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Effects of N-Methyl-D-Aspartate Receptor Blockade on Cross-Sensitization between D-Tyr^{11} Neurotensin and Amphetamine

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ABSTRACT

Effects of N-Methyl-D-Aspartate Receptor Blockade on Cross-Sensitization between D-Tyr^{11} Neurotensin and Amphetamine

Melodee A. Mograss

Blockade of neurotensin (NT) receptors with SR-48692 prevents the development of sensitization to the locomotor activating effects of amphetamine (AMPH). In addition, repeated icv injections of NT or of its analog, D-Tyr^{11}NT, sensitize animals to the locomotor activating effects of AMPH. Recent evidence indicates a role for glutamate (GLU) in the development of sensitization to psychostimulant drugs inasmuch as co-administration of GLU antagonists prevents induction of AMPH and cocaine sensitization. The present study was aimed at testing the hypothesis that endogenous glutamatergic systems also play a role in the induction of cross-sensitization between NT and AMPH. Experiments were performed on male rats implanted with a guide cannula above the left lateral ventricle. During the induction phase, locomotor activity was measured on four occasions every second day for two hours after an icv injection of 18nmol/10µl of D-Tyr^{11}NT, or saline, preceded 30 min before by a systemic injection of CPP, [(+/-)-3-(2-carboxypiperazine-4-yl)-propanephosphonic] (4 mg/kg), a GLU antagonist, or its vehicle. One week after the induction phase, locomotor activity to a single injection of AMPH (0.75mg/kg) was measured in all rats (sensitization test). Results show that AMPH induced greater ambulatory activity in animals pre-treated with D-Tyr^{11}NT alone, a sensitization effect that was attenuated by CPP given during the induction phase. These results suggest that GLU may play a role in the development of cross-sensitization between D-Tyr^{11}NT and AMPH.

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INTRODUCTION

Drug addiction (WHO, 1964) is a term replaced by substance dependence (American Psychiatric Association, 1994) since the 1960s. More recently, drug addiction has been defined as a syndrome characterized by compulsive drug seeking behaviors and uncontrolled drug use despite the negative consequences (American Psychiatric Association, 1994).

The possibility of developing animal models of addiction continues to attract attention. Animal studies of drug abuse have been helpful in identifying neurochemical and behavioral changes that occur with repeated drug use. A number of animal studies have demonstrated that when a drug such as amphetamine is repeatedly administrated, its locomotor activating effect may become enhanced rather than diminished, a phenomenon known as behavioral sensitization or reverse tolerance. Furthermore, there is evidence that psychological symptoms (e.g. dysphoria and craving) associated with withdrawal from a variety of drugs of abuse may be related to changes in brain neurotransmitter release (Rossetti, et al., 1992). A promising area of research has been the attempt to identify and understand the neurobiological factors involved in the process of behavioral sensitization. Sensitization of the mesolimbic dopamine system has been proposed as an explanation of drug abuse (Robinson & Berridge, 1993).

The purpose of this introduction is to provide a review of the research aimed at identifying neural substrates and brain loci thought to mediate the development of sensitization. The behavioral effects of both psychostimulant

drugs and amphetamine will be presented first. A description of central dopamingeric systems and the effect of amphetamine on dopamine neurotransmission will follow. After that, a review of the behavioral effects of neurotensin will be discussed, since this peptide has been shown to act like a psychostimulant-drug to produce behavioral sensitization in laboratory animals. Finally, the phenomenon of behavioral sensitization will be critiqued with an emphasis on the mechanisms involved in its development.

BEHAVIORAL EFFECTS

Behavioral Effects of Psychostimulants

Psychostimulant drugs belong to a subcategory of psychoactive drugs that alter both mood and behavior. Prototypical examples of psychomotor stimulants are cocaine and amphetamine. The effect of psychostimulant drugs on mood has been demonstrated by the subjective feeling of pleasure (euphoria) reported in humans. A driving force to repeated use of psychostimulants is the euphoria.

A variety of behavioral effects have been reported in laboratory animals (rodents). One such behavioral effect is an increase in locomotor activity often referred to as behavioral activation. Although there are many different mechanisms of action, psychomotor stimulants appear to activate common mechanisms responsible for approach or forward locomotion and reinforcement associated with natural rewards such as mating, food seeking and social interactions in animals (Wise, 1989). It should be mentioned that the terms "reward" and "reinforcer" are frequently used interchangeably, but they do not have exactly the same meaning (Wise, 1989). Reinforcers are defined as a stimulus that increases the probability of the occurrence of a response. Reward refers to the affective positive aspects of the stimulus.

In rodents, psychostimulant drugs have been associated with other behaviors linking the rewarding properties to the behavioral activating effect (Wise & Bozarth, 1987; Glickman & Schiff, 1967). The rewarding effect of psychostimulant drugs has been demonstrated using a number of behavioral methods; intravenous (iv) self-administration, intracranial self-administration and conditioned place preference.

Numerous studies have revealed that pychostimulants and opiates (e.g. morphine and heroin) reliably establish and maintain iv self-administration even after long periods of withdrawal (Lorrin, et al., 2000; Vezina, et al., 1996b; Weeks, 1962; Weeks and Collines, 1964). Drug injections are initially made contingent on the performance (lever press) and the number of lever presses by the animal receiving the drug is then compared with the vehicle, or no drug control. If a drug increases the occurrence of the behavior, (e.g. lever press) it is said to act as a reinforcer. Other models have been developed to circumvent problems such poor blood brain barrier penetration or peripheral side effects. For example, animals are trained to lever press to receive direct intracranial injections of a drug. This allows one to determine in which brain regions the drug acts to produce its reinforcing effect and offers an advantage over the other self-administration paradigm.

Yet another behavioral effect associated with rewarding properties of psychostimulants, is the ability to alter an animal's preference for drug-associated environment (Shippenberg & Bals-Kubik, 1995), a so-called conditioned place preference. To establish a conditioned place preference, animals are given several conditioning trials where either drug or saline is administered, followed by confined periods of time to 1 of 2 distinctly different compartments of the test environment. Following these conditioning trials, animals are given the opportunity, in a drug-free condition, to explore both compartments. If the animal increases the time in the compartment where the drug was given, it is inferred that the drug treatment was rewarding (see Van der Kooy, 1987).

Behavioral Effects of Amphetamines

Amphetamines have marked effects on the central nervous system resulting in behavioral changes such as elevated mood, anorexia, hyperactivity, insomnia and reduced fatigue. In the periphery, they stimulate the sympathetic nervous system resulting in sympathetic arousal thereby increasing heart rate, vasodilatation and bronchodilation.

Amphetamine-induced behavioral activation takes many forms depending on dose, time of injection and species. At low doses, behavioral activation in rodents is characterized by an increase in forward locomotion and rearing (Robinson & Becker, 1986; Russell, Giordano & Sanberg, 1987; but see Mazurski & Beninger, 1987). As the dose is increased a multiphasic response pattern occurs consisting of an initial period of locomotor activity followed by intense stereotypy (repetitive, species-specific behaviors) and, as the drug is metabolized, then locomotion. In the rodent, stereotypy consists of repetitive movements of head and limb, sniffing and/or oral behaviors such as gnawing, licking (Segal & Mandell, 1974) confined to a small area of the test cage. Based on the above, it is important that vertical, horizontal and stereotypic activity is measured separately; and that depending on the desired behavioral response, a correct dose is chosen. Monitoring all three types of locomotor activity allows for the exclusion of the occurrence of stereotypic movements that may interfere in the expression of the others.

In humans, higher doses of amphetamine create psychotic symptoms (hallucination and delusions) in normal individuals and worsen psychosis in schizophrenics (Ellinwood, 1972). The administration of amphetamine to humans

causes hyperactivity and stereotypic motor behaviors before developing psychosis.

DOPAMINE SYSTEMS

The midbrain dopamine (DA) system consists of the mesocorticolimbic system and the nigrostriatal system (Dahlstrom & Fuxe, 1964). The mesocorticolimbic system consists of two subsystems; mesolimbic and mesocortical systems. Mesolimbic and mesocortical cell bodies originate in the ventral tegmental area (VTA) or A10 region and project to several forebrain limbic and cortical areas including the nucleus accumbens (NAcc) and the prefrontal cortex (PFC), (Kandel et al., 1991; Lindvall & Bjorklund, 1983). DA release in the NAcc is thought to play a part in the behavioral activating effects of psychostimulants and other drugs of abuse. The nigrostriatal DA system originates in the substantia nigra or A9 region and projects mainly to the dorsal striatum and the globus pallidus via the medial forebrain bundle. Some investigators have emphasized separate motor and reward functions for the DA pathways, but such a distinction has been recently questioned (Salamone, 1994).

Psychostimulant drugs increase central DA neurotransmission. There is evidence that the repeated exposure to stimulant drugs leads to augmentation of responsiveness of the mesolimbic DA system to the same dose of the drug. This change in responsiveness of the DA system is consistent with the hypothesis that the mesocorticolimbic system mediates, at least in part, the behavioral characteristics seen in drug craving and addiction (Robinson & Berridge, 1993).

<u>Dopamine Systems & Amphetamine</u>

Amphetamine (AMPH) is an indirect agonist of the catecholamine systems

(norepinephrine and DA). It has the combined ability to increase DA-release from the pre-synaptic terminal and to block DA-reuptake thereby prolonging DA synaptic activity (Fisher & Cho, 1979; Heikkila et al., 1975a, 1975b). It also weakly inhibits, at high concentrations, the actions of monoaminooxidase (MAO), enzymes that degrade DA (Kuczenski, 1983).

The mechanisms that account for AMPH-induced increases in extracellular DA are exchange diffusion and active transport. AMPH enters the DA terminal by interacting with dopamine transporter (DAT). Although AMPH is a DA uptake inhibitor, it acts as a substrate for the transporter instead of blocking it. One model (reverse transport model) proposes that extracellular amphetamine binds to the DAT transporter where it is released into the DA cell (Fischer & Cho, 1979). The transporter is now reversed or facing inward allowing it to bind to intracellular DA, which is transported out of the cell into the extracellular space. The result is an increase in extracellular DA. Evidence for the interaction between AMPH and the DA transporter comes from the fact that drugs that block DA uptake (Fischer & Cho, 1979) inhibits AMPH-induced behavioral stimulation. Researchers have recently developed genetically altered strains of mice lacking the DA transporter, DAT knockout mice. Mice without the DA transporter re-uptake mechanism do not exhibit either increased DA release or DA -dependent locomotor activation in response to AMPH. (Giros et al., 1996).

The weak base model of AMPH action suggests that extracellular AMPH enters DA neurons via diffusion across the membrane and releases catecholamines from vesicular stores. This is followed by reverse transport. Because of this alteration in the intracellular concentration gradient, the reverse

transport mechanism (Sulzer, et al., 1995) acts to remove DA into the extra cellular fluid. Since there is evidence indicating that the DA transporter carries AMPH, it suggests that both mechanisms contribute to DA releasing effects of AMPH. Nevertheless, this hypothesis remains to be tested.

As mentioned previously, the behavioral activating effects of amphetamines are attributed to its actions on midbrain DA cells that project to NAcc and PFC (see Kalivas & Stewart, 1991 for review). Evidence implicating a role for DA neurons of the ascending mesocorticolimbic DA pathway in AMPH-induced locomotor effects comes from numerous studies. Systemic injections of psychostimulant drugs have been reported to increase extracellular DA in terminal regions, such as the NAcc and PFC (see Kalivas & Stewart, 1991 for review) and lesions of the mesolimbic DA system by 6-hydroxydopamine (6-OHDA), a neurotoxin that selectively destroy DA neurons, eliminate AMPH-induced locomotor activation (Iversen et al., 1975). In addition, acute injections of AMPH into the NAcc increase DA release and result in hyperlocomotion (Kalivas & Stewart, 1991; Pijnenburg & van Rossum, 1973) without sensitization.

NEUROTENSIN

Apart from psychostimulant drugs, there are a number of endogenous neurotransmitters that increase DA-minergic neurotransmission. A small number of neurotransmitters coexist with DA in mesocortiolimbic neurons (Hökfelt et al., 1984). One such neurotransmitter is the tridecapeptide (13 amino acids), neurotensin (NT). Carraway & Leeman (1973) were the first to isolate NT from bovine hypothalamus. It is heterogeneously distributed in both animal and

human brains, it is present in peripheral organs, and it meets all the criteria for a neurotransmitter (Mai et al., 1987).

NT is co-localized with DA in some of neurons in the VTA (Seroogy et al., 1987; Studler et al., 1988; Hökfelt et al., 1984) that project to the PFC and in neurons that innervate most limbic regions including the amygdala, bed nucleus of the stria terminalis, habenula, periaqueductal gray and anterodorsal nucleus of the thalamus (Quirion, 1983, 1985; Kalivas et al., 1985). This neuropeptide acts reciprocally with DA to modulate DA release at the terminals (Jolias & Aghajanian, 1997; Rostene & Alexander, 1997).

