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AMPHETAMINE: EFFECTS ON CATECHOLAMINE SYSTEMS AND BEHAVIOR

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INTRODUCTION

> "Amphetamine is one of the most versatile drugs known. It undergoes a complex metabolic fate, it markedly alters the physiological disposition of norepinephrine and it causes pronounced pharmacological and behavioral effects." Julius Axelrod (1).

Discovery, Effects and Early Uses

Amphetamine (AMPH) was first synthesized in 1887 (2). The sympathomimetic and respiratory stimulant effects of AMPH were described in 1933 (3–5) and in 1935 its stimulant actions were found to be useful in the treatment of narcolepsy (6). AMPH has been used for the treatment of obesity (7), attention deficit hyperactivity disorder (ADHD) (8), and occasionally for Parkinson's disease (9). AMPH causes euphoria and stimulation in humans, and these effects often lead to its habitual use or abuse. With repeated AMPH use, tolerance to its effects on mood often develops and the dose is escalated (7, 10). Large doses of AMPH can induce a psychotic state resembling paranoid schizophrenia (11–13). The effects of AMPH in humans have close parallels in animals. At low doses, AMPH increases stereotypic locomotor activity and species-specific stereotypies at higher doses (14); AMPH interferes with intake

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of both food and water (15, 16). This diversity of AMPH's actions in affecting physiology and behavior has led to its widespread clinical and experimental use. Further interest in this compound was engendered by the discovery that it interacted with catecholamine (CA) systems in the brain and peripheral autonomic nervous system (ANS) to produce these wide-ranging effects on physiology and behavior (See Refs. 17–21).

AMPH Interacts with Transmitter Release, Uptake, and Metabolism

Release, uptake, and enzymatic inactivation of transmitters are three fundamental processes underlying the mechanisms of action of AMPH at the neuronal level. Both the releasing and uptake-inhibiting actions of AMPH are mediated by the CA uptake transporter (22–24). Because of the prominence of the uptake transporter in AMPH's action, it is of interest to review the transporter from an historical perspective.

Burn (25) suggested that epinephrine could be taken up by sympathetic nerves. In 1959, Axelrod and colleagues demonstrated that epinephrine could be rapidly and selectively taken up by the heart, spleen, and glandular organs, each of which has sympathetic innervation (26). From these observations, it was inferred that norepinephrine (NE) was also taken up into a storage pool where it was protected against enzymatic degradation, thus making it available for re-utilization. NE uptake was rapid and saturable, and occurred with high affinity in both the ANS and the CNS (27–29). The discovery that NE-containing neurons could bind or take up NE against a concentration gradient led to the idea of a carrier-mediated active transport system as a mechanism for terminating the action of NE at the synaptic cleft (27, 28, 30). This carrier-mediated active uptake process was postulated to be similar to the transport of sugars and amino acids across cell membranes (31, 32). It was later determined that the uptake transporter could release CAs as well as reclaim them back into the nerve terminals (24, 33–35). Further investigation revealed that AMPH apparently inhibited the uptake and release of dopamine (DA), NE, or both (36–38). The finding that AMPH acted on the uptake transporter system led to further speculation and research on the functional importance of the amines, as well as to explorations of the transporter system in terms of release and uptake. Much of our knowledge of the physiology of synaptic transmission stems from data generated from the study of AMPH interactions with CAs and transporter complexes. Because of its diverse pharmacological effects and its interaction with CAs, AMPH has been useful for characterizing the functions of the CA systems (39). Our discussion of AMPH's effects stems from a convergence of data from biochemistry, pharmacology, physiology, and psychology.

AMPH has Effects on Neurochemistry and Behavior

There is considerable evidence that AMPH interacts not only with the uptake transporter but also with other aspects of neuronal functioning. AMPH has three effects at the monoaminergic synapse: (*a*) inhibition of monoamine oxidase (MAO); (*b*) blockade of uptake; and (*c*) promotion of release into the synaptic cleft. Therefore, we begin by reviewing the basic anatomy and physiology of CA neural systems. To discuss the mechanism of action of AMPH, we use the dopaminergic system as the prototypic system, recognizing both similarities and differences between DA and NE neurons (40).

After reviewing the mechanisms of AMPH at the cellular level we describe AMPH's effects on behavior. In the second part of this chapter we focus on AMPH as an anorectic agent and drug of abuse; we also discuss AMPH's effects on operant and motor behaviors.

THE CATECHOLAMINE SYSTEMS: A BRIEF OVERVIEW

Anatomy of Catecholaminergic Projections

Dopaminergic cell bodies in the brainstem (41) project widely to telencephalic structures (42). A major group of DA cell bodies lie in the zona compacta of the substantia nigra and project to the striatum. Another group of DA cell bodies lie in the ventral medial tegmentum and project to limbic system structures, including olfactory tubercle, septum, amygdala, nucleus accumbens, and prefrontal cortex. Some cell bodies from the zona compacta send projections to limbic structures while some DA cell bodies in the ventral medial tegmentum project to structures in the striatum. DA neurons have extensively arborized axons and dendrites and there are 10,000 to 100,000 synaptic contacts from each cell body. The degree of arborization suggests that dopaminergic influence on other neurons is tonic. There are four other DA-containing cell groups with shorter distances between the cell bodies and the terminal fields (43–47). NE in the brain also has a diffuse projection system with several major brain stem nuclei projections to both forebrain and spinal cord (48).

The Catecholaminergic Neurons

Dopaminergic and noradrenergic cell bodies contain a nucleus, golgi apparatus, mitochondria, endoplasmic reticulum, and are capable of transcribing messenger ribonucleic acid. These CA cell bodies produce the enzymes required for transmitter synthesis and degradation (49, 50), as well as other cell structures such as tubulin, phospholipids, and lipoproteins (51). The

physiology of the DA and NE neurons has been the subject of other reviews (49, 52–54).

With specific reference to the dopaminergic system, the nerve terminals contain structures required for the synthesis, storage, release, and inactivation of DA. Dopaminergic neuronal and storage vesicle membranes are lipid bilayers that are relatively impermeable to charged particles. The DA axon terminal forms a chemical junction with postsynaptic neurons. There is also evidence for autoregulatory somato-dendritic and dendro-dendritic connections on the DA cell body (55). DA release stimulates both postsynaptic and presynaptic DA receptors, initiating a chain of biochemical and electrophysiological events that are important to the physiological and behavioral functions accompanying DA release.

Transmitter Release

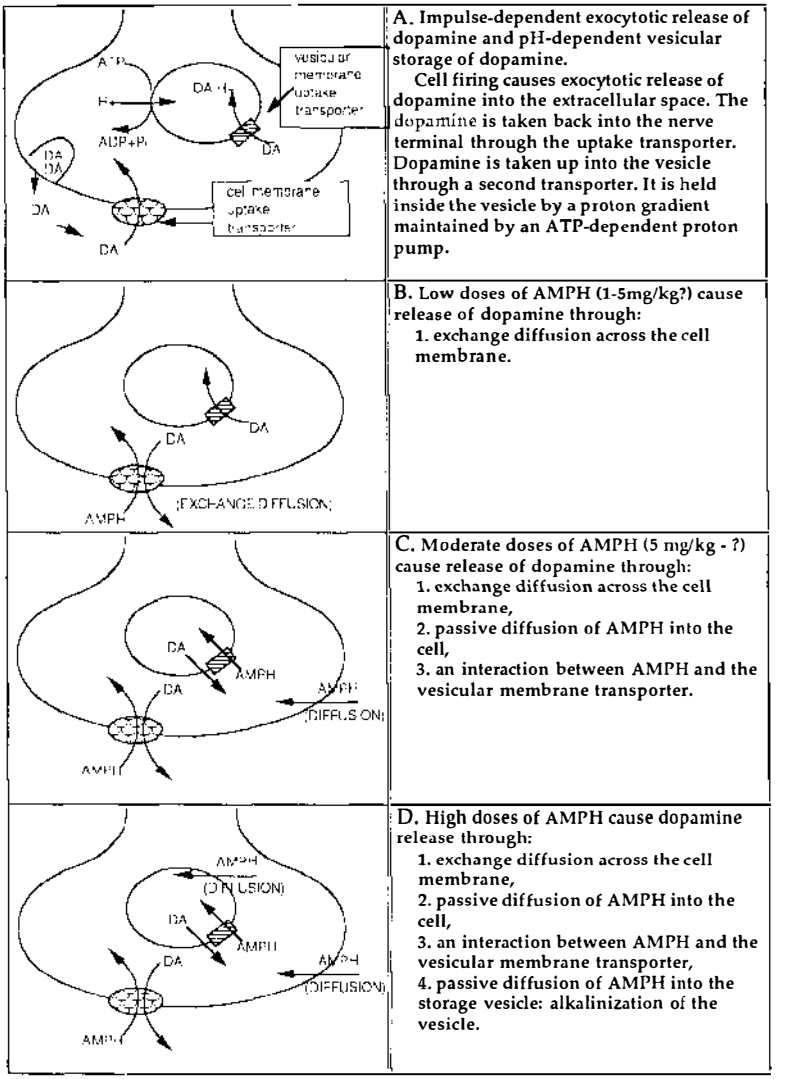
DA can be released through two mechanisms: exocytotic release which is impulse-dependent; and transporter-mediated release, which is not impulse-dependent and appears to be the mechanism by which AMPH releases CAs.

IMPULSE-DEPENDENT EXOCYTOTIC RELEASE The resting potential of the nerve cell results from the distribution of sodium, potassium, chloride, and protein ions across the lipid cell membrane, and is dependent largely upon the K^+ gradient across the cell membrane (56). Membrane depolarization can result in an action potential that causes exocytotic release of CAs into the synaptic cleft. Depolarization-induced exocytotic release of CA is dependent upon ATP hydrolysis, and is initiated by Ca^{++} influx (57). Exocytotic CA release that is experimentally induced by K^+ stimulation is not blocked by inhibition of the uptake transporter (24).

TRANSPORTER-MEDIATED RELEASE Release of CAs can be induced in vitro by reversing the Na^+ gradient across the lipid membrane; this release can be blocked by uptake inhibitors, and is therefore considered to be transporter-mediated (33, 35). Similarly, AMPH-induced DA release is Na^+-dependent and can be blocked by uptake inhibitors. Since this type of DA release is independent of Ca^{++} (58–60), dependent upon the distribution of Na^+ ions, and can be blocked by uptake inhibitors, it is thought to be mediated by the uptake transporter (22, 24). As discussed below, the transporter normally moves DA from the outside to the inside of the cell. However, in the presence of some drugs (AMPH) the direction of transport appears to be reversed and DA is moved from the inside to the outside of the cell (See Figure 1).

Transmitter Uptake

The uptake of transmitter back into nerve terminals is considered to be a major contributor to transmitter inactivation both in the sympathetic nervous system



A. Impulse-dependent exocytotic release of dopamine and pH-dependent vesicular storage of dopamine.

Cell firing causes exocytotic release of dopamine into the extracellular space. The dopamine is taken back into the nerve terminal through the uptake transporter. Dopamine is taken up into the vesicle through a second transporter. It is held inside the vesicle by a proton gradient maintained by an ATP-dependent proton pump.

B. Low doses of AMPH (1-5mg/kg?) cause release of dopamine through:

1. exchange diffusion across the cell membrane.

C. Moderate doses of AMPH (5 mg/kg - ?) cause release of dopamine through:

1. exchange diffusion across the cell membrane,
2. passive diffusion of AMPH into the cell,
3. an interaction between AMPH and the vesicular membrane transporter.

D. High doses of AMPH cause dopamine release through:

1. exchange diffusion across the cell membrane,
2. passive diffusion of AMPH into the cell,
3. an interaction between AMPH and the vesicular membrane transporter,
4. passive diffusion of AMPH into the storage vesicle: alkalinization of the vesicle.

