LITERATURE REVIEW

Methamphetamine acts on the pleasure circuit in the brain by altering the levels of certain neurotransmitters present in the synapse. Chemically, methamphetamine is closely related to amphetamine, but its effects on the central nervous system are greater than those of amphetamine (Derlet and Heischober 1990; MacKenzie and Heischober 1997). Methamphetamine is also chemically similar to dopamine. It produces effects by causing dopamine to be released into the synapse in several areas of the brain, including the nucleus accumbens, prefrontal cortex, and the striatum, a brain area involved in movement. Specifically, methamphetamine enters nerve terminals by passing directly through nerve cell membranes. It is also carried into the nerve terminals by transporter molecules that normally carry dopamine from the synapse back into the nerve terminal. Once in the nerve terminal, methamphetamine enters dopamine containing vesicles and hence causes the release of this neurotransmitter (Fischer and Cho 1979; Liang and Rutledg 1982; Schmidt and Gibb 1985; Di Chiara and Imperato 1988; O'Dell et al. 1991; Seiden et al. 1993; Cubells et al. 1994; Hoffman and Lefkowitz 1995; Katzung 1998). This is probably the main mechanism. Methamphetamine inhibits specific transporters responsible for reuptake of dopamine from the synaptic nerve ending (Schaeffer et al. 1976; Liang and Rutledg 1982; Schmidt and Gibb 1985; O'Dell et al. 1991; Seiden et al. 1993; Cubells et al. 1994). Enzyme monoamine oxidase in the cell normally chew up excess dopamine, however, methamphetamine blocks this breakdown, only in high dose (Robinson 1985; Kleven and Seiden 1992; Seiden et al. 1993; Katzung 1998). The excess neurotransmitters are then carried by transporter molecules out of the neuron and into the synapse. Once in the synapse, the high concentration of dopamine causes feelings of pleasure and euphoria. It is generally believed that dopaminergic transmission in the nucleus accumbens and the caudate nucleus mediates methamphetamine-induced hyperlocomotor activity and stereotyped behavior, respectively (Randrup and Munkvad 1970; Creese and Iversen 1974;

Kelly et al. 1975; Kelly and Iversen 1976). Dopamine is present in most parts of the central nervous system (CNS) but in particular in the nigrostriatal pathway comprising the neurons of the substantia nigra and projecting to neurons of the neostriatum and the mesocorticolimbic pathway composed of neurons of the ventral tegmental area connecting with those of the limbic cortex and other limbic structures. The involvement of the dopaminergic nigrostriatal pathway in extrapyramidal dysfunctions was shown by the discovery that degeneration of this pathway occurs in the brains of patients afflicted with Parkinson's disease. The mesocorticolimbic pathway has been implicated as the principal dopaminergic pathway involved in the etiology of psychoses.

On postsynaptic membrane, dopamine interacts with dopamine receptors. Dopamine receptors identified to date can be divided into two classes, the D_1-like (D_1 and D_5) and the D_2-like (D_2, D_3, and D_4) receptors (Civelli et al. 1993; Gingrich and Caron 1993). The D_1 and D_2 subtypes are highly enriched in mammalian neostriatum (Sibley and Monsma 1992). These two receptors exert their biological actions by coupling to and activating different G protein complexes. The D_1 receptor interacts with the Gs complex to activate adenylyl cyclase. The D_1 receptors were shown to mediate stimulation of cAMP formation, whereas the D_2 interacts with Gi to inhibit cAMP production (Spano et al. 1978; Kebabian and Caine 1979; Stoof and Kebabian 1984) and can be coupled to multiple effector systems, including Ca^{2+} and K^+ channels (Huff 1996). The anatomical distributions of these two receptors overlap in the CNS, yet their quantitative ratios differ significantly in particular anatomical areas. With respect to mental disorders, it is noteworthy that both D_1 and D_2 receptors are present in the nigrostriatal and mesocorticolimbic pathways.