Behavioral Effects of Neurotensin

Evidence for a role for NT in behavioral sensitization has resulted from examining its effects on DA neurotransmission and on behavioral. Microinjections of NT into VTA and NAcc (Kalivas et al., 1981) have been found to have different effects on locomotor activity. Direct microinjections of NT into the VTA stimulate locomotion (Kalivas et al., 1981; 1983; 1985) and increase extracellular DA in the NAcc (Kalivas & Duffy, 1990). Interestingly, the stimulatory effects of NT in the VTA are attenuated by microinjections of NT in the NAcc (Kalivas et al., 1982). In addition, intra-accumbens injections of NT antagonize systemic AMPH-induced locomotion (Ervin et al., 1981). It was its initial inhibitory effects on behavior and its antipsychotic actions that lead Nemeroff (1980) to suggest that NT was an endogenous neuroleptic. Others have shown that depending upon its site of action, NT may produce effects resembling that of psychostimulant drugs (Kalivas et al., 1984; Kalivas & Duffy,

1990; Jolicoeur et al., 1981; Rompré, 1995).

In addition to the above findings showing that NT stimulates DA neurons, are studies showing that animals readily self-administer NT into the VTA. Furthermore, VTA injections are sufficient to establish a conditioned place preference (Glimcher et al., 1984; 1987; Rompré et al., 1992; 1993). Although the administration of NT into the VTA increases the rewarding effects of electrical brain stimulation (brain stimulation reward, BSR), microinjections of NT into the NAcc decrease BSR (Nemeroff et al., 1982).

As is the case for most neuropeptides, central microinjections of NT have other numerous physiological and behavioral effects including: hypothermia (Bissette et al., 1976,1982; Nemeroff et al., 1979,1980; Martin et al., 1988; Kalivas et al., 1982, 1985; Handler et al., 1994; 1995), muscle relaxation (Osbahar et al., 1979; Jolicoeur, et al., 1981); analgesia (Behbehani & Pert, 1984; Behbehani, 1992; Dubuc et al., 1992; Kalivas et al., 1982), hypotension (Rioux et al., 1981), catalepsy (Snijders et al., 1982) and hyperglycemia (Yawata et al., 1984). In addition, NT has been found to act directly on smooth muscles in the digestive tract (Ohashi et al., 1994; Kitabgi et al., 1978; 1981).

In the attempt to better understand the pharmacological mechanisms involved in the physiological effects of NT, several analogs of the neuropeptide have been developed. One of them, D-Tyr^{11}-NT, is identical to NT except that the amino acid L-tyrosine has been replaced by a D-tyrosine in position 11. The consequence of this chemical modification is that the analog is more stable *in vivo* than the endogenous neuropeptide because of its lower sensitivity to enzymatic degradation (Checler et al., 1983). D-Tyr^{11}-NT acts as an agonist at

the NT receptors but displays less affinity for the some of the NT receptors than NT; yet it is more potent than NT *in vivo* (Kitabgi et al., 1980; Al-Thodan et al., 1991). When administered in equimolar concentrations, it has similar effects to NT but produces stronger and longer lasting behavioral effects; hence, lower concentrations of D-Tyr^{11}-NT are needed to initiate a given behavioral effect when injected centrally.

Neurotensin Receptors and NT-Induced Changes in Locomotion

To date, there are two functionally relevant NT receptors that have been identified and cloned (NTR1, NTR2), both belonging to the family of G-protein-coupled receptors (Chalon, et al., 1985; Tanaka, et al, 1990). A third NT binding site (NTR3) has been cloned, but its relevance as a functional NT receptor remains to be determined (Mazella, 1998; Vincent et al., 1999).

NT receptors are expressed on the DA cell bodies (Dana et al., 1989; Dilts & Kalivas, 1989; Palacios, et al., 1981) and dendrites within the VTA, and on mesostriatal DA terminals (Woulfe and Beaudet, 1989). NTR1 are found on DA cell bodies and dendrites (Boudin et al, 1996,1998; Dana et al., 1989, Quirion et al., 1985), whereas NTR2 subtype is expressed by both neurons and astrocytes (Schotte et al., 1986; Nouel, et al., 2000).

Although the exact mechanism(s) whereby NT alters locomotor responses remains unclear, several studies suggest that it involve, at least in part, NT receptors in the VTA and NAcc.

STIMULANT DRUGS, SENSITIZATION & DOPAMINE

One phenomenon that has been studied intensely over the years is the enhancement of the behavioral activating effects because of the drug influence on DA systems. The enhancement of drug-induced behaviors that occurs with repeated administration of a drug has been termed behavioral sensitization (Wallach & Gershon, 1971; Eikelboom & Stewart, 1982) or sensitization (Robinson & Becker, 1986), behavioral augmentation (Segal & Mandell, 1974), and reverse tolerance (Kibey & Ellinwood, 1977). An interesting characteristic of this phenomenon is that drug effects are not diminished over time but are actively increased by repeated drug exposure. Although a single injection of AMPH has been reported to sensitize the behavioral response to a subsequent AMPH injection (Robinson et al., 1982; Robinson, 1984), the magnitude of this response increases significantly with longer regimens of repeated exposures. Chronic, intermittent drug injections that are widely spaced over time produce a more vigorous sensitized response (Post, 1980) than acute injections or those given continuously (Robinson & Becker, 1986; Stewart & Badiani, 1993; Vanderschuren et al., 1997). In fact, animal studies have demonstrated that high doses of continuous administration of AMPH are associated with degenerative brain damage as a result of neurotoxicity (Robinson & Becker, 1986) rather than sensitization. Numerous studies have shown it to be a persistent phenomenon which develops gradually over time appearing days or weeks following withdrawal from drug (Paulson & Robinson, 1995; Paulson et al., 1991; Segal & Kuczenski, 1992b; Kolta et al., 1985). This behavioral hyperresponsiveness to

AMPH can be extremely long lasting as it has been reported up to one year or longer in rats (Paulson et al., 1991) following the last drug administration. Because of the persistent and progressive neuronal changes that continue long after withdrawal from drug, it has been implicated in some aspects of addiction such as drug relapse and drug craving (Robinson & Berridge, 1993).

Development of Sensitization

The neural mechanisms responsible for the induction of behavioral sensitization appear to be different from those responsible for the expression of sensitization (Kalivas & Stewart, 1991; Vezina, 1996). It is the action of the AMPH in the region of the VTA, not in the NAcc, that is required for the sensitization to develop; a phenomenon that appears to be dependent on dopamine and glutamate neurotransmission.

Direct microinjections of AMPH into the VTA (Kalivas & Weber, 1988; Vezina & Stewart, 1990), but not the NAcc (Dougherty & Ellinwood, 1981; Kalivas & Weber 1988; Vezina & Stewart, 1990), lead to the development of sensitization of the locomotor activating effects of the drug. Furthermore, repeated intra-VTA AMPH injections lead to an increase NAcc DA release following subsequent systemic or intra-NAcc injections of AMPH (Vezina, 1993; Perugini & Vezina, 1994). Although the VTA mechanisms of behavioral sensitization have not been fully characterized, it is thought to involve DA receptors. Dopamine receptors are classified into two main groups: D1-like receptors and D2-like receptors. In general, the D1 receptors are found postsynaptic to DA terminals, whereas the D2 receptors are located both postsynaptically in terminal regions, and

presynaptically on DA cell bodies and dendrites (Kebabian & Calne, 1979). In the VTA, the D1 receptors are found on terminals of neurons some of which likely release glutamate or GABA (Dewar et al., 1997; Lu et al., 1997; Cameron & Williams, 1993).

The D1 receptor is critical in the development of sensitization to AMPH. Hence, it was first demonstrated that a systemic injection of the D1 receptor antagonist, SCH23330, during the induction phase blocks the development of AMPH sensitization (Vezina and Stewart, 1989). Then, it was shown that blockade of VTA D1 receptors was also effective at preventing sensitization (Stewart & Vezina, 1989; Vezina, 1996; Bijou et al., 1996).

In contrast, D2 terminal receptor activation was not found to play a role in the development of sensitization (Vezina, 1996; Bjijou et al., 1996) but appears to play a role in the expression of sensitization to psychomotor stimulants, at least in the early period after termination of injections. The activation of D2 receptors associated with dopaminergic cell bodies and dendrites (autoreceptors) inhibits the neural activity of DA neurons and DA release (White, 1996). However, repeated, intermittent exposure to AMPH has been found to diminish DA autoreceptor effectiveness in suppressing DA synthesis and release (White & Wang, 1984). One hypothesis is that the DA somatodendrite autoreceptors becomes subsensitive, or less efficient at inhibiting DA cell functioning, leading to enhanced effectiveness of DA and DA agonist. The evidence for a lower firing threshold or DA autoreceptor subsensitivity following repeated exposure to AMPH comes form electrophysiological studies. White & Wang (1984) found that AMPH pretreatments decreased the ability of systemic AMPH or DA agonists to

suppress the firing of VTA DA neurons. Another view is that the repeated release of DA by AMPH resulting in the repeated stimulation of the D2 somatodendrite autoreceptor leads to down-regulation or decrease in receptor number. Seutin *et al* (1989) demonstrated that acute AMPH applied directly to DA autoreceptors caused a transient down-regulation following exposure to either DA or DA agonists. Whether DA autoreceptor subsensitivity or down regulation of the receptors provides the neural basis of sensitized DA function, is unknown.

A Role for Glutamate

A vast number of synapses in the mammalian brain utilize excitatory amino acids (EAA) as neurotransmitters (see Monaghan et al., 1989). One of the two major classes of glutamate receptors is the ionotropic receptor, which affect influx of ions through their channel pore and binding site. Three subtypes of the ionotropic glutamate receptors named after their selective agonist are; N-methyl-D-asparate, NMDA; kainate; and ∞-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, AMPA or non-NMDA. Glutamatergic receptors have been found in the VTA and substantia nigra and are expressed by DA cells (Carte, 1982). Furthermore, different types of NMDA antagonists act at different receptor binding sites to interfere or block activation. The competitive NMDA glutamate antagonist, CPP, [(+/-)-3-(2-carboxypiperazine-4-yl)-propanephosphonic], competes with the agonist for binding at the agonist binding site. Whereas, the noncompetitive antagonists do not compete with the agonist, instead they block activation by occupying a site within the ion channel. Competitive NMDA

antagonists, such as CPP, have more receptor selectivity and fewer unwanted side effects making them better research tools over the noncompetitive type (Wlaz, 1998).

The discovery of a role for glutamate in the development of sensitization was made in early studies showing that the NMDA antagonist, MK-801, prevents AMPH-sensitization (Karler et al., 1989; 1990; Wolf & Khansa, 1991; Stewart & Druhan, 1993; Wolf et al., 1994; Li & Wolf, 1999). Likewise, competitive NMDA antagonists, CGS 19755 and CPP are also effective at preventing sensitization (Wolf et al, 1995; Cador et al., 1999). An important study by Cador *et al* (1999) found that blockade of NMDA within the VTA prevented induction of AMPH sensitization, suggesting it is the release of glutamate in this region that is critical.

A Role for VTA Efferent Terminals from PFC

Glutamatergic inputs to the VTA arise from three major sources: PFC, pedunculopontine nuclei and subthalamic nucleus (Sesack & Pickel, 1992). Axon terminals from PFC efferent innervate DA cells within the VTA and NAcc, and converging lines of evidence from a number of studies, particularly those involving neurotoxic lesions, implicate those in the development of AMPH sensitization. Exocitotoxic lesions of the PFC have been found to prevent the development of sensitization to systemic and to intra-VTA AMPH (Cador et al., 1999; Wolf et al., 1995). Moreover, Wolf & Xue (1999) found that excitotoxic lesions of the PFC prevent AMPH-induced increases in glutamate within the VTA (Tong et al., 1996a; 1995). Interestingly, Dewar *et al* (1997) found that ibotenic acid lesions of the PFC decrease the number of D1 receptors in the VTA,

suggesting that these receptors are located on PFC efferent terminals. Moreover, activation of VTA D1 receptors seems to increase glutamate release in this region (Wolf and Xue, 1999). Taken together these findings suggest that AMPH sensitization is initiated by the following neural events: DA acting at D1 receptors enhances the release of glutamate from PFC efferent terminals, which in turn activates glutamate receptors. Activation of glutamate receptors, likely triggers neural plastic changes resulting in an enhancement of AMPH-induced locomotor activity.

CROSS SENSITIZATION

The repeated administration to one psychostimulant drug, such as cocaine, leads to sensitization of the behavioral activating effect of another psychostimulant drug, such as AMPH, a phenomenon known as cross-sensitization (Kalivas & Weber, 1988). Cross-sensitization has also been demonstrated between drugs of different classes, such as morphine and AMPH (Stewart & Vezina, 1987; Kalivas et al., 1988; Karler et al., 1989). In fact, cross sensitization is known to develop between psychostimulant drugs and the response to stress (Kalivas & Stewart, 1991; Robinson & Becker, 1986; Piazza & LeMoal, 1996). Antelman *et al* (1986) suggested that drugs of abuse and stress act synergistically. Support for this idea comes from studies showing that corticosterone (a hormone released during the stress response) enhances sensitization to psychostimulant drugs (Deroche et al., 1992b; but see Badiani et al., 1995). Other evidence for cross-sensitization comes from a study by Rompré (1997) who reported that repeated, intermittent administration of icv NT,

or of its analogue, D-Tyr^{11}-NT, sensitizes the locomotor activating effects of AMPH. Furthermore, blockade of NT subtype1 receptors with SR-48692 injected ip prevents the development of sensitization to the stimulant effect of AMPH (Rompré & Perron, 2000). These findings suggest that NT receptors are a relevant component of the neural mechanisms involved in the development of NT-induced sensitization to a subsequent injection of AMPH. This hypothesis is supported by evidence showing that systemic amphetamine releases endogenous NT in the PFC (During et al., 1992; Hertel et al., 1995), and that excitotoxic lesions of the PFC prevent the development of cross-sensitization between NT and AMPH (Blackburn et al., 1998). On the basis of these findings, it has been proposed that NT acts in the PFC to stimulate afferent glutamatergic inputs to the VTA.