Figure 1 Amphetamine-induced dopamine release: possible interactions between amphetamine and uptake transporters.

and the CNS (27, 30). This process can be blocked by a number of psychoactive drugs including antidepressants and psychomotor stimulants (27, 36, 61).

CHARACTERISTICS OF THE UPTAKE TRANSPORTER The DA uptake transporter on the neuronal membrane is thought to be a multipass transmembrane protein (62–64). The transport process has been characterized as being Na^+ and temperature-dependent and it demonstrates saturation kinetics similar to enzyme kinetics (65–67). The transport mechanism also appears to be rheogenic requiring 2 Na^+ and 1 Cl^- ion for activation (67). Similar characteristics have been described for the NE transporter (28, 31, 34, 68). Both the DA (62, 64) and NE (63) uptake transporters have recently been cloned. This advance will improve understanding of the dynamics of drug-transporter interactions, as well as our understanding of transporter-mediated release and uptake.

The kinetics of drug action at the uptake transporter follow the law of mass action Uptake of released amine from the synaptic cleft back into the presynaptic ending follows the law of mass action and can be quantified by using Michaelis-Menton kinetics (65, 69). As with enzyme kinetics, saturability, reversibility, affinity of the transmitter for the carrier, and the concentration of the released transmitter are important variables, and can be described by:

$$Vo = V_{max}(S)/K_m + (S) \qquad 1.$$

where Vo is the velocity of transport, K_m is a measure of the affinity of the transmitter for the transporter, V_{max} is the maximum velocity of transport (and is an indicator of the number of transporter sites available) and (S) is the concentration of transmitter. The Michaelis-Menton equation is useful in determining the extent and type of inhibition that is engendered by drugs that inhibit the transporter. Drugs that inhibit uptake are generally competitive inhibitors of transporters (67), and are described by:

$$Vo = (V_{max} \cdot (S)/(K_m(1+(I)/Ki)+(S)) \qquad 2.$$

where K_i is similar to K_m in that K_i characterizes the affinity of the inhibitor for a portion of the transporter at which the amine is transported. As K_i becomes smaller, the apparent K_m becomes larger.

Energy source of the DA transporter is indirectly coupled to the hydrolysis of ATP In the uptake process, DA moves from a region of low concentration

to high concentration; therefore, uptake requires energy, and is an active transport process (32). The Na^+ requirement discussed above suggests that the energy source for the transport is derived from the Na^+ gradient across the cell membrane [Na^+] out > [Na^+] in (66). As such, the DA transporter could make use of a co-transport mechanism where DA is carried "uphill" *against* its concentration gradient by being transported along with Na^+, which is carried "downhill" along its electrochemical gradient. Indirectly, this process is ATP-dependent because the Na^+/K^+-ATPase system is required for maintenance of the Na^+ gradient (65). Similarly, the NE transporter appears to rely on the Na^+ gradient across the cell membrane for energy (34, 70, 71). Because of this indirect reliance on ATP-derived energy, the DA uptake transporter is a secondary active transport system (72).

Possible mechanisms for the return of the transporter conformation from inside to outside Once the transporter has carried DA to the inside of the neuron, the transporter presumably must reorient to the outside surface again to continue its DA uptake function. One mechanism for the return of the transporter (for serotonin in this case) to the outside of the membrane is suggested by Nelson & Rudnick (73). They found that high external K^+ causes increases in serotonin efflux and inhibits serotonin uptake whereas high internal K^+ stimulates uptake. Nelson & Rudnick hypothesized that K^+ binds to the transporter on the inside of the membrane, facilitating its return to the outside surface. A similar role for K^+ also applies to NE and DA (34, 65, 66). Another mechanism for the return of the transporter to its original position is proposed by Sammet & Graefe (74; For discussion see 75). They suggest that the transporter naturally orients toward the membrane surface with the higher Na^+ concentration; Na^+ binds to the transporter and prevents the transporter from reorienting to the inside of the membrane. When DA binds to the transporter in combination with Na^+, the transporter becomes "mobile" and can transport DA to the inside of the cell. Since Na^+ concentrations on the inside are low, the transporter retains its mobility, can return to the outside of the membrane, and is held there by Na^+ until the cycle begins again.

The physical characteristics of the transporter are partially understood; the sequence of amino acids (62–64) and the manner in which the transporter is inserted into the membrane are known. However, the dynamics of moving substances from one side of the membrane to the other are not nearly as well understood for transporters as they are for ionic channels (56), and therefore the word orientation is used heuristically.

POSSIBLE MECHANISM FOR THE RETENTION OF DA IN THE NEURON AFTER UPTAKE The following putative mechanism is based on the Na^+ requirement for DA uptake, and on Sammet & Graefe's (74) theory of transporter

orientation. Binding to the transporter is Na^+-dependent; at the resting potential there is a high concentration of Na^+ on the outside of the cell. When the complex of transporter, DA, and Na^+ orient to the inside of the cell, where the Na^+ concentration is lower, the DA may be released from the transporter; by recycling to the outside of the membrane once again, the transporter can bind the available DA because of the high Na^+ concentration. DA that is taken to the inside of the cell does not stay on the transporter or rebind to the transporter because the concentration of Na^+ is not sufficient to allow binding to the transporter.

TRANSPORTER-MEASURING TECHNIQUES The characteristics of uptake transporters are usually measured by two assay techniques. First, functional uptake of amine into isolated synaptosomes or tissue slices is measured by using tissue that is metabolically viable (76). This procedure uses radioactively labeled neurotransmitter to measure affinity (K_m) and number of transporters/tissue weight (V_{max}). In the second assay, transporter affinity and number can be estimated by radioligand binding (77–80). In these studies, binding of a ligand (or drug) to the transporter molecule is measured as a high-affinity binding site similar to binding sites in studies measuring receptors (81). Both techniques have advantages and disadvantages and the resulting data can be interpreted differently. In uptake experiments, the measurement of labeled amine into synaptosomes requires comparatively larger amounts of fresh tissue with a Na^+/K^+ gradient; frozen tissue used in binding studies lacks the ATP-dependent Na^+/K^+ gradient and is not viable. In the binding experiment, tissue can be frozen; but binding to the putative transporter after freezing may give more than one site (82). The issue of freezing, the buffers used, and the ligand to displace, can all affect the binding results (82–84).

UPTAKE 1 vs UPTAKE 2 There are two different CA uptake processes in the peripheral nervous system. These have been studied in relation to NE (85). Uptake 1 is neuronal, has high affinity, is saturable and stereospecific, and requires that the cell be polarized. Uptake 1 is dependent on the presence of sodium and chloride ions. Uptake 2 is nonneuronal, has low affinity and is saturable; uptake 2 is not stereospecific, and is less dependent upon sodium than uptake 1 (30, 85–87). NE transported by uptake 2 is usually metabolized quickly; however, at high concentrations, some NE will accumulate in these nonneuronal sites (88).

With regard to the central dopaminergic system, there are also indications for more than one uptake transporter. Radioligand binding studies suggest that there are two DA transporter binding sites: a high-affinity, low-capacity site and a low-affinity, high-capacity site, each with different K_d and B_{max}

values (84, 89, 90). Binding studies also point to the existence of a Na^+-dependent and a Na^+-independent site (91). Animals with intact DA systems have Na^+-independent and Na^+-dependent cocaine binding, while in 6-hydroxydopamine (6-OHDA) lesioned animals, only cocaine binding, which is Na^+-independent, remains. This result has led the authors to conclude that in the CNS, a second cocaine binding site may exist on nondopaminergic terminals, cell bodies, or nonneural tissue (glia) (91).

Using the ligand WIN 35,065-2, other evidence suggests that while there are two DA uptake sites, both are Na^+-dependent (90). In addition, Ritz et al (90) reported that 6-OHDA lesions decreased both low- and high-affinity WIN 35,065-2 binding sites, suggesting that both high- and low-affinity sites are neuronal. Patel et al (92) found two binding sites on a single protein that is characteristic of the DA transporter and concluded that the multiple labeling of the transporter is due to the ligand interacting at different sites in close proximity on the same protein. It is at present difficult to determine whether results that indicate two binding sites for cocaine and other inhibitors of DA uptake refer to (*a*) neuronal vs nonneuronal uptake, (*b*) two different neuronal sites (i.e. different transmitter systems), (*c*) two different sites on the same terminal, or (*d*) two different conformational states of the same transporter.

Transmitter Storage

Evidence suggests that DA storage occurs in two pools in the nerve terminal: vesicular storage, which is dependent upon an inward proton pump and the maintenance of a low intravesicular pH; and cytoplasmic storage, which has neither of these requirements.

VESICULAR STORAGE The transporter used for uptake into storage vesicles differs in its functional requirements from the transporter embedded in the nerve cell membrane (see Figure 1). The mechanism for the transport of the amine across the vesicular membrane, and its subsequent retention in the vesicle, is made up of two components: a transporter for carrying the transmitter inside the vesicle, and an ATP, Mg^{++}- dependent proton pump that maintains an acid pH and electrochemical gradient across the vesicular membrane (93–95; Figure 1).

The maintenance of highly concentrated amine in the vesicle is dependent on several processes. Protons can be carried across the membrane by the hydrolysis of ATP in the presence of Mg^{++}, and this high concentration of protons within the vesicle maintains a low pH relative to the cytoplasm (5.6 vs 7.1, respectively) (94). The high proton concentration in vesicles also creates an electrochemical gradient with the inside of the vesicle positive

relative to the cytoplasm. Both the acidic environment and electrical gradient maintain the ability of the vesicle to store the amine. Amines in the cytoplasm are in a cationic form (NH^{3+}); they attach to the membrane transporter in neutral form (NH_2), and become protonated again within the acidic environment of the vesicle (94). The positive charge prevents diffusion of transmitter back across the lipid membrane of the vesicle within the cytoplasm. As the amine molecule is carried into the vesicle by the transporter, a proton is carried out of the vesicle by the vesicular transporter (93, 94).

Vesicular uptake mechanisms can therefore be summarized as follows. The vesicular membrane transporter carries amines into the vesicle in exchange for protons. This proton removal is balanced by the ATPase mechanism, which pumps protons back into the vesicle, to maintain the high acidic environment.

Reserpine and tetrabenazine block transport of amine into the vesicle by blocking the transporter (94, 96). Reserpine produces temporary amine depletions (97, 98), possibly by interfering with the replacement of amine in the storage vesicles after exocytotic release. However, this interpretation is only partially supported by results showing that ganglionic blocking agents (nicotinic receptor blockers) (99), as well as acute denervation (100), only partially diminish reserpine-induced depletion of peripheral NE. An alternate explanation of reserpine's depleting effects is suggested by Starne (see Ref. 101), who proposes that reserpine attaches to mitochondria and interferes with the ATP production essential for vesicular storage. Consistent with this view, Bonisch & Trendelenburg (75) assert that reserpine treatment causes leakage of amine from storage vesicles.

Other compounds, such as weak base amines, disrupt amine storage by alkalinization of the vesicle. As discussed below, certain drugs that enter amine-containing neurons may also enter the vesicle; in so doing they increase the pH inside the vesicle causing the release of transmitter into the cytoplasm (see below).

CYTOPLASMIC STORAGE Indirect evidence suggests that DA can also be stored in the cytoplasm of the nerve ending in addition to that stored in vesicles. Scheel-Kruger (102) and Braestrup (103) reported that DA-mediated (104) AMPH-induced behaviors are not blocked by reserpine pretreatment. These results point to the existence of a second nonvesicular, and reserpine-insensitive storage pool for DA within the nerve terminal. Using mathematical models of synaptosomal uptake experiments, Schoemaker & Nickolson (105) also concluded that DA storage within the nerve terminal exists both in the vesicles and in a cytoplasmic pool (newly synthesized pool) (see below). The existence of a releasable DA fraction in the nerve cell cytoplasm explains the actions of AMPHs and related compounds (see below).