Kropf and Kuschinsky (1993) have shown that stimulation of the dopamine D_1 receptor produces EEG effects in rats which are different from those produced by activation of D_2 receptors. Whereas activation of the D_1 receptor by SK&F 38393 induces signs of a desynchronization and a decrease in power in all of the frequency bands. Kropt et al. (1989) have shown that activation of the D_2 receptor or a combined activation of D_1 and D_2 receptors by quinpirole or apomorphine, respectively, produces a characteristic increase in the alpha-1 band. These drugs are direct agonists at postsynaptic

dopamine receptors: SK&F 38393 an agonist (although a partial one) at D_1 receptors (Setler et al. 1978), quinpirole at D_2 receptors (Tsuruta et al. 1981) or apomorphine at both types of receptors (Stoof and Kebabian 1984).

The acute administration of methamphetamine results in a variety of dose-dependent behavioral and EEG effects. Methamphetamine increases locomotor activity when administered at low doses and elicits stereotypic behavior when administered at higher doses (Kelly et al. 1975; Segal and Kuczenski 1994). Ferger et al. (1994) found the following process. A moderate dose of d-amphetamine produced: an EEG pattern which closely resembled to the pattern produced by the D_1 receptor agonist SK&F 38393; an EEG pattern which could be easily reversed by the blocker of D_1 receptor SK&F 38393; and an EEG pattern which was not influenced by a moderate dose of haloperidol, which mainly block D_2 receptor but not D_1 receptor apparently under these conditions. This dose of d-amphetamine produced no stereotyped behavior and only a slight increase in locomotor activity. A larger dose of d-amphetamine produced a pattern in the EEG which suggested an additional activation of D_2-like receptors, namely a selective increase in power in the alpha-1 band, accompanied by locomotor activation and stereotyped sniffing. Methamphetamine has the average distribution of effectiveness and its elimination over time. The peak effect is 9.2 min and the effective duration is 63.0 minutes (Riviere et al. 2000).

Melega et al. (1995) has studied i.v. amphetamine and methamphetamine pharmacokinetics in rats and found similar values. Extracellular concentrations of the dopamine and the drug exhibited similar temporal profiles, each achieving maximum concentrations within 30 min of drug administration. From the time of the peak dopamine responses until the end of the study, changes in striatal drug levels were correlated with extracellular dopamine levels; this correlation was similar for both drugs. Previous reports suggest self-administration of methamphetamine i.v. doses by the abused ranges from 10 to 50 mg per day for an average 70-kg adult (Cho 1990; Beebe and Walley 1995) or 0.1 to 0.8 mg/kg BW per day. Locomotor activity following low dose of amphetamine injection from 20-30 min, rats exhibit enhanced locomotor activity. As the dose is increased (e.g., 2.5 mg/kg), rats begin to show episodic bouts of repetitive head and limb

movements (stereotyped behavior). After a high dose of amphetamine (5-7.5 mg/kg), a similar sequence of behaviors may be observed as a function of time after amphetamine administration. Shortly after the drug was administered, rats showed a marked increase in rearing and sniffing, or locomotor activity, followed (30 min) by stereotyped head and limb movements. By 60 min after amphetamine administration, most animals were engaged in intense, continuous stereotyped, head oriented down toward the cage floor, often accompanied by oral stereotyped behavior such as licking or gnawing (Groves and Tepper 1983; Segal and Schuckit 1983).

The acute administration of 4.0 mg/kg amphetamine resulted in a multiphasic locomotor response profile which included an initial phase of enhanced locomotion, an intermediate period during which animals did not show locomotor activity but engaged in intense stereotyped behaviors (repetitive head or limb movements and/or oral behaviors), and a poststereotypy locomotor phase. In contrast, the acute administration of 0.5 mg/kg amphetamine produced an enhanced locomotor response in the absence of stereotyped behaviors (Kuczenski and Segal 1999).