The present study was aimed at determining the role of glutamate in the cross-sensitization between D-Tyr^{11}-NT and AMPH. Intracerebroventricular injections of D-Tyr^{11}-NT were made every second day (total of four injections) and locomotor activity monitored. An NMDA antagonist, CPP, was administered, systemically, 30 minutes before each D-Tyr^{11}-NT injection. Cross sensitization was assessed one week after the induction phase following a systemic injection of AMPH. This protocol allowed us to study a possible role of NMDA glutamate receptors in NT-induced AMPH sensitization.

METHODS

Subjects

Sixty Long-Evans male rats (Charles River, St. Constant, Quebec, Canada) weighing between 250-325 g at the time of surgery were housed in polyethylene cages, two per cage, with woodchip bedding and unlimited access to food and water. Lighting was maintained on 12-h light/dark cycle (lights on at 06:30 a.m.) in a temperature and humidity controlled room. All testing was performed during the light phase of the day/night cycle between 08:30 - 18:30 in a room separated from the housing colony. The animals were given one-week adaptation period prior to surgery. Subjects were treated in accordance with the guidelines of the Canadian Council on Animal Care.

Surgery

Following the adaptation period, rats were injected intraperitoneally (ip) with atropine methylnitrate (0.4 mg/kg) to minimize bronchial secretions and then anesthetized 15 minutes later with sodium pentobarbital (Somnotol, 65mg/kg, ip). Subjects were then mounted onto a stereotaxic apparatus, the surface of the skull exposed and a stainless-steel guide cannula (Plasticone Inc., VA, USA, Model C315G) implanted above the left lateral ventricle using the following midline flat-skull coordinates: 0.3 mm caudal to bregma, 1.5 mm lateral to the midline and 2.4 mm ventral to the skull surface (Paxinos and Watson, 1997). The incisor bar was adjusted to maintain the surface of the skull horizontal between

bregma and lamdba. The guide cannula was secured in place with four stainless steel screws covered with acrylic dental cement. At the end of the surgical procedure, Neosporin antibiotic paste (Hibitaine Antibacterial-Antifungal Ointment, 1.0% Chlorlexidine acetate) was applied around the wound surface. An obturator was inserted into the cannula with the tip flush with the end of the guide to maintain patency during the one-week recuperation period following the surgical procedure. The rats were returned to their homecage. Each animal was handled and weighed twice during a one-week recuperation period after the surgery.

Drugs and Vehicle Solutions

The glutamate antagonist, CPP, [(+/-)-3-(2-carboxypiperazine-4-yl)-propanephosphonic; Sigma RBI Chemical Co., St. Louis, MO], was dissolved in sterile 0.9% saline at concentrations of 4 mg/ml, stored frozen at -20°C in 6 ml aliquots and injected i.p. Neurotensin analogue, D-Tyr^{11}-NT, (Bachem, Sunnyvale, CA, USA) was dissolved in sterile 0.9% saline at a concentration of 1.8nmol/µl and stored frozen at -20°C in 50 µl vials pre-coated with silicone (Sigmacote, Sigma chemical Co., St. Louis, MO, USA). The dose of D-Tyr^{11} NT tested in this study was based on previous reports showing that this concentration induced cross sensitization to locomotor stimulant effects of d-amphetamine (Rompré, 1998). All drug solutions were thawed before testing and used only once. Amphetamine sulfate was dissolved in sterile 0.9% saline at a concentration of 0.75 mg/ml and injected i.p. A low dose (less than 1.0 mg/ml, ip)

of AMPH was selected based on previous reports of increase in forward locomotion without stereotypy, which masks the locomotor effects (Robbins, Koob and Iversen, 1980, Segal and Mandell, 1974).

Apparatus

Test cages (42 x 42 x 35 cm) consisted of four transparent Plexiglas walls and a wire mesh floor. Each cage was equipped with 30 photocells. Two arrays of 15 infrared photocells located 1.5 cm above the floor, monitored horizontal ambulatory movements (Fig. A). Ambulatory movements were defined as distance traveled in cm beyond a "virtual box" area of 9.6 x 9.6 cm (3 x 3 photocells). Movements detected within the "virtual box" drawn around the animal were considered non-ambulatory movements instead of stereotypy because of the uncertainty of the exact type of movement and were quantified as time (in sec) during which photocell beam interruptions were detected (Fig A). One photocell array located 14.5 cm above the floor, monitored vertical movements. Vertical activity was quantified as the total number of photocell beams broken by rearing. This arrangement allows one to dissociate ambulatory (locomotion) from non-ambulatory (stereotypy-like) movements in addition to vertical activity. The cages were kept in a dark room with white noise (approximately 60dB) continuously present. The OPTO-Varimax system (AutoTrack system, Columbus Instruments, Columbus, OH) of photocell sources and detectors were interfaced to a PC computer with software to quantify locomotor activity in an adjacent room.

Procedure

The experiment consisted of two parts: induction phase and sensitization test. Fig. B shows an outline of the timing of the induction phase and testing for sensitization used in the experiment. Subjects were randomly assigned to one of four groups depending on pretreatment injections they received. These groups were as follows:

1) Ss	(n = 14)	Saline (ip) - Saline (icv)
2) Cs	(n = 10)	CPP (ip) - Saline (icv)
3) SnT	(n = 13)	Saline (ip) - D-Tyr^{11}-NT (icv)
4) CnT	(n = 9)	CPP (ip) - D-Tyr^{11}-NT (icv)

Behavioral Testing

Induction Phase

During the induction phase, locomotor activity was assessed on four occasions, every other day for one week (Days 1, 3, 5, and 7) following ip injections of 4 mg/kg of glutamate antagonist or 0.9 % saline. After a delay of 30 min, icv microinjections of 18 nmol D-Tyr^{11}-NT or an equivalent 10 µl volume of vehicle (0.9% saline) was administered in freely moving animals. A 26-gauge cannula guided the insertion of the injector that extended 2 mm beyond the tip of the cannula and was connected with polyethylene tubing to a 50-µl microsyringe placed in an infusion pump (Harvard Apparatus, Model 11). The 10 µl peptide solution or saline was administered over a period of 5 minutes at a rate of 2 µl /min and remained in place for an additional 60 s following the termination of

the central injection. Ambulatory, non-ambulatory and vertical movements were monitored for 120 minutes immediately after the icv injection. At the end of the procedure, animals were returned to their homecage in the animal colony room. White noise (approximately 60 dB) was used to mask external noise.

Sensitization Test

Seven days after the end of induction phase, the effect of a single injection of amphetamine (0.75 mg/kg, ip) on locomotor activity was assessed in all animals. (Sensitization Test, Day 14). On this day, all of the animals received amphetamine 0.75 mg/kg ip (no antagonist) and locomotor activity was immediately monitored in the test cages for 120 minutes.

Statistical Analysis

Parameters of locomotor activity (distance traveled, non-ambulatory movements and vertical activity) were computed for each of the 120-minute test periods. Group means were analyzed with a two-way analysis of variance (ANOVA) with time as the repeated measure. Post-hoc comparisons among means were made with Duncan`s multiple range test, and the level of significance set at 0.05 (Statistical V5.1, Statsoft, Inc. OK, USA).

Histological Analysis

At the end of the experiment, animals were deeply anesthetized with urethane (0.2 mg/kg, ip) and transcardially perfused with 0.9% saline followed by a 10% formalin solution. Brains were removed, frozen and sliced in series at 40-µm sections that were mounted on gelatin-coated glass slides. Location of the injection site was determined under light microscopic examination. A formal-

thionin stain was carried out in a subset of brain slices with unclear injection sites. All data presented are from animals that had confirmed injection sites within the left lateral ventricle.

RESULTS

Histological analysis revealed that for 45 out of 60 animals initially prepared, the injection site was within the left lateral ventricle between -0.26 mm to -0.80 mm posterior to bregma (fig. C). For the 15 animals excluded from the study, the injection site was outside the ventricle, in the cortex or the dorso-medial striatum.

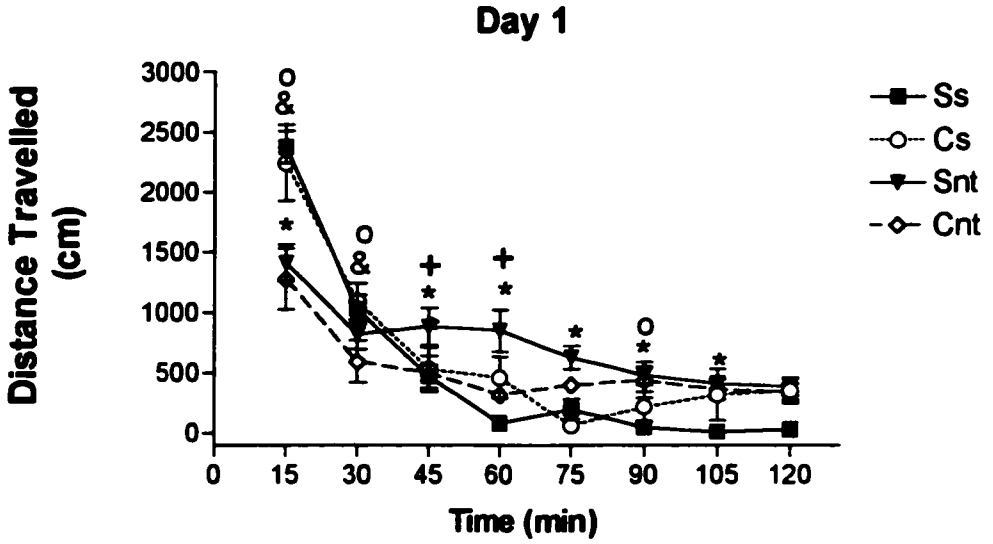
Induction Phase

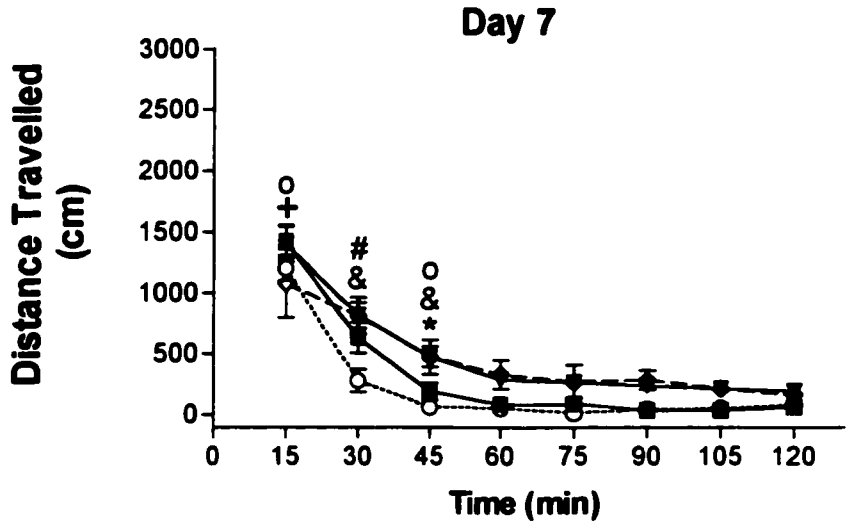
Ambulatory Movements

Measures of mean ambulatory movements, expressed as the distance traveled in cm, during each of the eight 15 min time periods on day 1 of the induction phase are shown in Fig. 1 (top panel) for each of the groups tested. The analysis of variance (ANOVA) revealed a significant time effect [$F(7,287) = 88.0$, $p < .001$] and Group by Time interaction [$F(21,287) = 7.08$, $p < .001$]. Post-hoc tests showed that animals treated with D-Tyr^{11}-NT alone (SnT) were less active than saline control animals (saline + saline, Ss) during the first 15 min, but were more active between 45 and 105 min after the injection. The initial suppressant effect of D-Tyr^{11}-NT was slightly stronger in the animals pre-treated with CPP; CnT animals (CPP + D-Tyr^{11}-NT) were less active than Ss- treated animals during the first 30 min (p`s < .01); there was no statistical difference

Fig. 1 INDUCTION PHASE. Mean (± SEM) ambulatory activity (expressed as distance traveled in cm within the test cage) on Day 1 (top panel) and Day 7 (bottom panel) as a function of time after injection. Animals were injected with ip CPP or saline prior to each D-Tyr^{11}-NT (Cnt, SnT) or saline (Cs, Ss) icv injection. Legend indicates for each of the four groups the drug treatments administered: Saline + saline (Ss, n = 14); CPP + saline (Cs, n = 10); Saline + D-Tyr (SnT, n = 13); CPP + D-Tyr (CnT, n = 8). Comparison among means were made with Duncan`s multiple range post-hoc tests; Ss versus Snt, *; CnT versus Cs, &; Snt versus CnT, +; Cs versus Ss, #, CnT versus Ss, o. ($p \leq 0.05$).