NEUROPHARMACOLOGY OF AMPHETAMINE

Under normal physiological conditions, the amount of DA in the synapse is determined by exocytotic release followed by the process of uptake and some metabolic degradation (see above). In the presence of AMPH the amount of DA in the synapse is determined by transporter-mediated DA release, inhibition of DA uptake, release from vesicular storage into the cytoplasm, and finally by inhibition of monoamine oxidase (MAO) activity. There are two membrane transporters in the CNS where AMPH and related drugs may act to increase the concentrations of monoamine in the synapse (vesicular and cell membrane transporters). Since the effects of AMPH at the presynaptic terminal may be accounted for almost entirely by the physiology and pharmacology of membrane transporters, the inhibitory effects of AMPH on MAO are only discussed briefly (106). In the following sections we discuss AMPH's role as inhibitor of uptake and promoter of release, and describe these properties in terms of how AMPH interacts with both the cell and vesicular membranes.

AMPH Inhibits Monoamine Oxidase Activity

AMPH inhibits the oxidation of aliphatic amines in vitro when tissues are prepared from several sources including heart, liver, and brain (107, 108). The degree of in vitro inhibition of monoamine oxidase by AMPH depends upon the substrate used in the assay, and is competitive. Because many MAO substrates (including naturally occurring DA, NE, and serotonin) have higher affinity for the enzyme than AMPH, AMPH is considered to be a weak inhibitor of the enzyme in vitro (109, 110). The notion that AMPH has major effects upon MAO in vivo is tenuous. When AMPH was compared to iproniazid, an irreversible and noncompetitive inhibitor of MAO (111, 112), the changes in oxidative metabolites catalyzed by MAO were completely different between iproniazid and AMPH (113, 114). In spite of these early negative findings on in vivo inhibition of MAO by AMPH, later work has suggested that AMPH at relatively high doses may act as a competitive inhibitor in vivo for type A MAO (115, 116). The role of MAO inhibition in the expression of the pharmacological effects of AMPH, while not discounted, seems to occur at the high dose range, and does not seem as robust an effect as the effect of AMPH on amine transporters.

AMPH Blocks Uptake and Causes Release

We have discussed evidence that NE and DA can be taken up with high affinity by nerve cells in the autonomic nervous system and CNS. We will now discuss how AMPH may block this uptake as well as induce release of DA in interacting with the uptake transporter.

One of the first indications of carrier-mediated drug-induced CA release came from work with tyramine in the peripheral nervous system. In experiments using guinea pig atria Furchgott et al (117) introduced the concepts of transfer sites in the cell membrane. They found that the sympathomimetics tyramine and cocaine both caused increased sensitivity to the positive inotropic effects of NE (increased force of muscular contraction). However, they also found that cocaine inhibited the effects of tyramine. This "cocaine paradox" had been identified earlier (118), but Furchgott et al (117) refined the explanation. They reasoned that tyramine caused release of NE, whereas cocaine blocked the uptake of NE, as well as tyramine, through an active site on the nerve terminal. Furchgott et al referred to these sites as "transfer sites". The work of these researchers was important for several reasons. It distinguished between sympathomimetic drugs that acted as uptake inhibitors vs releasers (cocaine and tyramine, respectively). Further, it suggested that the sympathomimetic drugs and CNS stimulants exerted their effects by interacting with the cell membrane's uptake site.

AMPH is thought to increase concentrations of CAs in the synapse by inducing CA release, blocking CA uptake, or both (119). Evidence for this comes from both in vivo and in vitro studies (120–122). Similar to that seen with tyramine, AMPH-induced release of DA can be blocked by uptake inhibitors (24). From these types of experiments it soon became apparent that the conceptual distinctions between release and inhibition of uptake as they relate to drug action were important, but difficult to differentiate experimentally.

RELEASE AND UPTAKE INHIBITION ARE DIFFICULT TO DIFFERENTIATE EXPERIMENTALLY AMPH-induced changes in DA dynamics can be measured using either tissue slices or synaptosomal preparations suspended in an incubation medium (69, 123). However, it has been argued that it is difficult to discriminate release from uptake inhibition (124–126). For example, uptake inhibition experiments are built on the following premise: if a compound (such as AMPH) prevents the accumulation of [^{3}H] DA into the synaptosome or slice, then uptake of [^{3}H] DA is inhibited. This interpretation is confounded by the fact that a drug that blocks uptake *and* causes release may release some of the previously taken up [^{3}H] DA making it *appear* that there is an inhibition of uptake.

Heikkila et al (23) addressed this problem and convincingly demonstrated that, under certain conditions, uptake inhibitors can be distinguished from releasing drugs. These investigators found that cocaine blocked the accumulation of [^{3}H] DA into slices, but did not induce release in slices preincubated with [^{3}H] DA. For compounds that are releasers, it is more difficult to determine whether they are also uptake inhibitors. As discussed above, both release and uptake inhibition would inhibit "apparent" accumulation of [^{3}H]

transmitter inside the cell, and would therefore be further characterized as uptake inhibitors. Heikkila et al (23) showed that the releasing compounds potassium chloride and tyramine, both induced release (i.e. increased the amount of tritiated amine in the medium in preincubated preparations in a dose-dependent manner) and decreased uptake (i.e. blocked accumulation of tritiated amine from the medium into the synaptosome in a dose-dependent manner). They therefore argued that compounds that are primarily uptake inhibitors should interfere with uptake at doses that are distinctly lower than those required to induce release. If the uptake inhibition and release dose-response curves superimpose, then the compound could be regarded as a releaser with uptake inhibition properties. From these and other studies (see below), it appears that AMPH's role as an inhibitor of uptake may derive entirely from the fact that it temporarily competes with DA for access to the terminal via the uptake transporter. This view is supported by the relatively weak affinities (micromolar range) AMPH has for the uptake transporter in binding studies (127–129).

Further attempts to separate releasers from uptake inhibitors led to the development of the superfusion technique (125). The superfusion experiment rests on the premise that the rate of perfusion is too rapid to permit uptake of DA to occur, and any departure from the baseline during the perfusion is due to additional release. Synaptosomes or slices are incubated with tritiated DA and perfused at a rapid rate, which measures primarily the release of tritiated DA. The rate of accumulation of tritiated DA in the superfusates is a good estimator of the rate of DA release from synaptosomes. If a releasing drug such as AMPH is added to the preparation, the rate of tritiated DA release increases, but if an uptake blocker such as nomifensine is added, the rate of tritiated DA release into the superfusate does not change. Hence, these results strongly indicate that nomifensine is a pure DA uptake blocker, but AMPH causes release (24, 126). However, the issue of uptake inhibitor vs releaser is complicated by the findings of Raiteri et al (284) who argue that AMPH blocks uptake and causes release of DA, but only blocks uptake of NE (see also Ref. 23).

One can also discriminate between uptake inhibition and release using in vivo dialysis. In intact animals, the exocytotic release of transmitter occurs during cell firing; therefore, the increase in transmitter induced by uptake inhibition should be blocked by decreased cell firing. On the other hand, since transporter-mediated release is independent of exocytotic release (60), blockade of cell firing should not affect release from the cytoplasm. Nomikos et al (130) reported that increases in extracellular DA induced by cocaine, nomifensine, and bupropion are almost entirely eliminated by tetrodotoxin (TTX) (Na^+ channel blocker, which blocks the action potential, and therefore blocks impulse-dependent release), while increases in extracellular DA

induced by AMPH occur in the presence of tetrodotoxin. In a similar experiment, Westerink et al (131) found that in the presence of TTX, AMPH-induced DA release was 66% of AMPH-induced release without TTX. These results confirm that cocaine, nomifensine, and bupropion are uptake inhibitors, and not releasers, while AMPH is a releaser that acts independent of cell firing.

The in vitro and in vivo experiments described above allow us to determine whether a drug is a "pure" uptake inhibitor or not; however, we still have no definitive technique for determining whether a releaser is a "pure" releaser, or also an uptake inhibitor. As discussed by Heikkila et al (23), the fact that releasers probably compete with endogenous transmitter for transporter sites ensures that all releasers are also uptake inhibitors and to that extent the two processes are not separable. It is possible, however, that while releasers enter the neuron through the uptake carrier to induce release (see above), some molecules may adhere to the transporter and block uptake without entering the neuron. To our knowledge, no one has yet developed the methods to answer this question. In summary, uptake inhibitors block uptake and have no effect on release; releasers induce release and probably block uptake as well. This latter effect is probably due to the competition between releasing compound and DA for entry into the nerve terminal via the uptake transporter.

AMPH-INDUCED RELEASE IS INDEPENDENT OF CELL FIRING Early experiments using a push pull cannula (132) found that after electrolytic lesions of the nigrostriatal dopaminergic bundle, there was a substantial attenuation of the AMPH-induced DA release; these studies also showed that electrical stimulation of the nigrostriatal pathway increased AMPH-induced DA release. These results suggested that the efflux of DA was dependent on impulse activity along the nigrostriatal system. However, this interpretation is confounded by the fact that lesions that reduce the number of DA axon terminals would be expected to reduce AMPH-induced DA release independent of an effect on impulse flow. Also, in the stimulation experiments, it is unclear how the effects of stimulation and amphetamine combine to produce greater DA release since impulse activity was not measured. Furthermore, later experiments employing TTX, which blocks action potentials, suggest that AMPH-induced DA release is independent of impulse flow. Using in vivo dialysis, it was shown that the AMPH-induced DA release in the presence of TTX was 94% of that without TTX in one experiment (130), and 65% of that without TTX in another experiment (131). Furthermore, Carboni et al (58) showed that pretreatment with gamma-butyrolactone (an inhibitor of DA cell firing) failed to alter AMPH-induced DA release in vivo.

AMPH INTERACTIONS WITH THE CELL MEMBRANE As discussed above, the DA uptake transporter in the cell membrane appears to play a critical role in AMPH's ability to release DA. In this section we discuss the theory of exchange diffusion which attempts to describe the way in which AMPH interacts with the membrane transporter.

Exchange Diffusion Model Fisher & Cho (22) and Liang & Rutledge (133) have suggested that AMPH-induced release results from an exchange diffusion process in which AMPH attaches to the transporter on the outside of the cell membrane, thereby blocking DA transport from the outside to the inside. The transporter moves the attached AMPH from the outside to the inside of the neuron where it exchanges with DA; the DA transporter complex then reorients to the outside where DA is released; there is a net increase in DA outside the cell, and a net increase of AMPH inside the cell. Fisher & Cho (22) argue that while AMPH may enter the neuron both through the transporter as well as through passive diffusion, only the AMPH that enters via the transporter causes DA release; they suggest that DA can only exit the terminal when a transporter is made available by an incoming AMPH molecule.

Liang & Rutledge (133) provide a different version of the exchange diffusion theory. While they agree that AMPH may enter the neuron through both the transporter and through passive diffusion, they argue that both types of entries contribute to DA release. They develop the notion that once inside the terminal, AMPH displaces DA from vesicular stores into the cytoplasm, making more DA available for release. Since passive diffusion probably represents entry at higher concentrations, more AMPH is available inside the cell to displace stored DA, and lead to more release (see Figure 1). Whether or not the availability of transporter sites is rate-limiting as suggested by Fischer & Cho (22) and Michaelis-Menton kinetics (see next section) is yet to be determined.

Although the physical changes in the transporter in terms of its orientation toward the inside or outside of the membrane are not understood, certain of the chemical requirements for an exchange diffusion process are better understood.

Characteristics of AMPH-induced DA release AMPH-induced DA release from synaptosomes has the same physical characteristics as the uptake of DA into the nerve terminal. AMPH-induced DA release shows saturation kinetics, is temperature- and sodium-dependent, and shows stereoselectivity, with the dextro isomer of AMPH being more potent at releasing DA than the levo isomer (22, 134). In addition, some compounds that block the uptake of DA into the neuron also attenuate AMPH-induced release of DA (22, 24, 60,

135–137). These characteristics of AMPH-induced DA release are consistent with exchange diffusion theory.

