the SN increase following amphetamine withdrawal of 7 to 14 days (Lu & Wolf, 1997; Shilling, Kelsoe, & Segal, 1997). Thus, it is possible that an amphetamine-induced increase in DA transporters is an adaptive modification to offset neural loss, as the DAT

assay does not directly measure the number of dopamine neurons (Deng et al., 1999). Alternatively, this apparent modification in DA transporter numbers may be a transitory means of counteracting the inactivation of pre-existing transporters that occurs during the metabolization of DA and subsequent ROS formation (Berman, Zigmond, & Hastings, 1996; Fleckenstein, Metzger, Beyeler, Gibb, & Hanson, 1997). A related possibility is that DA transporters may migrate from inside the cell to the cell surface as an initial response to increases in synaptic DA levels (Daws et al., 2002; Melikian & Buckley, 1999). According to this explanation, amphetamine-induced increases in DAT levels are not a result of toxicity, but are a compensatory response to the increased amount of synaptic DA.

Regardless of the mechanism driving the DA transporter increases, up-regulation may have important implications. Specifically, an up-regulation of DA transporters within the CP (see Figures 9 and 10) is potentially significant, as elevated DA in this structure may be necessary for behavioral sensitization (Berke & Hyman, 2000; Lu & Wolf, 1997). In other words, a psychostimulant-induced increase in DA transporters may be the mechanism by which augmented levels of synaptic DA is released in sensitized rats during

amphetamine challenge (Lu & Wolf, 1997). This explanation seems plausible, as reverse transport is the primary mechanism of amphetamine-induced DA release (Jones, 1998).

Increased DAT in the amygdala, hippocampal formation, CP, and cingulate cortex may be involved in both the learning and motivational aspects of behavioral sensitization. This is because: (1) DA neurons have been implicated in both long-term potentiation and depression (Alexander, 1994); (2) Amphetamine enhances both spatial and cued memory retention when injected into the hippocampus and caudate, respectively (Packard, Cahill, & McGaugh, 1994); (3) Mice with reduced DA and DAT levels also show a diminished capacity to develop psychostimulant-induced conditioned place preferences (Itzhak & Ali, 2002); and (4) The brain areas showing increased DAT levels constitute portions of the basal ganglia-thalamocortical "limbic" circuit (Alexander, Crutcher, & DeLong, 1990). Importantly, the basal ganglia-thalamocortical circuit not only underlies emotional and motivational processes, but has been linked to both drug craving and drug-seeking behaviors (Alexander et al., 1990; Berke & Hyman, 2000; Di Chiara & Imperato, 1988). Therefore, it appears that brain areas with elevated DAT levels serve dual roles, thus

providing compelling evidence for an overlap between learning, memory, and motivational processes in both behavioral sensitization and addiction. This idea of a functional duality is consistent with recent findings of increased neural activity in the basolateral amygdala, the CA₁ region of the hippocampus, and the dentate gyrus of rats following drug-seeking behavior in a familiar drug-paired environment (Neisewander et al., 2000). Furthermore, when given a psychostimulant-challenge prior to exposure to a drug-paired environment, increases in neuronal activity were found within the dorsal CP (Neisewander et al., 2000). It seems more than coincidental that these are the very same brain areas that showed elevated DAT levels after amphetamine exposure (see Figures 7 and 8).

Cellular Changes and Addiction

While increases in DAT have been found in the early periods following amphetamine exposure (Lu & Wolf, 1997; Shilling, Kelsoe, & Segal, 1997), a common finding is that an escalating or high-dose drug regimen causes significant reductions in DA transporter sites (Fleckenstein et al., 1999; Nakayama et al., 1993; Ricaurte et al., 1982; Wagner et al., 1980). This suggests that DA transporters may up-regulate in an effort to preserve homeostasis, with

sustained excesses of DA eventually overwhelming the system resulting in cell death (see Koff, Shuster, & Miller, 1994). It is possible that the degree of cell loss is important for both stereotypic behavior and tolerance. This is because intensity of stereotypic behavior is positively correlated with drug dosage levels (Kuczenski & Segal, 1988; Segal & Kuczenski, 1987; Segal et al., 1995). Likewise, tolerance, as opposed to sensitization, occurs when psychostimulant administration is continuous rather than intermittent (Blanchet et al., 1995; Kalivas & Duffy, 1993; Nelson & Ellison, 1978; Stewart & Badiani, 1993; Strakowski et al., 1996)

Stereotypic behaviors and tolerance are also observed in humans; and, these phenomena appear related to cell loss. More specifically, human addicts spend inordinate amounts of time ensuring drug attainment and often engage in ritualistic drug-taking behaviors, both of which are stereotypic in nature (Ellinwood, King, & Lee, 1998). Likewise, those addicted to psychostimulants report a reduction in the euphoric effects of drug exposure over time, clearly indicating tolerance (Topp & Darke, 1997). Drug tolerance results in an ever-higher escalation in drug dosage levels presumably exerting greater cellular stress.

That stereotypy and tolerance correspond with cell loss in humans is supported by findings of substantial reductions in DAT levels within the brains of chronic methamphetamine users (Sekine et al., 2001; Volkow et al., 2001; Wilson et al., 1996).

Summary

In conclusion, previous research has demonstrated a synergistic relationship between dopamine and glutamate that might serve as the basis for amphetamine-induced cell loss. The purpose of this thesis was to assess whether amphetamine-induced neurotoxicity may provide a foundational basis for behavioral sensitization. Therefore, I examined the effects of both acute and repeated amphetamine exposure on GFAP, GLT-1, and DAT levels. Consistent with initial predictions, GFAP, a measure of general neurotoxicity, was elevated after repeated amphetamine treatment. However, GLT-1, an indirect measure of glial cell viability, was unaffected by amphetamine exposure. And, DAT levels, a commonly used indirect measure of DA neurotoxicity, was elevated, rather than diminished, following amphetamine treatment. Therefore, although neurotoxicity is perhaps partially

responsible for behavioral sensitization, it appears that intermediate neuroprotective and/or homeostatic processes (e.g., increases in transporter numbers) may produce the range of behaviors that exist within the sensitization/tolerance continuum.

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