INDUCTION PHASE AMBULATORY MOVEMENTS





between SnT and CnT animals at this time period. During the last hour and a half animals in the CnT group were not more active than controls, except at minute 90, suggesting that CPP partially attenuated the stimulant effect of D-Tyr^{11}-NT. By itself, CPP did not alter ambulatory activity, as the animals treated with CPP alone (Cs) were not different from Ss-treated animals at any time period.

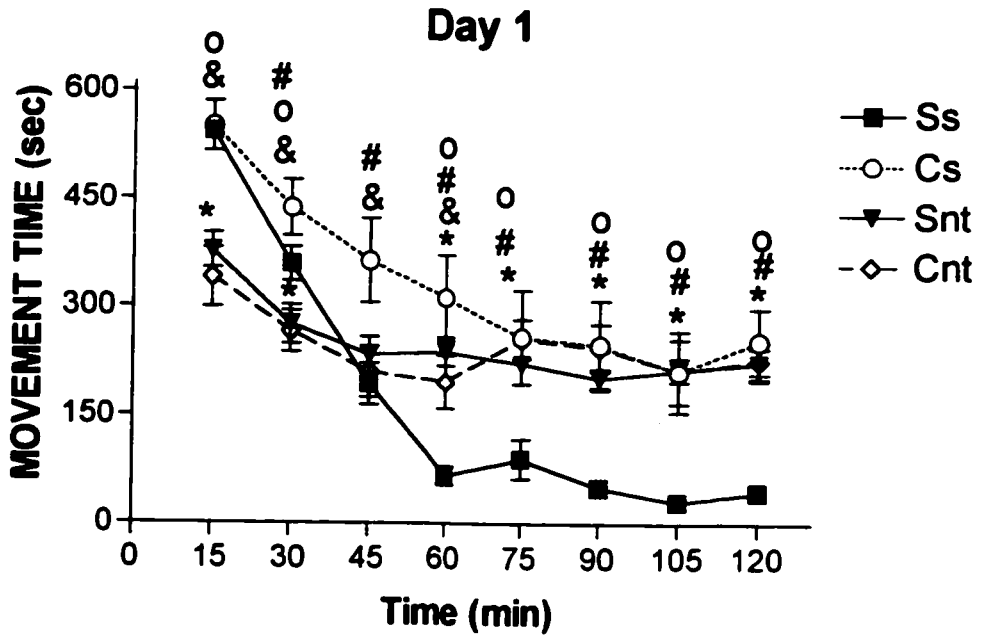
The ANOVA performed on measures of mean ambulatory movements obtained on Day 7 (Fig. 1, bottom panel) revealed a significant main effect of group [$F(3,41) = 4.18$, $p < .02$] and time [$F(7,287) = 88.2$, $p < .001$], and Group by Time interaction [$F(21,287) = 1.66$, $p < .05$]. Post-hoc tests revealed that ambulatory movements in SnT animals were different from in Ss animals. Animals treated with CPP + D-Tyr11-NT were less active than saline control (Ss) in the initial 15 min ($p < .01$), and subsequently did not differ from Ss treated animals, except at 45 min after the injection ($p < .05$). Animals pretreated with CPP alone tended to be less active than controls, and this suppression was significant at 30 min ($p < .01$).

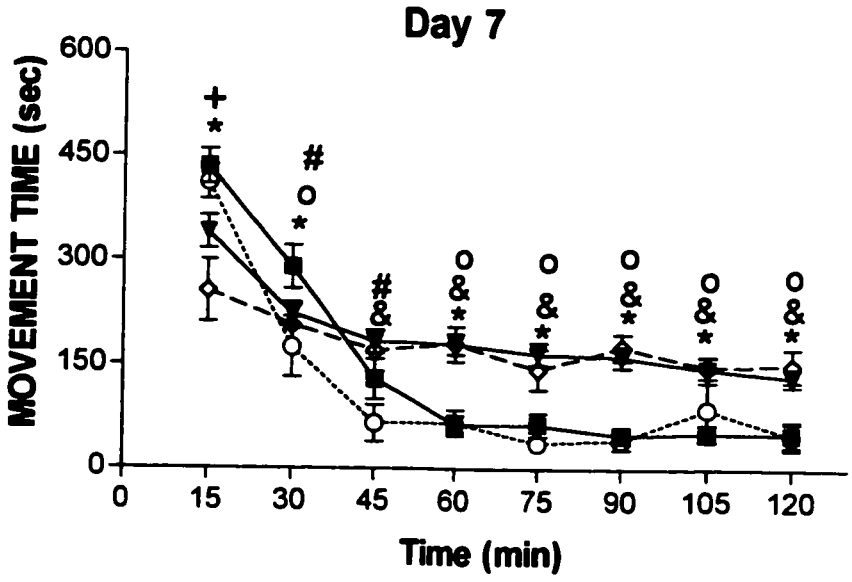
Non-Ambularoty Movements

Measures of mean non-ambulatory movements, expressed as the time of movement detection within the virtual box (see methods), during each of the eight 15 min time period, obtained on day 1 of the induction phase are shown in Fig. 2 (top panel) for each group tested. The ANOVA revealed a significant main effect of group [$F(3,41) = 8.73$, $p < .001$] and main effect of time [$F(7,287) = 71.06$, $p < .001$]; the Group x Time interaction was significant [$F(21,287) = 10.22$, $p < .001$].

Fig. 2 INDUCTION PHASE. Mean (± SEM) non-ambulatory activity (expressed as time in seconds making movement within the "virtual box," see methods) on Day 1 (top panel) and Day 7 (bottom panel) measured over eight consecutive 15-min periods following drug treatments. See Figure 1 for details.

INDUCTION PHASE
NONAMBULATORY MOVEMENTS
(Stereotypy-like Movements)





Post-hoc test showed that animals treated with SnT were less active than saline control during the first 30 min, but were more active between 60 and 120 min after the injection (p`s < .0001). The initial suppressant effect of D-Tyr$^{11}$-NT and the subsequent stimulant effect were not altered by CPP, as CnT animals were also less active than control during the first 30 min and more active after 60 min (p`s < .001). Interestingly, CPP alone produced a stimulant effect on non-ambulatory movements that occurred between 30 and 120 min after the injection ($p < .05$) however non-ambulatory movements recorded from Cs compared to CnT animals was different during the first 60 min after the injection ($p < .01$).

The ANOVA performed on measures of mean non-ambulatory movements obtained on Day 7 (Fig. 2, bottom panel) revealed a significant effect of Group [$F(3,41) = 6.77$, $p < .001$], time [$F(7,287) = 97.0$, $p < .001$] and Group x Time interaction [$F(21,287) = 7.19$, $p < .001$]. Post-hoc test revealed that suppression of D-Tyr^{11} activity during the initial 30 min and stimulated it between 60 and 120 min; these effects were not altered by CPP as CnT animals were different from Ss animals at the same time periods but were not different from SnT animals (p`s < .05). When given alone CPP did not stimulate activity as seen on day 1, instead it suppressed non-ambulatory activity between 30 and 45 min after the injection ($p < .05$).

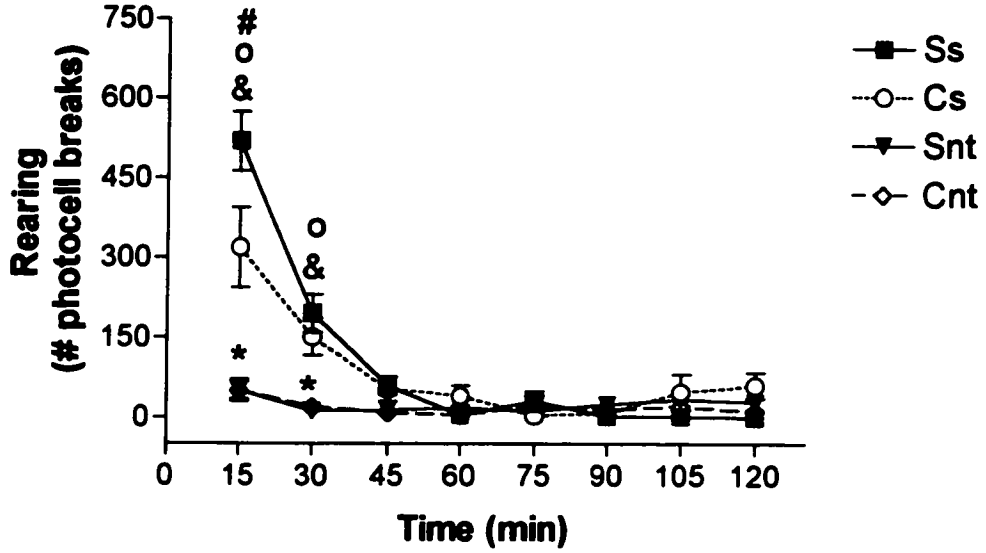
Vertical Activity

Measures of mean rearing activity, expressed as number of photocell breaks during each of the eight 15 min time period, obtained on day 1 of the induction phase are shown in Fig. 3 (top panel) for each group tested. The ANOVA revealed a significant main effect of group [$F(3,41) = 19.57$, $p < .001$], of

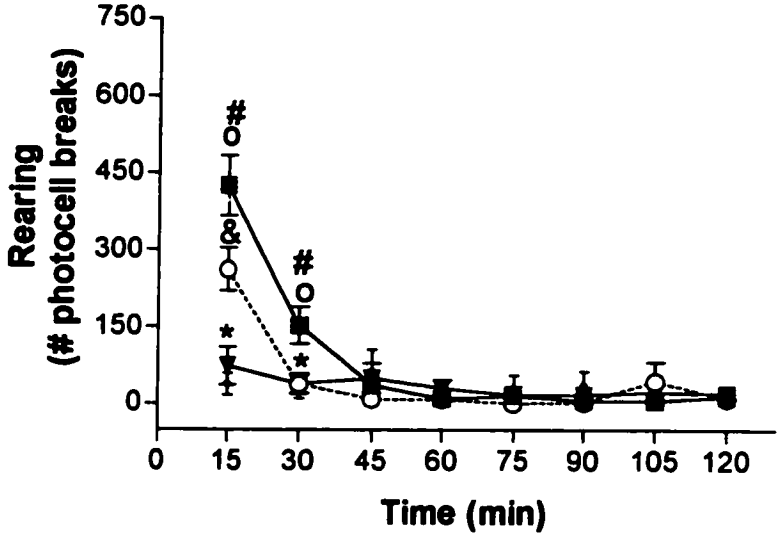
Fig. 3 INDUCTION PHASE. Mean (± SEM) vertical activity on Day 1 (expressed as total number of photocell breaks, top panel) and Day 7 (bottom panel) as a function of time after injection. See Figure 1 for details. The ANOVA conducted on these data revealed a significant effect of groups ($F(3,41) = 19.57$, $p < 0.0001$).

INDUCTION PHASE
VERTICAL ACTIVITY

Day 1



Day 7



time [$F(7,287) = 43.58$, $p < .001$] and Group x Time interaction [$F(21,287) = 14.7$, $p < .001$]. Post-hoc test showed that D-Tyr^{11}-NT significantly suppressed vertical activity during the first 30 min, an effect not prevented by CPP ($p < .001$). By itself, CPP suppressed vertical activity during the first 15 min only, as Cs animals were significantly less active than Ss animals at this time period ($p < .001$).

The ANOVA performed on measures of mean rearing activity obtained on Day 7 (Fig. 3, bottom panel) revealed a significant main effect of group [$F(3,41) = 3.3$, $p < .03$], main effect of time [$F(7,287) = 35.52$, $p < .001$] and a Group x Time interaction [$F(21,287) = 11.16$, $p < .001$]. Post-hoc test revealed that D-Tyr^{11}-NT produced a suppressant effect on vertical activity during the first 30 min as on day 1, and CPP failed to prevent it ($p < .001$); no significant difference was found between SnT and CnT animals at any time. When given alone, CPP suppressed vertical activity during the first 30 min, an effect slightly stronger than that seen on Day 1 ($p < .001$).

Test for Sensitization

Ambulatory Movements

Measures of mean ambulatory movements obtained following a single injection of amphetamine on Day 14 in each group are shown in Fig. 4. The ANOVA revealed a significant main effect of time [$F(21,287) = 85.1$, $p < .001$], and a significant Group x Time interaction [$F(21,287) = 1.64$, $p < .05$]. Post-hoc tests showed that animals treated with D-Tyr^{11}-NT (SnT) during the induction phase displayed more ambulatory activity than Ss animals over the entire two-hour test session ($p < .03$). The glutamate antagonist, CPP, attenuated the

development of sensitization by D-Tyr^{11}-NT; animals pre-treated with CPP + D-Tyr^{11}-NT were less active than the SnT animals during the last 30 min (between 90 and 120 min post-injection) or only in the last 30 min ($p < .05$). The CnT animals were less active than saline control animals (Ss) in the first half hour (between 15 min & 30 min) and then again at 90 min ($p < .04$). Pre-treatment with the glutamate antagonist alone did not alter responses to amphetamine; Cs animals did not differ from Ss animals at any time period.