Characteristics of uptake of AMPH into synaptosomes Similar to the uptake of DA, Zaczek et al (138) found that the uptake of AMPH is an active transport process. It follows saturation kinetics, is Na^+-dependent, shows stereospecificity, but may (138) or may not (139) be temperature-dependent. In addition, Zaczek et al (140, 141) reported a process in which AMPH is sequestered into synaptosomes with lower affinity. Under conditions of sequestration, [^{3}H] AMPH is taken up into synaptosomes, but this process is disrupted by procedures that disrupt the synaptosomal membrane itself (sonication, hypotonic media, and digitonin), and is not stereospecific. The authors draw a parallel between their results and the low- and high-concentration effects of AMPH on DA release (22) : low-concentration effects of AMPH reflect transport, while high-concentration effects of AMPH reflect sequestration.

One problem with exchange diffusion
AMPH uses for making DA available for transport out of the cell. As discussed above, the low Na^+ concentration inside the nerve terminal may prevent DA from binding to the transporter, thereby preventing DA's return to the outside of the cell (74); in fact, the low Na^+ concentration may promote the dissociation of the DA/transporter complex. According to exchange diffusion theory, AMPH-induced DA release occurs through reversal of the uptake transporter, but the evidence in favor of this hypothesis is indirect (see above). Although the transporter can be reversed by inverting the usual Na^+ gradient (24, 35), the manner in which AMPH reverses the transporter is unknown.

AMPH RELEASES DA FROM NONVESICULAR AND VESICULAR STORES[1] There is evidence that AMPH releases DA from nonvesicular stores. AMPH in rats induces a dose-dependent behavioral syndrome beginning with locomotion, sniffing, and rearing at low doses, and ending with focused intense licking and gnawing at higher doses (14, 102). These AMPH-induced behaviors are inhibited by blockade of DA synthesis with the tyrosine hydroxylase inhibitor, alpha methyl-para tyrosine (AMPT), but not by reserpine, suggesting that the effects of AMPH are mediated by a nonvesicular newly synthesized pool of DA (14, 102, 103, 142–145). Furthermore, AMPH-induced DA release from newly synthesized stores was demonstrated by the use of tritiated tyrosine in vitro. It was shown that more tritiated DA was released by AMPH early in

[1]Material in this section appeared in part in Sabol, K. E., Seiden, L. S. 1992. Transporters of delight. *Curr. Biol.* 2:414–16

the tyrosine infusion than was released latter in the infusion; furthermore, the total amount of tritiated DA in the tissue was constant throughout the infusion. These results can be interpreted to mean that early in the infusion cytoplasmic DA did not have time to equilibrate with vesicular stores and more was available for release. As the two pools became more homogeneous in terms of tritiated DA, a smaller amount of tritiated DA was available for release by AMPH (146–148). Consistent with these results, AMPT but not reserpine blocks AMPH-induced release of DA in vivo (135, 149). In addition, Chiueh & Moore (150) present evidence that newly synthesized DA is important for AMPH's action; however, they also suggest that DA from vesicular storage contributes to AMPH-induced DA release.

Evidence indicating that AMPH releases DA from vesicular stores comes from Parker & Cubeddu (137). These investigators have shown that AMPH releases less DA from brain slices taken from rabbits pretreated with reserpine than from slices taken from control animals. These results indicate that AMPH-induced DA release is, at least in part, dependent upon the vesicular storage pool (disrupted by reserpine). Based on these and similar findings (151), Parker & Cubeddu proposed that AMPH releases DA from a cytoplasmic storage pool that is supplied both by newly synthesized DA and by the vesicular storage pool. Movement from vesicular storage into the cytoplasmic pool is both spontaneous and drug-induced. Consistent with this view are previous reports that AMPH interacts with the storage vesicle membrane. It blocks the uptake of NE (152, 153) and DA (153, 154) into synaptic vesicles.

As discussed above, a pH gradient is maintained across the vesicular membrane (94, 155). Weak base amines such as ammonia and tyramine alkalinize the amine storage vesicles (93). AMPH, also a weak base, causes alkalinization of storage vesicles (156). AMPH increases alkalinization of (*a*) intraneuronal compartments in cultured ventral tegmental area (VTA) neurons, and (*b*) chromaffin granule ghosts (organelles with the same membrane transporter that exists on the intraneuronal storage vesicle (93)). Reserpine does not block AMPH-induced alkalinization; nor is AMPH-induced alkalinization stereospecific. Finally, AMPH induces the release of [^{3}H] serotonin from chromaffin granules from adrenal medulla (156).

The results of this series of experiments indicates that AMPH causes release of transmitter from the intracellular storage vesicles; this release can be linked to alkalinization of the storage vesicles. To alter the pH of the vesicle, AMPH probably enters the vesicle through diffusion since (*a*) reserpine does not block AMPH-induced alkalinization, and (*b*) both the D and L isomers of AMPH are similar in their ability to alter the proton gradient across the storage vesicle membrane.

In addition to the effect of AMPH on the pH of the vesicular storage compartment, other AMPH-like compounds are capable of a direct interaction

with the vesicular transporter. Rudnick & Wall (157) reported that methylenedioxymethamphetamine (MDMA) inhibits the uptake of serotonin into the chromaffin granules, as well as facilitates the release of serotonin from the chromaffin granules; both of these results were stereospecific, with the + isomer more potent than the – isomer. As mentioned above, the chromaffin granules are the experimental model for studying intraneuronal storage vesicles. Rudnick & Wall also evaluated the effects of MDMA on the pH gradient maintained across the chromaffin granule membrane. They found a concentration-dependent dissipation of this gradient that was not stereospecific; however, the concentration required to dissipate the pH gradient was greater than that needed to block uptake and induce release from the chromaffin granule. It can be concluded that MDMA interacts with the storage vesicle membrane in two ways. At low concentrations, it blocks uptake into and facilitates release from the vesicle by direct interaction with the serotonin carrier. At high concentrations, MDMA causes release by dissipating the pH gradient. Because the disruption of the pH gradient lacks stereospecificity, MDMA probably enters the storage vesicles by diffusion across the vesicular membrane at these concentrations. Similar findings were reported using the AMPH-like compound para-chloroamphetamine (158).

With both AMPH and MDMA, therefore, it appears that one mechanism of drug-induced transmitter release from storage vesicles into the cytoplasm occurs through dissipation of the pH gradient. This relies on high concentrations of either compound entering the vesicle through diffusion (156, 157). At intermediate doses, AMPH-like compounds may disrupt transmitter storage in vesicles by direct interaction with the transporter on the vesicular membrane (see Figure 1).

One difficulty with the weak base explanation of AMPH-vesicle interactions is that neurotransmitters themselves are weak bases, and yet are much less potent in inducing alkalinization of the chromaffin granules. Based only on this characteristic, one would expect serotonin to be more potent in altering the pH gradient than AMPH. As discussed by Sulzer & Rayport (156), however, other factors such as lipophilicity, binding to intravesicular constituents, and interactions with membrane-uptake systems may be responsible for the differences in alkalinization observed with the different amines.

INTEGRATION OF EXCHANGE DIFFUSION WITH VESICULAR ALKALINIZATION: DIFFERENTIAL DOSE THEORY[2] The differences between two sets of data described in the literature are difficult to reconcile. On the one hand, AMPH-induced behaviors are not blocked by reserpine, indicating that

[2]Material in this section appeared in part in Sabol, K. E., Seiden, L. S. 1992. Transporters of delight. *Curr. Biol.* 2:414–16

functional AMPH-induced DA release is independent of DA stored in vesicles (102). On the other hand, experiments with in vitro slices (137) and chromaffin granules (156, 157) indicate that AMPH and MDMA are capable of releasing transmitter stored in these intracellular vesicles. These apparently contradictory results may be attributable to the concentrations/doses of AMPH used. Rudnick & Wall (157), and Sulzer & Rayport (156) both reported that the effects of the AMPH-like compounds on release are concentration-dependent. Although the assays were different, and may not be directly comparable, Rudnick & Wall found that the concentrations required to release serotonin from the cell membrane preparation were smaller than those required to release serotonin from the vesicular membrane preparation. In the behavioral assessment experiments discussed above (102, 103), the AMPH doses used to induce stereotypic locomotion and intense stereotypic licking, biting, and gnawing may correspond to those concentrations of AMPH that only release DA across the cell membrane in vitro (1–5mg/kg; see Figure 1, panel B).

At moderate and high doses (above 5 mg/kg; see Figure 1, panels C & D), AMPH-induced DA release uses both vesicular and cytoplasmic stores. As previously suggested (159), low doses of AMPH may release cytoplasmic stores of DA while high doses release both the cytoplasmic and vesicular pools of DA. Further support of this theory comes from the work of Liang & Rutledge (133). These authors suggested that low doses of AMPH enter the neuron through the exchange diffusion process causing DA to leave the terminal in the exchange. At higher doses, when the transporters are saturated, AMPH is more likely to enter the neuron through passive diffusion, and cause release by displacing DA from vesicular storage into the cytoplasm. Kuzcinski (20) also suggested that AMPH disrupts vesicular storage. Similarly, Zaczek et al (138) suggested that there are two processes of AMPH uptake, corresponding to low- and high-dose effects of the drug. The low-dose process is a high-affinity active transport process, and the high-dose uptake refers to a sequestration process (see above).

Based on the papers reviewed here, a working model of the mechanism by which AMPH releases DA is depicted in Figure 1. At low doses (1–5 mg/kg), AMPH enters the neuron and releases DA through exchange diffusion (see Figure 1, panel B). AMPH makes DA available for this exchange by displacing it from cytoplasmic storage. Low-dose (1–5 mg/kg) DA release induces stereotypic locomotion and oral movements. The release of DA is derived from newly synthesized DA since both the DA release and behavioral effects can be blocked by AMPT. At higher doses, (>5 mg/kg), AMPH enters the neuron through the transporter and passive diffusion. At these concentrations, AMPH is more likely to enter the storage vesicles (see Figure 1, panel C). Initially, this effect is mediated through the vesicle-uptake transporter; as doses further increase, AMPH crosses this second lipid membrane by passive

diffusion. With sufficient AMPH entry into the vesicle, alkalinization of the vesicle results in further release of vesicular stores into the cytoplasm of the cell (see Figure 1, panel D). One assumption made with this model is that at low doses of AMPH the drug is removed from the neuron (back out through the uptake carrier, perhaps) before a significant amount can enter the vesicle and cause release of DA into the cytoplasm (see Figure 1).

In vivo dialysis data documenting DA release from the striatum, support this theory (160). When four successive injections of 4.0 mg/kg of meth-AMPH were administered to rats at 2-hr intervals, small increases in DA were seen after the first three injections; however, the fourth injection induced a very large increase in DA. This result suggests that the fourth injection in the sequence recruited a second pool of DA for release. According to the theory proposed above, this would be the vesicular storage pool.

AMPHETAMINE AND BEHAVIOR

In the first part of this chapter we reviewed the cellular mechanisms of AMPH's action on the catecholamine systems. In so doing, we developed some concepts in depth that we felt were important to our understanding of AMPH's mechanisms of action. This has been the primary emphasis of the chapter. In the second part of this chapter we will review AMPH's effects on behavior. This review is not meant to be exhaustive, but a survey of the behavioral effects of AMPH. Since each area is sufficiently large and complex as to warrant a review of its own, our intent is to direct the reader to papers and reviews that have dealt with complex and controversial issues.