Non-Ambulatory Movements

Measures of mean non-ambulatory movements obtained following a single injection of amphetamine on Day 14 in each group are shown in Fig. 5. The ANOVA yielded no significant effect of group [$F(3,33) = 2.14$, $p.> .05$], nor of Group by Time interaction [$F(21,287) = 1.13$, $p > .05$].

Vertical Activity

Measures of mean rearing activity obtained following a single injection of amphetamine on Day 14 in each groups are shown in Fig. 5. The ANOVA yielded no significant effect of group [$F(3,33) = 2.78$, $p > .05$], nor of group by time interaction [$F(21,287) = 1.1$, $p > .05$].

Fig. 4 TEST FOR SENSITIZATION. All animals received 0.75mg/kg of amphetamine ip for the first time before being place in the test boxes. Mean (± SEM) ambulatory movements activity in animals exposed to icv D-Tyr^{11}-NT or saline prior to either CPP ip or saline ip pre-treatment. Legend indicates for each group the drug treatments administered during the induction phase: Saline + saline (Ss, n = 10); CPP + saline (Cs, n = 8); Saline + D-Tyr (SnT, n = 11); CPP + D-Tyr, (CnT, n = 9). Comparison among means were made with Duncan`s multiple range post-hoc tests; Ss versus Snt, *; CnT versus Cs, &; SnT versus CnT, +; Cs versus Ss, #, CnT versus Ss, o. ($p \leq 0.05$).

TEST FOR SENSITIZATION (Day 14)
AMBULATORY MOVEMENTS

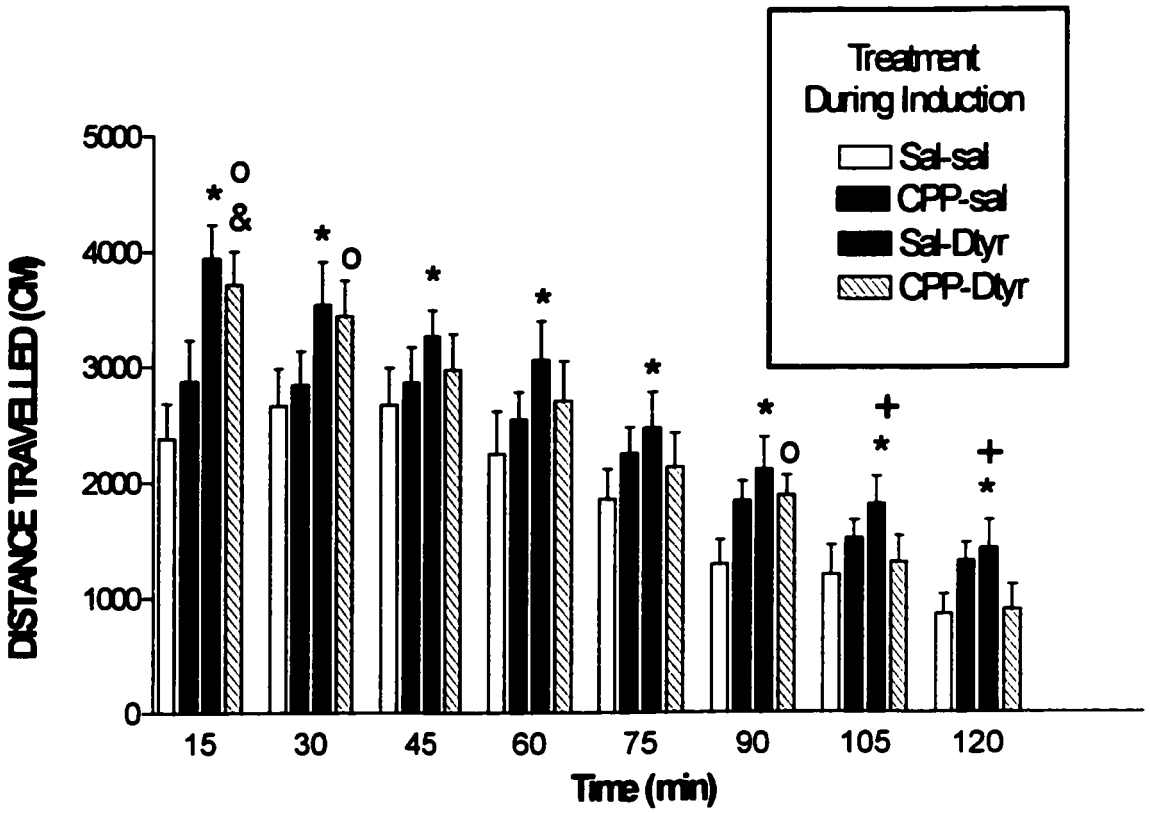
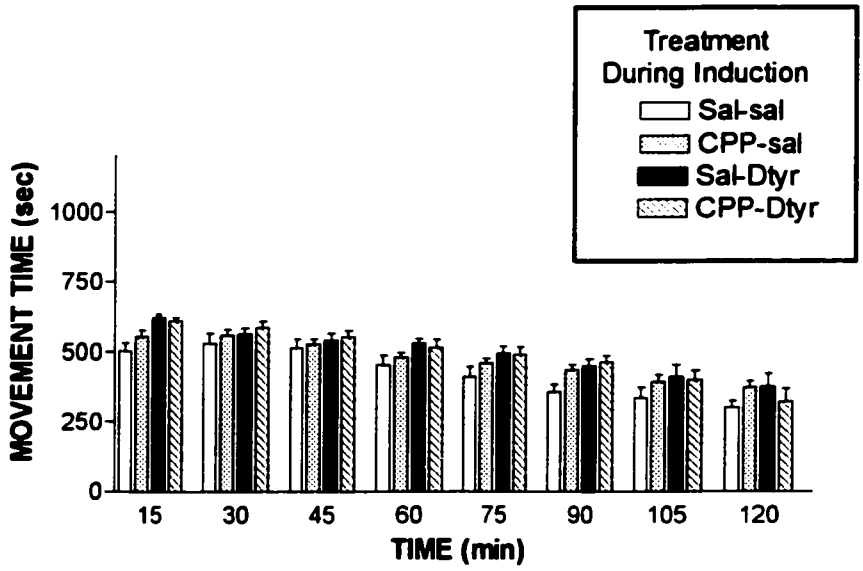


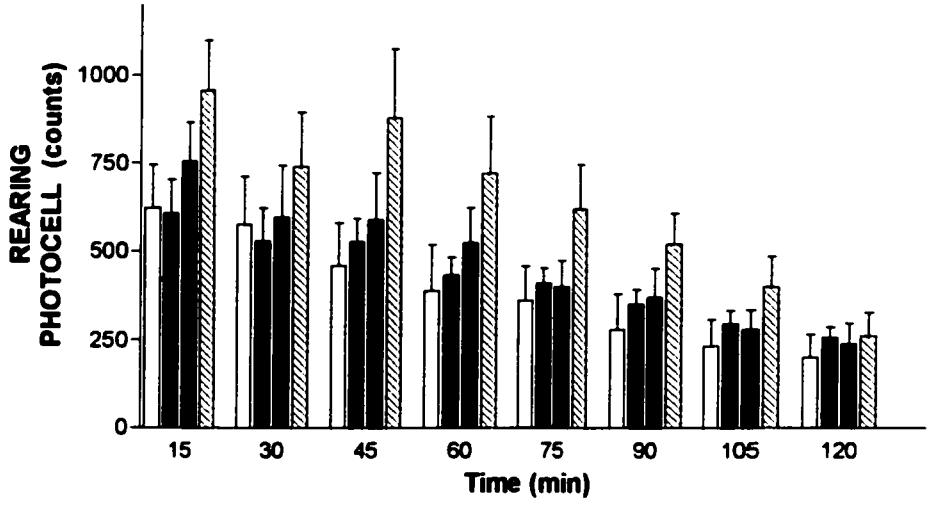
Fig. 5 TEST FOR SENSITIZATION. All animals received 0.75mg/kg of amphetamine ip for the first time before being place in the test boxes. Mean (± SEM) non-ambulatory movements (top panel) and vertical activity (bottom panel) in animals exposed to icv D-Tyr^{11}-NT or saline prior to either CPP ip or saline ip pre-treatment. See figure 4 for details.

TEST FOR SENSITIZATION (Day 14)

NON-AMBULATORY MOVEMENTS
(Stereotypy-like Movements)



VERTICAL ACTIVITY



DISCUSSION

This study was aimed at determining the effects of NMDA receptor blockade on NT receptor activation of locomotor activity and on the development of cross sensitization to the locomotor activating effect of AMPH induced by repeated central NT receptor activation. The primary findings were that activation of NT receptors during the induction phase resulted in behavioral sensitization to AMPH and that pretreatment of the competitive NMDA glutamate antagonist slightly attenuated the development of cross sensitization between NT and AMPH sensitization.

Induction Phase

On the first day of the induction phase, D-Tyr^{11}-NT alone produced a strong suppression of vertical activity during the first 15 min of test (see next page) an effect though still observed following the fourth injection on day 7. This suppressant effect cannot be accounted for by an increase in ambulatory and/or non-ambulatory responses since these were attenuated during the same time period. A close examination of the data, reveals that, on day 1, animals treated with D-Tyr^{11}-NT alone displayed a more or less constant level of ambulatory and non-ambulatory movements during the last 90 min; this contrasts with that seen in saline treated animals which displayed initially high activity followed by a rapid decrease. These effects of D-Tyr^{11}-NT are consistent with those previous findings with this NT analog (Jolicoeur et al., 1981; Rompré, 1997). When given centrally, NT, and its active analogs such as D-Tyr^{11}-NT, are known to produce significant muscle relaxation which may account for the initial suppression of the three

parameters of locomotor activity (Nemeroff,1980; Jolicoeur et al., 1981). But the suppressant effect of D-Tyr^{11}-NT can also be attributed to its action in the NAcc. In fact, previous studies have shown that activation of NT receptors in this region suppresses locomotor activity (Jolicoeur et al., 1985; Ford and Marsden, 1990; Ervin et al., 1981; Kalivas et al., 1982; 1984); it did so when locomotion was stimulated by systemic, or central, administration of DA agonists, but had no effect on spontaneous locomotion. An important factor may have contributed to higher levels of locomotor activity in the saline group. Testing in novel environment stimulated the spontaneous locomotion. Novelty may have contributed to our ability to detect a suppressant effect of D-Tyr^{11}-NT on locomotion. Exposure to novelty stimulates locomotion and release of DA in NAcc (Legault and Wise, 2001) and, as mentioned above, activation of NAcc NT receptors inhibits locomotion initiated by NAcc DA receptor activation (Nemeroff, 1980; Jolicoeur et al., 1981). This factor could explain why control animals had higher locomotor activity than those treated with D-Tyr^{11}-NT in the first 15 min.

It is noteworthy that the initial suppressant effect of D-Tyr^{11}-NT (see previous page) was weaker (i.e. ambulatory activity) on day 7. This may be due, at least in part, to a decrease in activity in control animals resulting from habituation to the test environment. However, the development of tolerance to D-Tyr^{11}-NT cannot be excluded, particularly because of the decrease in the stimulatory effect in the second hour (see below).

The stimulatory effects of D-Tyr^{11}-NT on ambulatory and non-ambulatory activity seen in the second hour suggest that the NT analog either had no effect or had a marginal effect in the NAcc at this time period. It could also have acted

at other sites to counteract its action in the NAcc and one such possible site is the VTA. Hence, several lines of evidence support a role for VTA NT receptors in the locomotor stimulant effect of icv D-Tyr^{11}-NT. First, icv injection of NT increases NAcc DA release, an effect that is dependent upon DA impulse flow (Blaha et al., 1990; Blaha and Phillips, 1992). Second, Nouel & Costentin (1994) showed that icv injection of D-Trp11-NT, an analog that possesses pharmacological properties similar to D-Tyr^{11}-NT, stimulates locomotor activity via a DA-dependent mechanism. Third, microinjection of NT, and of D-Tyr^{11}-NT into the VTA stimulates locomotor activity, an effect that is associated with an increase in DA release in the NAcc (Kalivas et al, 1981, 1983; Kalivas & Duffy, 1990; Steinberg et al., 1995).

Taken together, these findings suggest that in the present study D-Tyr^{11}-NT action in the VTA outweighed its action in the NAcc leading to higher levels of ambulatory and non-ambulatory activity than control. In further support of this hypothesis are Kalivas' findings (1982) that microinjection of NT into the NAcc abolished the locomotor stimulant effect of microinjection of NT in the VTA.

The NMDA antagonist had no effect by itself on ambulatory activity but it did attenuate the stimulatory effect of D-Tyr^{11}-NT at 45 and 60 min post-injection on Day 1. Again, such an attenuation cannot be accounted for by an increase in non-ambulatory and in vertical activity, as D-Tyr^{11}-NT -treated animals did not differ from CPP + D-Tyr^{11}-NT -treated animals on these measures. This effect of CPP suggests that endogenous NMDA receptor activation mediates, at least in part, the stimulant effect of D-Tyr^{11}-NT on ambulatory activity. There is evidence from in vitro studies that activation of NT receptors in the NAcc stimulates

glutamate release (Ferraro et al., 2000). However, it is unlikely that D-Tyr^{11}-NT acted in NAcc to stimulate locomotion. A more likely site of action is the PFC since it contains neurotensin receptors (Nicot et al., 1994; Boudin et al., 1996) and microdialysis studies have shown that systemic amphetamine increases extracellular neurotensin in this region (During et al., 1992; Hertel et al., 1995). The activation of NT receptors in this region stimulates local glutamate release (Sanz et al., 1993) and VTA DA impulse flow (Rompré et al., 1998; Fatigati et al., 2000). This later effect may contribute to D-Tyr^{11}-NT -induced increase in ambulatory activity. This remains highly speculative, as the role of NMDA receptors in the effect NT in the PFC is not known. Tolerance may have developed to the effect of CPP on the suppressive effect of D-Tyr^{11}-NT, as it was not observed on day 7.

The NMDA receptor antagonist failed to block D-Tyr^{11}-NT -induced initial suppression, and a late stimulation, of non-ambulatory activity on day 1. On day 7, however, CPP potentiated the initial suppressant effect of D-Tyr^{11}-NT. Interestingly CPP alone produced a strong and long lasting increase in non-ambulatory activity on day 1, but not on day 7. This confirms that, at the dose used, CPP was still behaviorally active 2.5 hours after its injection, which is consistent with a previous report (Jerram et al, 1996). These findings are similar to the results of previous studies showing that the noncompetitive NMDA receptor antagonists, PCP and MK 801, stimulate locomotor activity (Svensson et al., 1991). Previous studies have shown that competitive NMDA receptor antagonist, such as CGS-19755, and D-CPPene, an isomer of CPP, administered systemically also increased locomotion, but they do so at doses higher than that

used in the present study. (Svensson et al., 1991; Kretschmer et al., 1992; Waters et al., 1996). It is conceivable that the enhanced activity in the CPP alone condition on the first day may be due to lack of habituation to test environment (Ahmed, 1995) since the stimulatory effect of CPP was not seen after the second injection on Day 3 (figure E, see appendix A). Doherty and Gratton (1997) showed that intra-accumbens administrations of competitive NMDA receptors antagonist potentiates stress-induced increases in dopamine in both the NAcc and VTA, findings consistent with those reported by Imperato *et al* (1990). Others have also shown that in animals pre-exposed to stress, there is enhancement of locomotor activation and release of DA in the striatum in vitro (Wilcox, et al., 1986; Antelman, et al., 1980). It could be that novelty acted as a stressor and that CPP potentiated its stimulant effect on non-ambulatory movement.

Blockade of NMDA receptor alone also had a suppressant effect on vertical activity on day 1 and on day 7. This effect cannot be explained by an increased in ambulatory activity or by an increase in non-ambulatory; the later motor activity is indeed increased following CPP alone, but not at the same time period. A decrease in vertical activity has been reported following systemic administration of D-CPPene, eliprodil and VEA-1021, selective NMDA antagonists (Bespalov et al., 2000). The opposite effects of CPP alone on non-ambulatory and vertical activity are hard to reconcile through an action on a common site that likely mediates both locomotor responses, such as the NAcc. It is more likely explained by motor disruption, such as ataxia, reported in previous studies following systemic, and central, injections of CPP (O'Neil & Liebman, 1987; Turski et al., 1985; Jerram et al, 1996). Since we had not observed the

animals during the testing period, we cannot confirm whether CPP, at the dose used in the present study, produced an ataxic motor response that could have interfered with the expression of vertical activity.

Sensitization Test

The aim of the present study was to determine whether endogenous glutamatergic system plays a role in the development of NT-induced AMPH sensitization. A sensitization effect was found in D-Tyr^{11}-NT treated animals to AMPH-induced ambulatory activity but not to non-ambulatory or to vertical activity. Such a sensitization effect is in agreement with previous reports (Rompré, 1997; Del Vecchio et al., 1998). The essential finding is that the competitive NMDA antagonist, CPP, administered before D-Tyr^{11}-NT during the induction phase, attenuated sensitization to AMPH-induced ambulatory movements, and had no effect by itself. This suggests that endogenous NMDA receptors may be involved in the induction of NT-induced AMPH.

A major question is what is the site of action. Data gathered to date strongly suggest that VTA is a critical site for the development of sensitization to AMPH. Sensitization can be induced by direct microinjections of AMPH into the VTA, and this effect is prevented by DA D1 (Kalivas & Weber, 1988; Perugini & Vezina, 1994; Vezina, 1996) or by NMDA (Cador et al., 1999; Vezina and Queen, 2000), receptor blockade in this region. It has been proposed that sensitization is induced by release of glutamate from PFC afferents to the VTA following activation of D1 receptors by DA. In further support for this hypothesis are data showing that i) VTA efferent terminals from the PFC likely express D1 receptors

(Dewar et al., 1997), ii) activation of VTA D1 receptor releases glutamate into the VTA (Wolf & Xue, 1998; 1999), and iii) excitotoxic lesions of the PFC block the development of AMPH sensitization (Wolf et al., 1995; Cador et al., 1999). Since NT stimulates both DA cell firing and DA release (Blaha et al., 1990; Litwin & Goldstein, 1994), one hypothesis to account for the present results, is that D-Tyr^{11}-NT acted in the VTA to induce AMPH sensitization. A previous study, however, has shown that repeated VTA NT injection does not sensitize to AMPH (Elliott & Nemeroff, 1986). In this later study, the AMPH challenge test was performed 1 and 2 days after induction phase, and that may have contributed to the negative findings. As mentioned previously, the extent to which sensitization is induced is time dependent, and sensitization has been shown to be more pronounced with withdrawal periods of 1 to 3 weeks following termination of drug (Vanderschuren et al, 1999; Kolta, et al., 1985; see Robinson, 1991). Another possibility is that the sensitized behavioral effects are due to activation of NT receptors in the PFC. Activation of PFC NT receptors stimulate VTA DA cell firing (Rompré et al., 1998; Fatigati et al., 2000), and ibotenic acid lesion of the PFC was found to block the development of cross-sensitization between D-Tyr^{11}-NT and AMPH (Blackburn et al., 1998). This hypothesis implies that PFC NT receptor activation stimulates VTA glutamate release to induce sensitization, and that systemic CPP acts in this region to block the relevant NMDA receptors. It also predicts that cross-sensitization between NT and AMPH will be insensitive to VTA D1 receptor blockade. These speculations wait further empirical testing since they cannot be determined by the present study that employed intra-ventricular injections.

The evidence gathered to date indicates that the acute effect of NT on the induction of AMPH sensitization may be due to NT subtype 1 receptor (NTR1). A previous study showing that the preferred NTR1 receptor antagonist, SR48692, administered during the induction phase prevented behavioral sensitization (Rompré & Perron, 2000), suggests not only that NTR1 receptor subtype may be involved in sensitization but that endogenous NT may play a role in the development of AMPH-induced sensitization. It remains unclear whether or not the induction of sensitization by repeated NT is also NTR1-dependent. There is, however, indirect evidence for this. For instance, the NTR1 receptor has been found in ventral midbrain region and in the PFC (Nicot et al., 1994; Boudin et al., 1996) areas that are known to be critical in the development of sensitization. Furthermore, systemic AMPH has been shown to release NT in the PFC (During et al., 1992; Hertel et al., 1995). Taken together these observations suggest that the neural substrates mediating NT induced sensitization is similar to AMPH induced changes in AMPH sensitization (Kalivas & Stewart, 1991).

An unexpected aspect of the data obtained in this experiment is the lack of sensitization to AMPH-induced vertical movements (rearing) as assessed on sensitization test. Previous studies following repeated exposure to AMPH (Robinson & Becker, 1986; Russell et al., 1987) report significant increases in both locomotion and rearing. Other studies show, however, that repeated AMPH (Mazurski & Beninger, 1987) failed to produce a sensitized response in vertical activity. Although differences in rearing between groups receiving NT by itself (SnT) and saline control was not significant, it was approaching significance.

GENERAL DISCUSSION

One factor that limits the interpretation of the present study is that environmental conditioning may have contributed to the sensitization response observed on day 14. This type of behavioral sensitization is observed when the Sensitization Test (day 14) is performed in the environment associated with the drug injections. For example, animals pretreated with drug in the presence of a set of environmental stimuli may on the Sensitization Test show a greater response to drug in the drug-taking environment (Tilson & Rech, 1973). It has been shown that the sensitized locomotor response to AMPH is stronger when the sensitization is performed in the environment that the animal was exposed to during the induction phase. Under such conditions, the environment acts as a conditioned stimulus, which by itself stimulates locomotion, a phenomenon that is likely to be additive to the effects of amphetamine. In fact, several studies have shown that behavioral stimulation of the locomotor activation produced by psychostimulants can be conditioned to environmental stimuli (Tilson and Rech, 1973; Stewart and Eikelboom, 1987). In the present study, the enhanced locomotor response to amphetamine observed in D-Tyr^{11}-NT alone group compared to the saline control may be due to a sensitized effect of AMPH, to a conditioned effect or to both. To date, there is no experimental evidence that D-Tyr^{11}-NT can induce a conditioned locomotor response. There is, however, evidence that AMPH sensitization can occur without conditioning. For instance, repeated injections of AMPH directly into the VTA region during the induction phase (Kalivas & Weber, 1988; Perugini & Vezina, 1994; Cador et al., 1995) are known to produce sensitization independent of environmental exposure.

Moreover, Robinson and Becker (1986) have reported AMPH sensitization to a single injection of AMPH, a condition that is likely free of a conditioned effect. In order to resolve this issue, we would have to determine two things. First, if D-Tyr^{11}-NT alone can induce conditioned locomotion. This can be determined by simply pre-exposing animals to repeated D-Tyr^{11}-NT injections during the Induction Phase followed by challenge test vehicle (Sensiziation Test, day 14) in the same environment. The second issue is if repeated NT-induced AMPH sensitization is under stimulus-control. This question can be resolved by having one group receiving D-Tyr^{11}-NT paired with test chamber and another group receiving D-Tyr^{11}-NT unpaired with the environment. A higher locomotor response to AMPH challenge in the paired environment compared to the unpaired suggests contributions to conditioning. Although environmental conditioning cannot be ruled out entirely in the present study, a review of the above literature indicates that conditioning is not necessary for behavioral sensitization to occur.

In conclusion, the present findings support our hypothesis that glutamate receptors plays, at least in part, in the initiation of NT-induced AMPH cross sensitization. These findings make an addition to an accumulation of literature that endogenous glutamate participates in the development AMPH-induced sensitization, hence contributing to some features of drug abuse such as drug craving and compulsive drug seeking behaviors (Robinson & Berridge, 1993).

Results of this study shed some new light on the mechanism(s) by which NT contributes to the development of an increased sensitivity to psychostimulant drugs. Since these drugs produce neuroadaptation long after drug withdrawal,

such findings contribute to our understanding of addiction, in particular drug relapse and craving.

Future research should focus on substantiating a complete dose-response curve, since in this study pre-exposure to glutamate antagonist only attenuated the behavioral effects of NT-induced AMPH sensitization. Moreover, the competitive NMDA receptor antagonist alone has been reported to have locomotor stimulating properties (Svenesson et al., 1990; Imperato et al., 1990), albeit at very high doses. Further clarification of this issue would be feasible by testing different concentrations of the drug.

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APPENDIX A

Figure A. A diagram outlining the induction phase and test for sensitization protocol. During the induction phase, systemic injection of CPP (4mg/kg) or its vehicle is administered 30 min prior to icv injection of 18nmol/ul of D-Tyr^{11}-NT or equal volume of saline four times every second day. One week after the induction phase, a single injection of AMPH (0.75mg/kg, ip) is given to all rats (sensitization test).

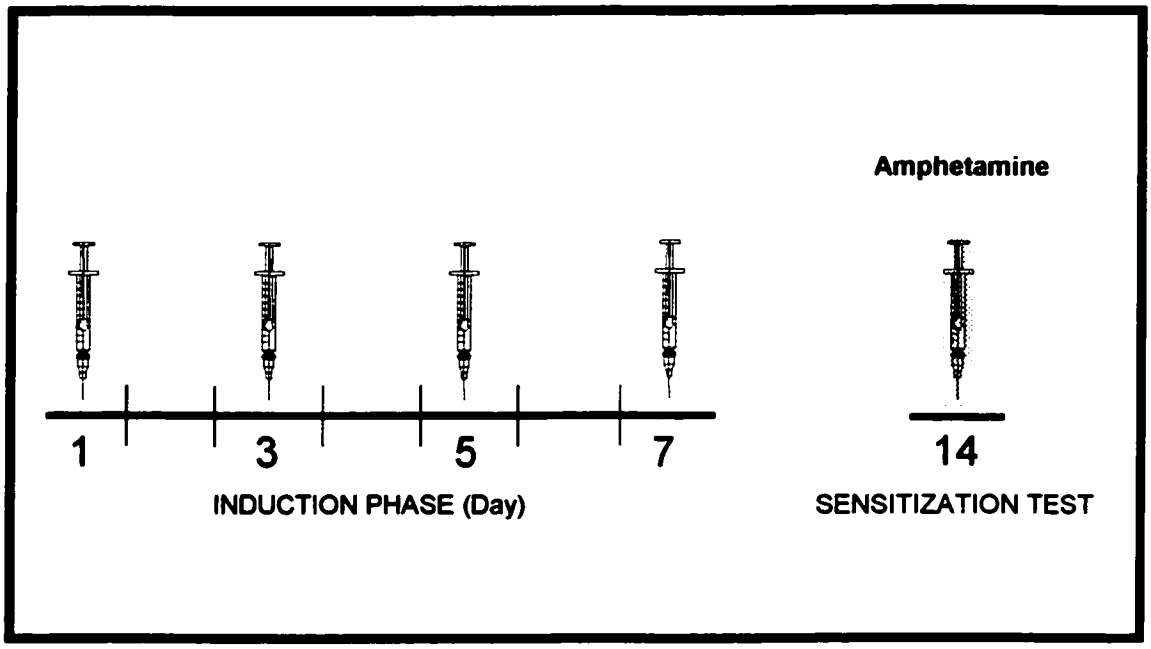

Amphetamine
1
3
5
7
14
INDUCTION PHASE (Day)
SENSITIZATION TEST

Figure B. A diagram of 1 of the 4 test cages used in the experiment. Include in the figure are the photocell arrangements and "virtual-area" or box surrounding the rat.