AMPH has Wide-Ranging Effects on Behavior

The diversity of human behavioral effects engendered by AMPH has led to detailed research on the effects of AMPH in animals. AMPH research in both animals and humans has implicated a role for either DA, NE or both in behavioral disorders, including schizophrenia (161–163) and obesity (7, 10), as well as in the mediation of the rewarding aspects of drugs of abuse (164, 165). AMPH has profound effects on a wide range of physiological and behavioral processes: motor activity (102, 143, 166–168); ingestive behavior (169–173); sleep (174–177); attention (178, 179); aggression (180–182); sexual behavior (183); learning and memory (184–187); classical conditioning (188); and operant behavior (189–191). In addition, AMPH affects sensory modalities as evidenced by its ability to serve as a discriminative stimulus (50). The ability of AMPH to serve as a reinforcer in self-administration paradigms probably accounts for and predicts its abuse liability in humans (192–194). (For detailed reviews of the behavioral effects of AMPH see 17, 166, 169, 190, 195–199.)

AMPH Is Used as a Therapeutic Agent as Well as a Drug of Abuse in Humans

AMPH AS AN APPETITE SUPPRESSANT AMPH reduces appetite and food intake in humans (7, 200), and has been used as an adjunct to dieting for the treatment of obesity. When given daily for several days, AMPH causes a loss in body weight in both obese and nonobese humans and dogs. Since there is no evidence that AMPH alters metabolism, the decrease in body weight is attributed to reduced food intake, caused by a decrease in appetite (201, 202). The AMPH reductions in food intake often dissipate shortly after the drug is initiated and the dose needs to be escalated. In addition, in some individuals the euphoria engendered by AMPH increases the risk that these individuals will become AMPH-dependent (7). Although AMPH is a short-term (i.e. 10–14 days) anorectic agent, it has the risk of tolerance and dependence.

AMPH AS A TREATMENT FOR ATTENTIONAL-DEFICIT HYPERACTIVE DISORDER AMPH is useful in treating children suffering from attentional-deficit hyperactive disorder (ADHD). These children (and occasionally adults) are hyperkinetic and have difficulty focusing their attention for prolonged periods of time. ADHD is associated with learning impairments and inappropriate social behavior (8, 203). Since AMPH increases locomotion in animals and frequently decreases attention in normal children and adults, the effects of AMPH on ADHD are often referred to as paradoxical (204). However, as discussed below, when viewed in relation to its effects in experimental animals, the effects of AMPH in the treatment of ADHD are consistent with a broader interpretation of its mechanism of action (199, 205).

AMPH AS A DRUG OF ABUSE The amphetamines are widely abused by humans (10, 206–208). AMPH users have been known to self-administer as much as a 500–1000 mg within 24 hr (13, 193, 209). Large doses of AMPH lead to stereotypic motor activity in humans, such as compulsive cleaning and grooming, sorting, and disassembling objects (12). Individuals self-administering such high doses of AMPH eat and sleep less while they are taking AMPH (12, 176, 193). Upon discontinuing AMPH, characteristic signs of withdrawal include periods of depression and hypersomnolence (11, 210).

AMPH PSYCHOSIS AMPH psychosis occurs in two forms: toxic psychosis, which usually occurs after a single large dose, is characterized by confusion and disorientation; and repeated-use psychosis, which is considered to resemble schizophrenia. AMPH psychosis with chronic use can occur after

continuous high-dose use (500–1000 mg/day) (13), or after lower-dose use (0.3–1.2 mg/kg, or 20–80 mg/day) (197), and is characterized by increased activity, repetitive and compulsive behavior, social withdrawal, delusions, and paranoia (13, 209, 211, 212). AMPH psychosis after chronic use may be accompanied by auditory hallucinations; although visual hallucinations have been seen with AMPH psychosis it is usually seen only in the acute toxic form (209, 213). Both the toxic and repeated-use AMPH psychoses clear after withdrawal of AMPH.

Snyder (214) points out the similarities and differences between AMPH psychosis and schizophrenia. The two conditions are considered similar because (*a*) chronic AMPH abusers are often misdiagnosed as schizophrenics; (b) both conditions respond to treatment with antipsychotic drugs; (*c*) AMPH will often heighten psychotic symptoms in schizophrenic patients; and (*d*) both conditions have auditory hallucinations, delusions, and paranoia. The two conditions are different because (*a*) schizophrenic patients demonstrate a diminished affect, while the altered affect of chronic AMPH users is not considered to be diminished or flattened; (*b*) the "formal thought disorder" characteristic of schizophrenia is absent in AMPH psychosis; (*c*) AMPH psychosis is characterized by stereotypic motor behaviors whereas schizophrenia is not. Although Snyder (214) asserts that schizophrenia is not characterized by stereotypies, Ellinwood et al (215), and Ellinwood & Sudilovsky (12) argue that schizophrenic patients demonstrate stereotyped behavioral or thought patterns. According to Freedman & Kaplan (216), stereotyped behavior is seen in schizophrenia, but it is not invariably associated with the disease (217).

AMPH IN THE TREATMENT OF NARCOLEPSY AMPH has been used in the treatment of narcolepsy (218, 219). The cause of narcolepsy is not known, but is characterized by sleep attacks, usually lasting for about 15 min, loss of muscle tone, and difficulty in voluntary motion during the transition from sleep to waking during a sleep attack. Hypnagogic hallucinations also occur, with rapid eye movements and reduced muscle tone (220). People suffering from narcolepsy often fall asleep at inappropriate times. AMPH can ward off sleepiness and the loss of alertness. However, narcoleptic patients taking AMPH, as a treatment, may use up to 200 mg per day and become dependent on its mood-elevating effects. Furthermore, these large doses of AMPH can interfere with sleep during the normal sleep cycle and cause unwanted side effects such as sleep deprivation, weight loss due to anorexia, hypertension, irritability, and occasionally, AMPH-induced psychosis (218, 219). AMPH also decreases the total amount of rapid eye movement (REM) sleep in normal humans during a normal night sleep cycle (177). The REM-like features of narcolepsy, and the possible involvement of catecholamines in REM sleep

(221), make catecholamine release a possible mechanism for the effects of AMPH in the treatment of narcolepsy.

Effects of AMPH on Animal Behavior Parallel the Effects Seen in Humans

AMPH REDUCES FOOD INTAKE AMPH decreases food intake in rats with free access to food and water, and in rats with restricted access to food (16). However, there is evidence for an interaction between the decrease in food intake caused by AMPH and the condition of food availability (15). In addition to food intake, AMPH interferes with water consumption in rats. Repeated administration of AMPH results in the development of tolerance to both the anorexic and adipsic effects of AMPH (222, 223). Regions of the hypothalamus have been considered to play a key role in the regulation of food intake (169, 224–227) and therefore the way in which AMPH effects hypothalamic nuclei, especially with respect to NE and DA, are of considerable interest (see Ref. 40).

AMPH DECREASES ACTIVITY IN HYPERACTIVE RATS Under most circumstances AMPH increases locomotion and other types of species-specific behavior. However, rats depleted of DA by 6-OHDA as neonates become hyperactive throughout their life span; when the hyperactive (DA-depleted) rat is treated with AMPH as an adult, the locomotor activity of the rat is decreased (228–231). This effect in hyperactive rats parallels the AMPH-induced decrease in hyperactivity observed in patients with attentional-deficit hyperactive disorder (ADHD). The AMPH-induced decrease in hyperactivity in this rat model, as well as in patients with ADHD, seems paradoxical. As discussed below, AMPH's effects are related to baseline levels of a particular behavior. For low-rate behaviors, AMPH increases their occurrence, for high-rate behaviors, AMPH decreases their occurrence. Patients suffering from ADHD, as well as the neonatal DA-depleted rat model, may fall into this latter category.

The hyperactive rat model is induced by neonatal DA depletions (6-OHDA), but no known DA deficiency exists in the human patient with ADHD. Furthermore, the effects of AMPH on hyperactivity induced by the neonatal DA depletions appear to be related to the serotonin system (232). Again there is little evidence regarding this point in humans. Therefore, the neurochemical basis for ADHD and AMPH's treatment of this condition remains unknown.

AMPH SELF-ADMINISTRATION AND DRUG DISCRIMINATION PARADIGMS Drugs self-adminstered by humans are also self-administered by laboratory animals. The animal self-administration test has become a standard benchmark for

determining the abuse potential of drugs (194, 233). The pattern of self-administration in animals is often similar to that of humans when using the i.v. route of injection (234–236). When the drug unit dose in animals is small, AMPH is self-administered at a high rate, particularly if the opportunity for self-administration is limited (234, 237). When the unit dose is high or access is unlimited, monkeys self-administer AMPH in a cyclic pattern (236–238). A large amount of drug is administered over a short period of time followed by cessation of administration for a time, after which the administration pattern is repeated. These cyclic episodes can continue for several days (237). This cyclic pattern has been identified in human AMPH abusers in the field (193).

Another paradigm used in animals to assess the subjective effects of drugs is drug discrimination. In a two-lever operant chamber, the animal is trained to press one lever for food after saline pretreatment, and the second lever for food after AMPH pretreatment. Animals learn to press the appropriate lever, which indicates that there is an internal state (i.e. discrimination) associated with AMPH vs saline. When the animal learns the discrimination, different drugs may be used to determine whether the test drug substitutes for saline or AMPH. A large number of stimulant-like drugs of abuse, such as cocaine and meth-AMPH, substitute for AMPH in this paradigm. (239–243).

Treatment with DA antagonists as well as lesioning of the DA system both attenuate the self-administration of AMPH and drugs that substitute for AMPH in the self-administration paradigm (244). Furthermore, DA antagonists and lesions of the DA system can interfere with the acquisition and maintenance of drug discrimination when one is considering saline vs AMPH.

AMPH-INDUCED STEREOTYPIES AS AN ANIMAL MODEL FOR SCHIZOPHRENIA As discussed above, both AMPH psychosis and schizophrenia in humans have behavioral and biochemical similarities (13, 215). Accordingly, it was demonstrated that AMPH-induced stereotypic behaviors in rats can be blocked by the same drugs that are successful in the treatment of schizophrenia (245, 246). Human users of amphetamines sometimes develop psychosis with a single dose after a period of abstinence (247); that is, sensitization to the drug appears to develop after chronic use. Behavioral sensitization also develops in rats given chronic, intermittent AMPH treatment (see 197, 248–250). Because of the behavioral and biochemical similarities between schizophrenia and chronic AMPH psychosis in humans (see above), the behavioral sensitization model of chronic AMPH treatment is considered a useful animal model of schizophrenia (215, 251).

The compounds used as antipsychotic agents usually fall into the category of dopaminergic postsynaptic receptor blockers (161, 252, 253). Since antipsychotic compounds block both schizophrenic symptoms in humans as

well as AMPH-induced stereotypies in animals, both syndromes are thought to have a common neurochemical basis: overactivity of the dopaminergic system (254). Further evidence that AMPH-induced stereotypies are dependent upon an intact dopaminergic system comes from the work of Creese & Iversen (104). Lesions of the ascending DA systems, but not the NE systems, inhibit AMPH-induced locomotor and oral stereotypies. DA theories of schizophrenia have been widely reviewed (162, 163, 197).

AMPH ACTS AS A SYMPATHOMIMETIC AMPH affects all major systems in the sympathetic nervous system. It causes an increase in blood pressure by augmenting cardiac output and causing vasoconstriction. AMPH also causes dilation of the pupils and stimulates piloerection. AMPH stimulates respiratory rate through its actions on the brain-stem (4, 5, 68, 169).

Experimental Analysis of the Behavioral Effects of AMPH in Animals

AMPH STIMULATES STEREOTYPIC BEHAVIORS Considerable efforts have been made to understand the mechanisms that underlie AMPH-induced stereotypies (102, 166, 255, 256). Low doses of AMPH are said to increase locomotion, while higher doses induce stereotypy, i.e. implying that low doses of AMPH do not induce stereotyped behavior while high doses do. As Rebec & Bashore (256) point out, however, it is inaccurate to make this kind of dichotomy. They maintain that the term stereotypic behavior applies to both the repetitive locomotion associated with low doses of AMPH, as well as the repetitive oral movements associated with high doses of AMPH. In other words, both the locomotor effects of low doses of AMPH and the intense oral movements seen with high doses of AMPH are stereotypic in nature.