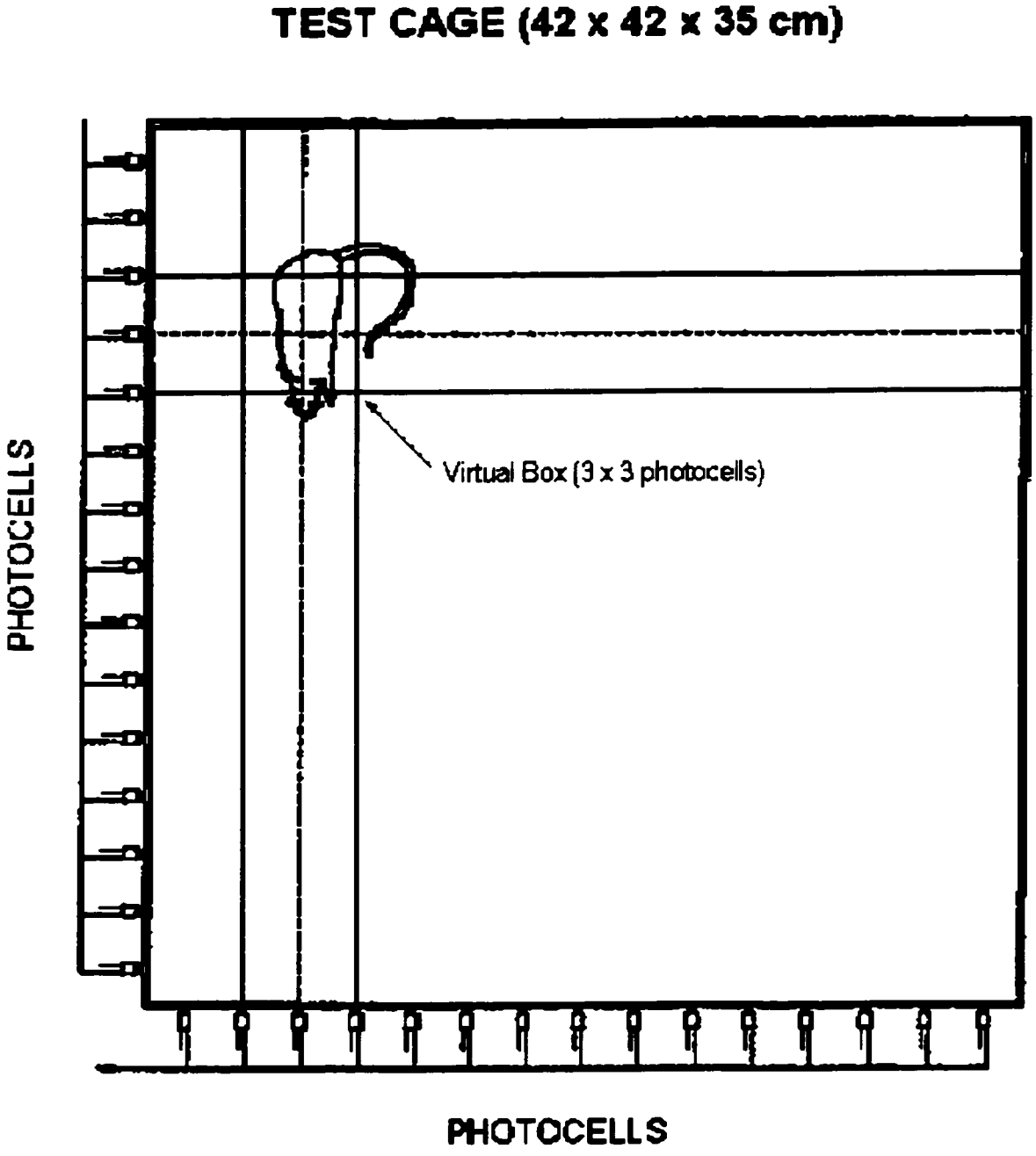
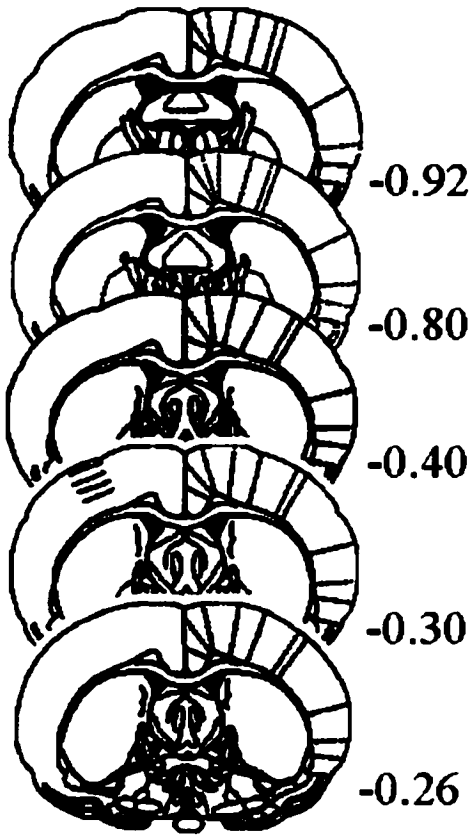
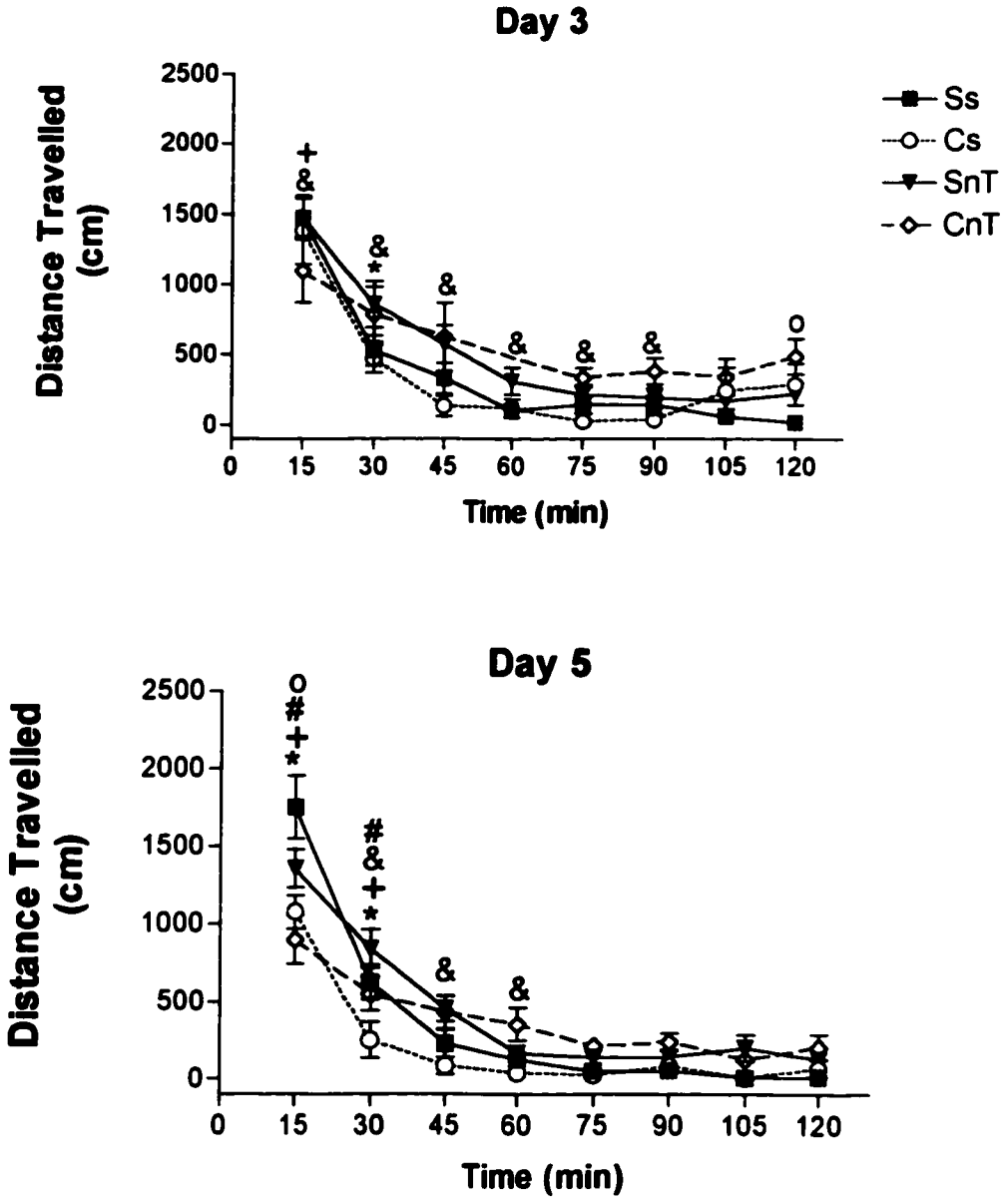

TEST CAGE (42 x 42 x 35 cm)
PHOTOCELLS
Virtual Box (3 x 3 photocells)
PHOTOCELLS

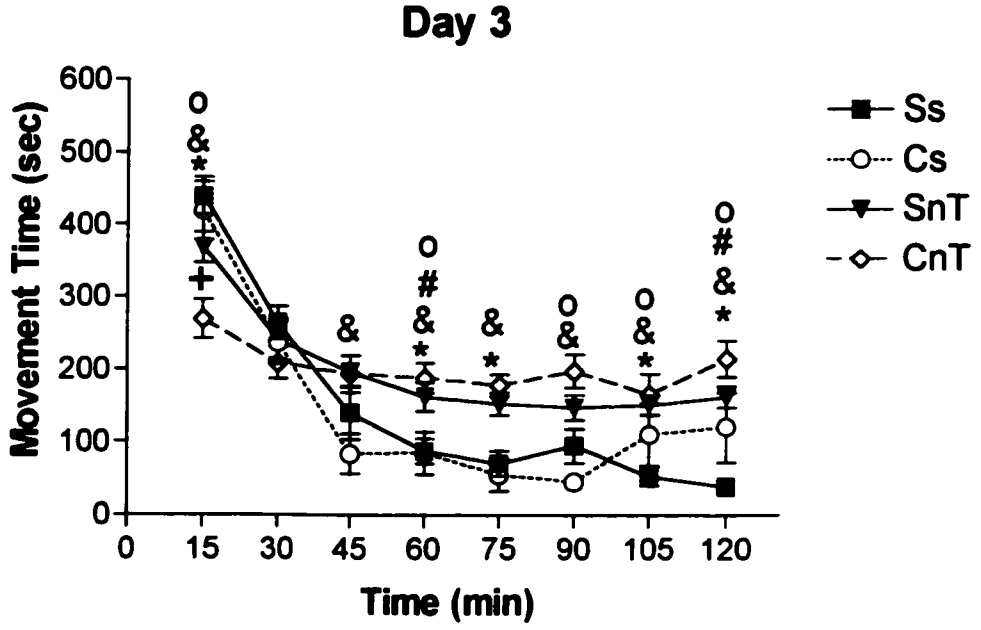
Figure C. The range of the unilateral cannula placements in the left lateral ventricle, for the 45 out of 60 animals included in the experiment. The coronal sections are from Paxino & Watson (1997). The numbers to the right indicate mm from bregma.