This distinction can be clarified by looking at the theory of AMPH's behavioral mechanism of action presented by Lyon & Robbins (166). These investigators describe the effects of AMPH on behavior in a manner that is consistent with the view presented by Rebec & Bashore (256). According to Lyon & Robbins (166), the effects of AMPH are dose-dependent, with increasing doses causing shorter and shorter duration behaviors to occur. Low doses of AMPH cause an increase in all types of behavior. With increasing doses of the drug, smaller duration behavioral sequences are emitted, while longer duration behavioral sequences (such as locomotion) are truncated. With high doses of AMPH many behaviors may be initiated, but only those of short duration, such as licking and gnawing, are completed. From this perspective, it is inappropriate to view AMPH's effects on behavior as a strict dichotomy between locomotion and stereotyped oral movements. With this distinction in

mind, we continue with our discussion of AMPH's motor effects by focussing on the stereotyped locomotor vs stereotyped oral movements most frequently described in the literature.

NEUROANATOMICAL SUBSTRATES OF STEREOTYPED LOCOMOTION VS ORAL MOVEMENTS While on the one hand there is a dose-related difference in the topography of responses produced by AMPH, there are also different neuroanatomical substrates that can mediate the different behavioral responses induced by AMPH. After selective 6-OHDA lesions of striatum, AMPH-induced nonlocomotor stereotypy is decreased whereas AMPH-induced stereotyped locomotion is increased relative to controls (257–259). Further, selective 6-OHDA lesions of the nucleus accumbens decrease AMPH-induced locomotion, sniffing, and rearing (259, 260). These results suggest that nucleus accumbens mediates AMPH-induced locomotion, and striatum mediates AMPH-induced oral movements. Consistent with these results, direct injections of AMPH into the nucleus accumbens induces locomotion (261). Although the data discussed here strongly support a role for the nucleus accumbens in the mediation of AMPH-induced locomotion, other anterior forebrain regions have also been implicated (see Ref. 262). AMPH injections into striatum induced oral stereotypies (263, 264) or failed to induce oral stereotypies (licking, biting, and gnawing) (265). This discrepancy may relate to the specific site of AMPH injection within striatum: Kelley et al (266) have recently reported that ventrolateral striatum is important for AMPH-induced oral movements.

RATE DEPENDENCY AND OPERANT BEHAVIOR Given that AMPH has effects on both consummatory behavior and motor function, it is not surprising that AMPH has effects on operant behaviors in animals where the rate and pattern of responding are controlled by schedules of negative and positive reinforcement. When AMPH is administered in low doses to rats pressing on low fixed ratio (FR) schedules of reinforcement, the response rate tends not to change. At higher doses the response rate decreases (190, 199, 205, 267, 268). On very high FR schedules, low doses of AMPH induce an increase in response rate. Consistent with the Lyon & Robbins theory discussed above, this AMPH-induced increase in response rate has been accounted for by the elimination of pauses that occur to a large extent on high ratio schedules (205). The effects of AMPH on fixed interval (FI) responding are complex insofar as the low rates in the beginning of the interval are increased and the high rates at the end of the interval are decreased (190, 199, 267–269). The effects of AMPH on FR and FI behavior led to the "rate-dependency" theory of AMPH action. Simply put, rate-dependency asserted that the effects of AMPH depend on the predrug response rate: low baseline response rates are

increased by AMPH, and high baseline response rates are decreased by AMPH (190, 199, 267, 270). Rate-dependency theory, in regard to both the behavioral effects of AMPH as well as its underlying drug and neurochemical interactions, has generated interesting research and theory over the years (198, 271, 272).

AMPH has marked effects on the differential reinforcement of low-rate behavior (DRL) schedule (273, 274). Consistent with rate-dependency theory, predrug DRL response rates are low, and AMPH causes them to increase.

AMPH increases the rate of lever pressing in a nondiscriminated continuous avoidance situation. Since the response requirements for avoiding shock engender a low rate of responding, the effect of AMPH on this schedule is consistent with rate-dependency theory (275–278). In operant schedules with a punished component, AMPH does not increase responding that has been suppressed by shock (279–283). Since the baseline rate of responding suppressed by shock is low, these results are not consistent with rate-dependency theory.

INTEGRATION OF RATE-DEPENDENCY WITH LYON AND ROBBINS THEORY OF AMPH Rate-dependency offers a description of AMPH's effects on operant behavior, i.e. high rate responding is reduced while low rate responding is increased by AMPH. Rate-dependency describes the effects of AMPH on operant performance in most cases.

The observations of rate-dependency on operant performance are consistent with the interpretations of AMPH's effects on behavior presented by Lyon & Robbins (166). As previously discussed, these authors (166) argued that increasing doses of AMPH cause shorter and shorter duration behaviors to occur. Many longer duration behaviors are initiated, but may be truncated before they come to completion. In this regard, a rat performing an operant task after AMPH treatment may touch the lever repeatedly, but fail to depress it, decreasing the rate of recorded lever presses. Their interpretation (166) of this decrease in response rate would be that the rat was unable to complete responses that may have in fact resulted in an increase in response rate had they all been successful switch closures.

A second explanation of AMPH's effects consistent with rate-dependency suggests that with AMPH treatment, there is an increased occurrence of behaviors in direct competition with the operant response (198). The competing behavior (such as stereotypic licking and gnawing) increases in rate, causing the operant response to decrease in rate.

So, although rate-dependency may accurately describe the pattern of switch closures (completed bar presses) the rat makes under AMPH treatment, a more complete consideration of response topography is required in order to adequately understand the animal's behavioral response to AMPH.

CONCLUSION

Since the initial discovery of amphetamine in 1887, much has been learned regarding its cellular mechanisms of action. Further, insights into the cellular and behavioral actions of amphetamine contributed to important advances in our understanding of endogenous catecholamines (CAs): (*a*) CAs are compartmentalized in at least two different pools within the nerve ending; (*b*) CAs interact with neuronal transporters located on nerve endings as well as on synaptic vesicles; (*c*) CA projections to one area of the brain (e.g. striatum) may be differently regulated than those projecting to other brain regions (e.g. nucleus accumbens; (*d*) CAs play a role in a variety of normal functions of the peripheral sympathetic and central nervous systems; (*e*) CAs are involved in a number of disease states (schizophrenia, feeding disorders, etc).

Despite these advances, several gaps remain in our understanding of the molecular mechanisms of amphetamine. However, a fuller understanding of AMPH neuropharmacology will surely emerge as more is learned regarding the following areas: (*a*) the mode of entry of amphetamine into CA neurons; (*b*) the molecular biology of transporter interactions with amphetamine and CAs; (*c*) the relation between the CA transporters on nerve endings and synaptic vesicles; (*d*) the interaction between the cytoplasmic and vesicular pools of CAs in the nerve ending; (*e*) the role of other neurotransmitter systems in the behavioral effects of amphetamine; and (*f*) the precise relation between amphetamine's neurochemical and behavioral effects.

Literature Cited

1. Axelrod, J. 1970. Amphetamine: metabolism, physiological disposition and its effects on catecholarmine storage. In *Int. Symp. Amphetamines and Related Compounds,* ed. E. Costa, S. Garattini, pp. 207–16. New York: Raven
2. Edeleano, L. 1887. Uber einige Derivate der Phenylmethacrylsaure und der Phenylisobuttersaure. *Berl. Dtsch. Chem. Ges.* 20:616–22
3. Alles, G. A. 1933. The comparative physiological actions of dl-beta-phenylisopropylamines. I. Pressor effect and toxicity. *J. Pharmacol. Exp. Ther.* 47:339–54
4. Alles, G. A., Prinzmetal, M. 1933. The comparative physiological actions of dl-beta-phenylisopropylamines. II. Bronchial effect. *J. Pharmacol. Exp. Ther.* 48:161–74
5. Piness, G., Miller, H., Alles, G. A. 1930. Clinical observations on phenylaminoethanol sulphate. *J. Am. Med. Assoc.* 94:790–91
6. Prinzmetal, M., Bloomberg, W. 1935. The use of benzedrine for the treatment of narcolepsy. *J. Am. Med. Assoc.* 105:2051–54
7. Ersner, J. S. 1940. The treatment of obesity due to dietary indiscretion (overeating) with benzedrine sulfate. *Endocrinology* 27:776–80
8. Whalen, C. K., Henker, B. 1980. The social ecology of psychostimulant treatment: a model for conceptual and empirical analysis. In *Hyperactive Children,* ed. C. K. Whalen, B. Henker. New York: Academic
9. Hornykiewicz, O. 1966. Dopamine (3-hydroxytyramine) and brain function. *Pharmacol. Rev.* 18:925–64
10. Knapp, P. H. 1952. Amphetamine and addiction. *J. Nerv. Ment. Dis.* 115:406–32
11. Angrist, B. M., Shopsin, B., Gershon,

S. 1971. Comparative psychotomimetic effects of stereoisomers of amphetamine. *Nature* 234:152–53
12. Ellinwood, E. H., Sudilovsky, A. 1973. Chronic amphetamine intoxication: behaviorial model of psychoses. In *Psychopathology and Psychopharmacology*, ed. J. O. Cole, A. M. Freedman, A. J. Friedhoff, pp. 51–70. Baltimore: John Hopkins Press
13. Snyder, S. H., Banerjee, S. P., Yamamura, H. I., Greenberg, D. 1974. Drugs, neurotransmitters, and schizophrenia. *Science* 184:1243–53
14. Randrup, A., Munkvad, I., Udsen, P. 1963. Adrenergic mechanisms and amphetamine induced abnormal behaviour. *Acta Pharmacol. Toxicol.* 20: 145–57
15. Cole, S. O. 1963. Interaction of amphetamine with conditions of food deprivation. *Psychol. Rep.* 13:387–90
16. Spengler, J., Waser, P. G. 1959. Influence of various drugs on food consumption of albino rats in acute experiments. *Arch. Exp. Pathol. Pharmakol.* 237:171–85
17. Groves, P. M., Rebec, G. V. 1976. Biochemistry and behavior: some central actions of amphetamine and antipsychotic drugs. *Annu. Rev. Psychol.* 27:91–127
18. Axelrod, J. 1972. Biogenic amines and their impact in psychiatry. *Semin. Psychiatry* 4:199–210
19. Moore, K. E. 1978. Amphetamines: biochemical and behavioral actions in animals. In *Handbook of Psychopharmacology*, ed. L. L. Iversen, S. D. Iversen, S. H. Snyder, pp. 41–98. New York: Plenum
20. Kuczenski, R. 1983. Biochemical actions of amphetamine and other stimulants. In *Stimulants: Neurochemical, Behavioral, and Clinical Perspectives*, ed. I. Creese, pp. 31–61. New York: Raven
21. Leake, C. D. 1958. *The Amphetamines*. Toronto, Canada: Ryerson. 167 pp.
22. Fischer, J. F., Cho, A. K. 1979. Chemical release of dopamine from striatal homogenates: evidence for an exchange diffusion model. *J. Pharmacol. Exp. Ther.* 208:203–9
23. Heikkila, R. E., Orlansky, H., Cohen, G. 1975. Studies on the distinction between uptake inhibition and release of (^{3}H)dopamine in rat brain tissue slices. *Biochem. Pharmacol.* 24:847–52
24. Raiteri, M., Cerrito, F., Cervoni, A. M., Levi, G. 1979. Dopamine can be released by two mechanisms differentially affected by the dopamine transport inhibitor nomifensine. *J. Pharmacol. Exp. Ther.* 208:195–202
25. Burn, J. H. 1932. The action of tyramine and ephedrine. *J. Pharmacol. Exp. Ther.* 46:75–95
26. Axelrod, J., Weil-Malherbe, H., Tomchick, R. 1959. The physiological disposition of H3-epinephrine and its metabolite metanephrine. *J. Pharmacol. Exp. Ther.* 127:251–56
27. Dengler, H. J., Spiegel, H. E., Titus, E. O. 1961. Effects of drugs on uptake of isotopic norepinephrine by cat tissues. *Nature* 191:816–17
28. Dengler, H. J., Spiegel, H. E., Titus, E. O. 1961. Uptake of tritium-labeled norepinephrine in brain and other tissues of cat in vitro. *Science* 133:1072–73
29. Whitby, L. G., Axelrod, J., Weil-Malherbe, H. 1961. The fate of ^{3}H-norepinephrine in animals. *J. Pharmacol. Exp. Ther.* 132:193–201
30. Iversen, L. L. 1974. Uptake mechanisms for neurotransmitter amines. *Biochem. Pharmacol.* 23:1927–35
31. Bogdanski, D. F., Tissari, A., Brodie, B. B. 1968. Role of sodium, potassium, ouabain and reserpine in uptake, storage and metabolism of biogenic amines in synaptosomes. *Life Sci.* 7:419–28
32. Wilbrandt, W., Rosenberg, T. 1961. The concept of carrier transport and its corollaries in pharmacology. *Pharmacol. Rev.* 13:109–83
33. Blaszkowski, T. P., Bogdanski, D. F. 1972. Evidence for sodium dependent outward transport of the ^{3}H-norepinephrine mobilized by calcium at the adrenergic synapse. Inhibition of transport by desipramine. *Life Sci.* 11:867–76
34. Bogdanski, D. F., Brodie, B. B. 1969. The effects of inorganic ions on the storage and uptake of ^{3}H-norepinephrine by rat heart slices. *J. Pharmacol. Exp. Ther.* 165:181–89
35. Paton, D. M. 1973. Mechanism of efflux of noradrenaline from adrenergic nerves in rabbit atria. *Br. J. Pharmacol.* 49:614–27
36. Axelrod, J., Whitby, L. G., Hertting, G. 1961. Effect of psychotropic drugs on the uptake of ^{3}H-norepinephrine by tissues. *Science* 133:383–84
37. Glowinski, J. 1975. Properties and functions of intraneuronal monoamine compartments in central aminergic neurons. See Ref. 166, pp. 139–67
38. Iversen, L. L. 1975. Uptake processes for biogenic amines. See Ref. 166, pp. 381–442
39. Mason, S. T. 1984. *Catecholamines and Behaviour*. Cambridge: Cambridge University Press. 464 pp.

40. Sugrue, M. F. 1987. Neuropharmacology of drugs affecting food intake. *Pharmacol. Ther.* 32:145–82
41. Dahlstrom, A., Fuxe, K. 1964. Evidence for the existence of monoamine-containing neurons in the central nervous system. I. Demonstration of monoamines in the cell bodies on brain stem neurons. *Acta Physiol. Scand.* 62(Suppl. 232):1–55
42. Lindvall, O., Bjorklund, A. 1974. The organization of the ascending catecholamine neuron systems in the rat brain as revealed by the glyoxylic acid fluorescence method. *Acta Physiol. Scand. Suppl.* 412:1–48
43. Beckstead, R., Domesick, V. B., Nauta, W. J. H. 1979. Efferent connections of the substantia nigra and ventral tegmental area in the rat. *Brain Res.* 175:191–217
44. Fallon, J. H., Koziell, D. A., Moore, R. Y. 1978. Catecholamine innervation of the basal forebrain. II. Amygdala, suprarhinal cortex and entorhinal cortex. *J. Comp. Neurol.* 180:509–32
45. Fallon, J. H., Moore, R. Y. 1978. Catecholamine innervation of the basal forebrain. III. Olfactory bulb, anterior olfactory nuclei, olfactory tubercle and piriform cortex. *J. Comp. Neurol.* 180:533–44
46. Fallon, J. H., Moore, R. Y. 1978. Catecholamine innervation of the basal forebrain. IV. Topography of the dopamine projection to the basal forebrain and neostriatum. *J. Comp. Neurol.* 180:545–80
47. Moore, R. Y., Bloom, F. E. 1978. Central catecholamine neuron systems: anatomy and physiology of the dopamine systems. *Annu. Rev. Neurosci.* 1:129–69
48. Moore, R. Y., Bloom, F. E. 1979. Central catecholamine neuron systems: anatomy and physiology of the norepinephrine and epinephrine systems. *Annu. Rev. Neurosci.* 2:113–68
49. Cooper, J. R., Bloom, F. E., Roth, R. H. 1991. *The Biochemical Basis of Neuropharmacology*. New York: Oxford Univ. Press. 454 pp.
50. Seiden, L. S., Dykstra, L. A. 1977. *Psychopharmacology: A Biochemical and Behavioral Approach.* New York: Van Nostrand Reinhold. 451 pp.
51. Raine, C. S. 1989. Neurocellular anatomy. In *Basic Neurochemistry,* ed. G. J. Siegel, B. W. Agranoff, R. W. Albers, P. B. Molinoff, pp. 3–33. New York: Raven
52. Chesselet, M.-F. 1990. Presynaptic regulation of dopamine release. Implications for the functional organization of the basal ganglia. *Ann. NY Acad. Sci.* 604:17–22
53. Conde, H. 1992. Organization and physiology of the substantia nigra. *Exp. Brain Res.* 88:233–48
54. Horn, A. S. 1990. Dopamine uptake: A review of progress in the last decade. *Progr. Neurobiol.* 34:387–400
55. Groves, P. M., Wilson, C. J., Young, S. J., Rebec, G. V. 1975. Self-inhibition by dopaminergic neurons. *Science* 190:522–29
56. Alberts, B., Bray, D., Lewis, J., Raff, M., Roberts, K., Watson, J. D. 1989. *Molecular Biology of the Cell.* New York: Garland. 1219 pp.
57. Winkler, H. 1988. Occurrence and mechanism of exocytosis in adrenal medulla and sympathetic nerve. In *Catecholamines I.* ed. U. Trendelenburg, N. Weiner, pp. 43–118. New York: Springer-Verlag
58. Carboni, E., Imperato, A., Perezzani, L., Di Chiara, G. 1989. Amphetamine, cocaine, phencyclidine and nomifensine increase extracellular dopamine concentrations preferentially in the nucleus acccumbens of freely moving rats. *Neuroscience* 28:653–61
59. De Boer, P., Damsma, G., Fibiger, H. C., Timmerman, W., De Vries, J. B., Westerink, B. H. C. 1990. Dopaminergic-cholinergic interactions in the striatum: the critical significance of calcium concentrations in brain microdialysis. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 342:528–34
60. Hurd, Y. L., Ungerstedt, U. 1989. Ca^{2+} dependence of the amphetamine, nomifensine, and Lu 19–005 effect on in vivo dopamine transmission. *Eur. J. Pharmacol.* 166:261–69
61. Hertting, G., Axelrod, J., Kopin, I. J., Whitby, L. G. 1961. Lack of uptake of catecholamines after chronic denervation of sympathetic nerves. *Nature* 189:66
62. Kilty, J. E., Lorang, D., Amara, S. G. 1991. Cloning and expression of a cocaine-sensitive rat dopamine transporter. *Science* 254:578–80
63. Pacholczyk, T., Blakely, R. D., Amara, S. G. 1991. Expression cloning of a cocaine-and antidepressant-sensitive human noradrenaline transporter. *Nature* 350:350–53
64. Shimada, S., Kitayama, S., Lin, C.-L., Patel, A., Nanthakumar, E., et al. 1991. Cloning and expression of a cocaine-sensitive dopamine transporter complementary DNA. *Science* 254: 576–78

65. Harris, J. E., Baldessarini, R. J. 1973. The uptake of [^{3}H]dopamine by homogenates of rat corpus striatum: effects of cations. *Life Sci.* 13:303–12
66. Holz, R. W., Coyle, J. T. 1974. The effects of various salts, temperature, and the alkaloids veratridine and batrachotoxin on the uptake of [^{3}H] dopamine into synaptosomes from rat striatum. *Mol. Pharmacol.* 10:746–58
67. Krueger, B. K. 1990. Kinetics and block of dopamine uptake in synaptosomes from rat caudate nucleus. *J. Neurochem.* 55:260–67
68. Iversen, L. L. 1967. *The Uptake and Storage of Noradrenaline in Sympathetic Nerves*. Cambridge: Cambridge Univ. Press. 253 pp.
69. Snyder, S. H., Coyle, J. T. 1969. Regional differences in ^{3}H-norepinephrine and ^{3}H-dopamine uptake into rat brain homogenates. *J. Pharmacol. Exp. Ther.* 165:78–86
70. Iversen, L. L., Kravitz, E. A. 1966. Sodium dependence of transmitter uptake at adrenergic nerve terminals. *Mol. Pharmacol.* 2:360–62
71. Tissari, A. H., Schonhofer, P. S., Bogdanski, D. F., Brodie, B. B. 1969. Mechanism of biogenic amine transport II. Relationship between sodium and the mechanism of ouabain blockade of the accumulation of serotonin and norepinephrine by synaptosomes. *Mol. Pharmacol.* 5:593–604
72. Siegel, G. J., Agranoff, B. W., Albers, R. W., Molinoff, P. B. 1989. *Basic Neurochemistry*. New York: Raven
73. Nelson, P. J., Rudnick, G. 1979. Coupling between platelet 5-hydroxytryptamine and potassium transport. *J. Biol. Chem.* 254:10084–89
74. Sammet, S., Graefe, K.-H. 1979. Kinetic analysis of the interaction between noradrenaline and Na+ in neuronal uptake: kinetic evidence for CO-transport. *Naunyn-Schmiedeberg's Arch. Pharmacol.* 309:99–107
75. Bonisch, H., Trendelenburg, U. 1988. The mechanism of action of indirectly acting sympathomimetic amines. See Ref. 57, pp. 247–77
76. Coyle, J. T., Snyder, S. H. 1969. Catecholamine uptake by synaptosomes in homogenates of rat brain: stereospecificity in different areas. *J. Pharmacol. Exp. Ther.* 170:221–31
77. Hrdina, P. D., Elson-Hartman, K., Roberts, D. C. S., Pappas, B. A. 1981. High affinity [^{3}H] desipramine binding in rat cerebral cortex decreases after selective lesion of noradrenergic neurons with 6-hydroxydopamine. *Eur. J. Pharmacol.* 73:375–76
78. Langer S. Z., Raisman, R., Briley, M. 1981. High affinity [^{3}H]DMI binding is associated with neuronal noradrenaline uptake in the periphery and the central nervous system. *Eur. J. Pharmacol.* 72:423–24
79. Lee, C-M., Snyder, S. H. 1981. Norepinephrine neuronal uptake binding sites in rat brain membranes labeled with [^{3}H]-desipramine. *Proc. Natl. Acad. Sci. USA* 78:5250–54
80. Rehavi, M., Skolnick, P., Hulihan, B., Paul, S., M. 1981. 'High affinity' binding of [^{3}H]-desipramine to rat cerebral cortex: relationship to tricyclic antidepressant-induced inhibition of norepinephrine uptake. *Eur. J. Pharmacol.* 70:597–99
81. Yamamura, H. J. I., Enna, S. J., Kuhar, M. J. 1985. *Neurotransmitter Receptor Binding*. New York: Raven
82. Kirifides, A. L., Harvey, J. A., Aloyo, V. J. 1992. The low affinity binding site for the cocaine analog, WIN 35,428 is an artifact of freezing caudate tissue. *Life Sci.* 50:L139–42
83. Boja, J. W., Carroll, F. I., Rahman, M. A., Philip, A., Lewin, A. H., Kuhar, M. J. 1990. New, potent cocaine analogs: ligand binding and transport studies in rat striatum. *Eur. J. Pharmacol.* 184:329–32
84. Madras, B. K., Spealman, R. D., Fahey, M. A., Neumeyer, J. L., Saha, J. K., Milius, R. A. 1989. Cocaine receptors labeled by [^{3}H]2 beta-carbomethoxy-3 beta-(4-fluorophenyl) tropane. *Mol. Pharmacol.* 36:518–24
85. Iversen, L. L. 1965. The uptake of catecholamines at high perfusion concentrations in the rat isolated heart: A novel catecholamine uptake process. *Br. J. Pharmacol.* 25:18–33
86. Gillespie, J. S. 1973. Uptake of noradrenaline by smooth muscle. *Br. Med. Bull.* 29:136–41
87. Gillespie, J. S., Towart, R. 1973. Uptake kinetics and ion requirements for extraneuronal uptake of noradrenaline by arterial smooth muscle and collagen. *Br. J. Pharmacol.* 47:556–67
88. Lightman, S. L., Iversen, L. L. 1969. The role of uptake2 in the extraneuronal metabolism of catecholamines in the isolated rat heart. *Br. J. Pharmacol.* 37:638–49
89. Calligaro, D. O., Eldefrawi, M. E. 1987. High affinity stereospecific binding of [^{3}H] cocaine in striatum and its