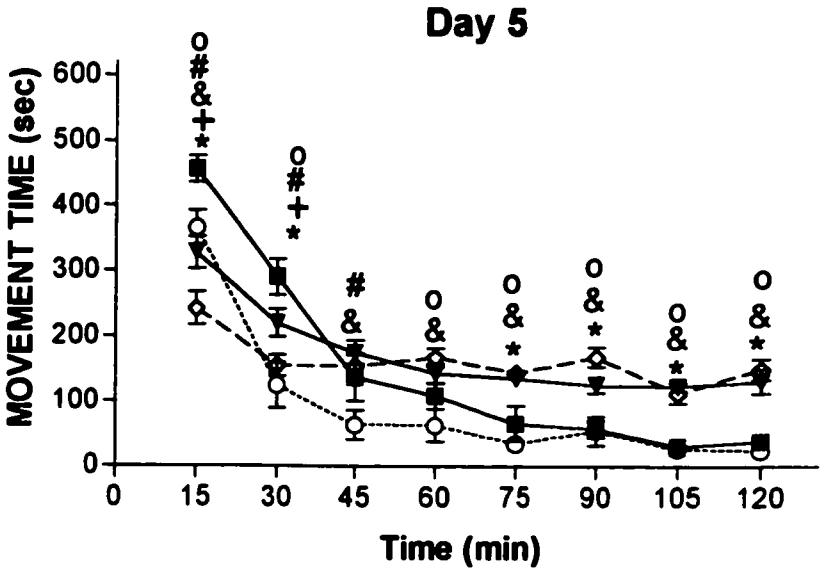

-0.92
-0.80
-0.40
-0.30
-0.26

INDUCTION PHASE AMBULATORY ACTIVITY



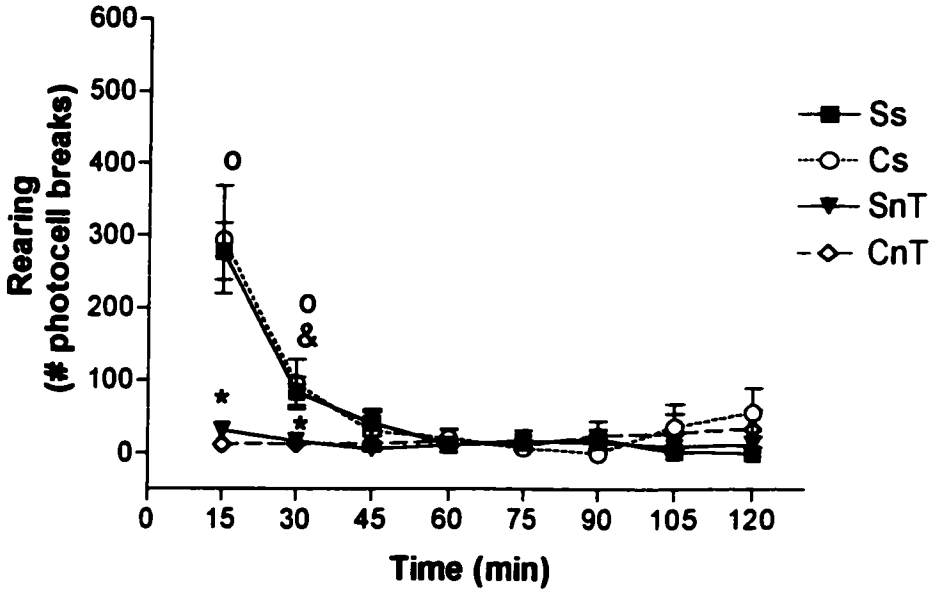
INDUCTION PHASE NONAMBULATORY MOVEMENTS (Stereotypy-like Movements)



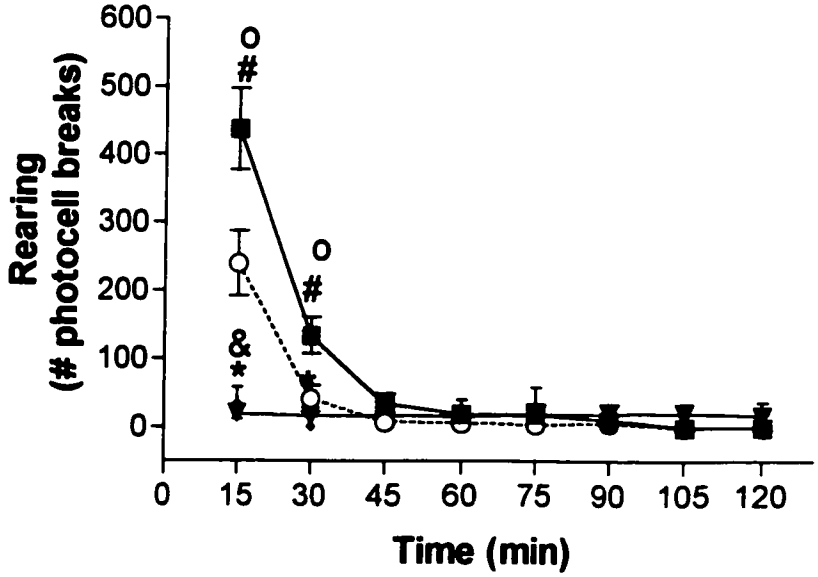


INDUCTION PHASE VERTICAL ACTIVITY

Day 3



Day 5



APPENDIX B

TABLES 1 & 2

INDUCTION PHASE: ANOVA Summary Tables for Locomotor Activity

Figure 1., Table 1 Ambulatory (horizontal) Movement, Day 1

			Between Subjects			
Source	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (1)	3	962542	41	456765.9	2.10730	0.114090
Time (2)	7	12187721	287	138474.0	88.01453	0.000000
1 X 2	21	980792	287	138474.0	7.08286	0.000000

			Within Subjects		
	Sum of Squares	df	Mean Square	F	p-level
Effect	85314048	7	12187721	88.01453	0.00
Error	39742024	287	138474		

Figure 1., Table 2 Ambulatory (horizontal) Movements, Day 7

			Between Subjects			
Source	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (1)	3	1097571	41	62429.5	4.18234	0.011323
Time (2)	7	6809172	287	77188.9	88.21435	0.000000
1 x 2	21	128446	287	77188.9	1.66405	0.035796

			Within Subjects		
	Sum of Squares	df	Mean Square	F	p-level
Effect	47664204	7	6809172	88.21435	0.00
Error	22153228	287	77189		

TABLES 3 & 4

INDUCTION PHASE: ANOVA Summary Tables for Locomotor Activity

Figure 2., Table 3. Non-Ambulatory (stereotypy-like) Movements, Day 1

			Between Subjects			
Source	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (1)	3	388539.4	41	44490.50	8.73309	0.000134
Time(2)	7	409159.5	287	5757.69	71.06318	0.000000
1 x 2	21	58884.2	287	5757.69	10.22706	0.000000

			Within Subjects		
	Sum of Squares	df	Mean Square	F	p-level
Effect	2864116	7	409159.5	71.06318	0.00
Error	1652456	287	5757.7		

Figure 2., Table 4. NonAmbulatory (stereotypy-like) Movements, Day 7

			Between Subjects			
Source	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (1)	3	102068.4	41	5058.17	6.77828	0.000812
Time (2)	7	362007.2	287	4411.67	82.05666	0.000000
1 x 2	21	31720.7	287	4411.67	7.19017	0.000000

			Within Subjects		
	Sum of Squares	df	Mean Square	F	p-level
Effect	2534051	7	362007.2	82.05666	0.00
Error	1266151	287	4411.7		

TABLES 5 & 6

INDUCTION PHASE: ANOVA Summary Tables for Locomotor Activity

Figure 3., Table 5 Vertical (rearing) Activity, Day 1

			Between Subjects			
Source	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (1)	3	161067.3	41	8229.848	19.57112	0.000000
Time (2)	7	250420.7	287	5745.698	43.58404	0.000000
1 x 2	21	84956.2	287	5745.698	14.78605	0.000000

			Within Subjects		
	Sum of Squares	df	Mean Square	F	p-level
Effect	1752945	7	250420.7	43.58404	0.00
Error	1649015	287	5745.7		

Figure 3., Table 6 Vertical (rearing) Activity, Day 7

			Between Subjects			
Source	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (1)	3	57422.8	41	7357.01	3.30833	0.029379
Time (2)	7	173224.7	287	4876.72	35.52073	0.000000
1 x 2	21	54459.0	287	4876.72	11.16714	0.000000

			Within Subjects		
	Sum of Squares	df	Mean Square	F	p-level
Effect	1212573	7	173224.7	35.52073	0.00
Error	1399619	287	4876.7		

TABLES 10 & 11

INDUCTION PHASE: ANOVA Summary Tables for Locomotor Activity

Figure D, Table 10 Ambulatory (horizontal) Movements, Day 3

			Between Subjects			
Source	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (1)	3	1068152	41	493619.1	2.16392	0.106929
Time (2)	7	7023696	287	97685.4	71.90121	0.000000
1 x 2	21	198188	287	97685.4	2.02884	0.005581

			Within Subjects		
	Sum of Squares	df	Mean Square	F	p-level
Effect	49165872	7	7023696	71.90121	0.00
Error	28035698	287	97685		

Figure D, Table 11 Ambulatory (horizontal) Movements, Day 5

			Between Subjects			
Source	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (1)	3	831700	41	214150.8	3.8837	0.015626
Time (2)	7	7076522	287	64101.1	110.3963	0.000000
1 x 2	21	312856	287	64101.1	4.8807	0.000000

			Within Subjects		
	Sum of Squares	df	Mean Square	F	p-level
Effect	49535652	7	7076522	110.3963	0.00
Error	18397014	287	64101		

TABLES 12 & 13

INDUCTION PHASE: ANOVA Summary Tables for Locomotor Activity

Figure E, Table 12 Non-Ambulatory (stereotypy-like) Movements, Day 3

			Between Subjects			
	df	MS	df	MS		
Source	Effect	Effect	Error	Error	F	p-level
Group (1)	3	82983.2	41	15055.77	5.51172	0.002832
Time (2)	7	350368.2	287	5557.80	63.04076	0.000000
1 x 2	21	29419.2	287	5557.80	5.29331	0.000000

			Within Subjects		
	Sum of		Mean		
	Squares	df	Square	F	p-level
Effect	2452577	7	350368.2	63.04076	0.00
Error	1595090	287	5557.8		

Figure E, Table 13 Non-Ambulatory (stereotypy-like) Movements, Day 5

			Between Subjects			
	df	MS	df	MS		
Source	Effect	Effect	Error	Error	F	p-level
Group (1)	3	99942.2	41	14040.70	7.1180	0.000588
Time (2)	7	354706.6	287	3380.43	104.9293	0.000000
1 x 2	21	32289.6	287	3380.43	9.5519	0.000000

			Within Subjects		
	Sum of		Mean		
	Squares	df	Square	F	p-level
Effect	2482946	7	354706.6	104.9293	0.00
Error	970184	287	3380.4		

TABLES 14 & 15

INDUCTION PHASE: ANOVA Summary Table for Locomotor Activity

Figure F, Table 14 Vertical (rearing) Activity, Day 3

			Between Subjects			
Source	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (1)	3	61786.09	41	10291.76	6.00345	0.001729
Time (2)	7	98273.37	287	3811.46	25.78369	0.000000
1 x 2	21	32505.00	287	3811.46	8.52824	0.000000

			Within Subjects		
	Sum of Squares	df	Mean Square	F	p-level
Effect	687914	7	98273.37	25.78369	.000000
Error	1093888	287	3811.46		

Figure F, Table 15 Vertical (rearing) Activity, Day 5

			Between Subjects			
Source	df Effect	MS Effect	df Error	MS Error	F	p-level
Groupe (1)	3	90367.7	41	10561.37	8.55644	0.000157
Time (2)	7	151148.5	287	3369.88	44.85278	0.000000
1 x 2	21	62902.1	287	3369.88	18.66597	0.000000

			Within Subjects		
	Sum of Squares	df	Mean Square	F	p-level
Effect	1058040	7	151148.5	44.85278	0.00
Error	967156	287	3369.9		

APPENDIX C

TABLE 7

SENSITIZATION TEST: ANOVA Summary Tables for Locomotor Activity

Figure 4. Ambulatory (horizontal) Movements, Day 14

			Between Subjects			
Source	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (1)	3	9091806	33	4315822	2.10662	0.118234
Time (2)	7	22433426	231	263565	85.11543	0.000000
1 x 2	21	432445	231	263565	1.64075	0.041853

		Within Subjects			
	Sum of Squares	df	Mean Square	F	p-level
Effect	157033984	7	22433426	85.11543	0.00
Error	60883456	231	263565		

TABLES 8 & 9

SENSITIZATION TEST: ANOVA Summary Tables for Locomotor Activity

Figure 5., Table 8 Non-Ambulatory (stereotypy-like) Movements, Day 14

			Between Subjects			
Source	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (1)	3	80406.0	33	37544.42	2.14162	0.113728
Time (2)	7	253881.2	231	2899.22	87.56874	0.000000
1 x 2	21	3278.2	231	2899.22	1.13071	0.317055

			Within Subjects		
	Sum of Squares	df	Mean Square	F	p-level
Effect	1777168	7	253881.2	87.56874	0.00
Error	669720	231	2899.2		

Figure 5., Table 9 Vertical (rearing) Activity, Day 14

			Between Subjects			
Source	df Effect	MS Effect	df Error	MS Error	F	p-level
Group (1)	3	1299930	33	467493.2	2.78064	0.056379
Time (2)	7	961394	231	33668.6	28.55462	0.000000
1 x2	21	37106	231	33668.6	1.10209	0.346694

			Within Subjects		
	Sum of Squares	df	Mean Square	F	p-level
Effect	11083912	7	1583416	52.01876	0.00
Error	10014538	329	30439		