relationship to the dopamine transporter. *Membr. Biochem.* 7:87–106
90. Ritz, M. C., Boja, J. W., Grigoriadis, D., Zaçzek, R., Carroll, F. I., et al. 1990. [^{3}H]WIN 35,065–2: a ligand for cocaine receptors in striatum. *J. Neurochem.* 55:1556–62
91. Kennedy, L. T., Hanbauer, I. 1983. Sodium-sensitive cocaine binding to rat striatal membrane: possible relationship to dopamine uptake sites. *J. Neurochem.* 41:172–78
92. Patel, A., Boja, J. W., Lever, J., Lew, R., Simantov, R., et al. 1992. A cocaine analog and a GBR analog label the same protein in rat striatal membranes. *Brain Res.* 576:173–74
93. Johnson, R. G. 1988. Accumulation of biological amines into chromaffin granules: a model for hormone and neurotransmitter transport. *Physiol. Rev.* 68:232–307
94. Philippu, A., Matthaei, H. 1988. Transport and storage of catecholamines in vesicles. See Ref. 57, pp. 1–42
95. Rudnick, G. 1986. ATP-driven H+ pumping into intracellular organelles. *Annu. Rev. Physiol.* 48:403–13
96. Baldessarini, R. J. 1975. Release of catecholamines. See Ref. 166, pp. 37–137
97. Carlsson, A., Rosengren, E., Bertler, A., Nilsson, J. 1957. Effect of reserpine on the metabolism of catecholamines. In *Psychotropic Drugs,* ed. S. Garattini, V. Ghetti, pp. 363–72. New York: Elsevier
98. Shore, P. A., Pletscher, A., Tomich, E. G., Carlsson, A., Kuntzman, R., Brodie, B. B. 1957. Role of brain serotonin in reserpine action. *Ann. NY Acad. Sci.* 66:609–17
99. Hertting, G., Potter, L. T., Axelrod, J. 1962. Effect of decentralization and ganglionic blocking agents on the spontaneous release of H3-norepinephrine. *J. Pharmacol. Exp. Ther.* 136:289–92
100. Weiner, N., Perkins, M., Sidman, R. L. 1962. Effect of reserpine on noradrenaline content of innervated and denervated brown adipose tissue of the rat. *Nature* 193:137–38
101. Palm, D., Grobecker, H., Bak, I. J. 1970. Membrane effects of catecholamine releasing drugs. In *New Aspects of Storage and Release Mechanisms of Catecholamines,* ed. H. J. Schumann, G. Kroneberg, pp. 188–98. New York: Springer-Verlag
102. Scheel-Kruger, J. 1971. Comparative studies of various amphetamine analogues demonstrating different interactions with the metabolism of the catecholamines in the brain. *Eur. J. Pharmacol.* 14:47–59
103. Braestrup, C. 1977. Biochemical differentiation of amphetamine vs methylphenidate and nomifensine in rats. *J. Pharm. Pharmacol.* 29:463–70
104. Creese, I., Iversen, S. D. 1975. The pharmacological and anatomical substrates of the amphetamine response in the rat. *Brain Res.* 83:419–36
105. Schoemaker, H., Nickolson, V. J. 1983. Dopamine uptake by rat striatal synaptosomes: a compartmental analysis. *J. Neurochem.* 41:684–90
106. Arbilla, S., Langer, S. Z. 1980. Influence of monoamine oxidase inhibition on the release of ^{3}H-dopamine elicited by potassium and by amphetamine from the rat substantia nigra and corpus striatum. *Naunyn Schmiedebergs Arch. Pharmacol.* 311:45–52
107. Blaschko, H., Richter, D., Schlossmann, H. 1937. The oxidation of adrenaline and other amines. *Biochem. J.* 31:2187–96
108. Mann, P. J. G., Quastel, J. H. 1940. Benzedrine (β-phenylisopropylamine) and brain metabolism. *Biochem. J.* 34:414–31
109. Horita, A. 1958. Beta-phenylisopropylhydrazine, a potent and long acting monoamine oxidase inhibitor. *J. Pharmacol. Exp. Ther.* 122: 176–81
110. Zirkle, C. L., Kaiser, C. 1964. Monoamine oxidase inhibitors (nonhydrazines). In *Psychopharmacological Agents,* ed. M. Gordon, pp. 445–554. New York: Academic
111. Seiden, L. S., Westley, J. 1963. Mechanism of iproniazid inhibition of brain monoamine oxidase. *Arch. Int. Pharmacodyn.* 146:145–62
112. Zeller, E. A., Blanksma, A., Burkard, W. P., Pacha, W. L., Lazanas, J. C. 1959. In vitro and in vivo inhibition of amine oxidases. *Ann. NY Acad. Sci.* 80:583–89
113. Schayer, R. W. 1953. In vivo inhibition of monoamine oxidase studied with radioactive tyramine. *Proc. Soc. Exp. Biol. Med.* 84:60–65
114. Schayer, R. W., Wu, K. Y. T., Smiley, R. L., Kobayashi, Y. 1954. Studies on monoamine oxidase in intact animals. *J. Biol. Chem.* 210:259–67
115. Mantle, T. J., Tipton, K. F., Garrett, N. J. 1976. Inhibition of monoamine oxidase by amphetamine and related compounds. *Biochem. Pharmacol.* 25: 2073–77
116. Miller, H. H., Shore, P. A., Clarke, D. E. 1980. In vivo monoamine oxidase

inhibition by d-amphetamine. *Biochem. Pharmacol.* 29:1347–54

117. Furchgott, R. F., Kirpekar, S. M., Rieker, M., Schwab, A. 1963. Actions and interactions of norepinephrine, tyramine,and cocaine on aortic strips of rabbit and left atria of guinea pig and cat. *J. Pharmacol. Exp. Ther.* 142:39–58
118. Tainter, M. L., Chang, D. K. 1927. The antagonism of the pressor action of tyramine by cocaine. *J. Pharmacol. Exp. Ther.* 30:193–207
119. Glowinski, J., Baldessarini, R. J. 1966. Metabolism of norepinephrine in the central nervous system. *Pharmacol. Rev.* 18:1201–38
120. Ferris, R. M., Tang, F. L. M., Maxwell, R. A. 1972. A comparison of the capacities of isomers of amphetamine, deoxypipradrol and methylphenidate to inhibit the uptake of tritiated catecholamines into rat cerebral cortex slices, synaptosomal preparations of rat cerebral cortex, hypothalamus and striatum and into adrenergic nerves of rabbit aorta. *J. Pharmacol. Exp. Ther.* 181:407–16
121. Glowinski, J., Axelrod, J. 1965. Effects of drugs on the uptake release and metabolism of H3-norepinephrine in the rat brain. *J. Pharmacol. Exp. Ther.* 149:43–49
122. Ross, S. B., Renyi, A. L. 1964. Blocking action of sympathomimetic amines on the uptake of tritiated noradrenaline by mouse cerebral cortex tissues in vitro. *Acta Pharmacol. Toxicol.* 21:226–39
123. Azzaro, A. J., Ziance, R. J., Rutledge, C. O. 1974. The importance of neuronal uptake of amines for amphetamine-induced release of ^{3}H-norepinephrine from isolated brain tissue. *J. Pharmacol. Exp. Ther.* 189:110–18
124. Baumann, P. A., Maitre, L. 1976. Is drug inhibition of dopamine uptake a misinterpretation of in vitro experiments? *Nature* 264:789–90
125. Raiteri, M., Angelini, F., Levi, G. 1974. A simple apparatus for studying the release of neurotransmitters from synaptosomes. *Eur. J. Pharmacol.* 25: 411–14
126. Raiteri, M., Cerrito, F., Cervoni, A. M., del Carmine, R., Ribera, M. T., Levi, G. 1978. Studies on dopamine uptake and release in synaptosomes. In *Advances in Biochemical Psychopharmacology,* ed. P. J. Roberts, G. N. Woodruff, L. L. Iversen, pp. 35–56. New York: Raven
127. Madras, B. K., Fahey, M. A., Bergman, J., Canfield, D. R., Spealman, R. D. 1989. Effects of cocaine and related drugs in nonhuman primates. I. [^{3}H]cocaine binding sites in caudate-putamen. *J. Pharmacol. Exp. Ther.* 251:131–41
128. Ritz, M. C., Kuhar, M. J. 1989. Relationship between self-administration of amphetamine and monoamine receptors in brain: comparison with cocaine. *J. Pharmacol. Exp. Ther.* 248:1010–17
129. Ritz, M. C., Lamb, R. J., Goldberg, S. R., Kuhar, M. J. 1987. Cocaine receptors on dopamine transporters are related to self- administration of cocaine. *Science* 237:1219–23
130. Nomikos, G. G., Damsma, G., Wenkstern, D., Fibiger, H. C. 1990. In vivo characterization of locally applied dopamine uptake inhibitors by striatal microdialysis. *Synapse* 6:106–12
131. Westerink, B. H. C., Tuntler, J., Damsma, G., Rollema, H., De Vries, J. B. 1987. The use of tetrodotoxin for the characterization of drug-enhanced dopamine release in conscious rats studied by brain dialysis. *Naunyn Schmiedeberg's Arch. Pharmacol.* 336:502–7
132. Von Voigtlander, P. F., Moore, K. E. 1973. Involvement of nigro-striatal neurons in the in vivo release of dopamine by amphetamine, amantadine and tyramine. *J. Pharmacol. Exp. Ther.* 184:542–52
133. Liang, N. Y., Rutledge, C. O. 1982. Comparison of the release of [^{3}H]dopamine from isolated corpus striatum by amphetamine, fenfluramine and unlabelled dopamine. *Biochem. Pharmacol.* 31:983–92
134. Arnold, E. B., Molinoff, P. B., Rutledge, C. O. 1977. The release of endogenous norepinephrine and dopamine from cerebral cortex by amphetamine. *J. Pharmacol. Exp. Ther.* 202: 544–57
135. Butcher, S. P., Fairbrother, I. S., Kelly, J. S., Arbuthnott, G. W. 1988. Amphetamine-induced dopamine release in the rat striatum: an in vivo microdialysis study. *J. Neurochem.* 50: 346–55
136. Parker, E. M., Cubeddu, L. X. 1986. Effects of d-amphetamine and dopamine synthesis inhibitors on dopamine and acetylcholine neurotransmission in the striatum. I. Release in the absence of vesicular transmitter stores. *J. Pharmacol. Exp. Ther.* 237:179–92
137. Parker, E. M., Cubeddu, L. X. 1988. Comparative effects of amphetamine,

phenylethylamine and related drugs on dopamine efflux, dopamine uptake and mazindol binding. *J. Pharmacol. Exp. Ther.* 245:199–210

138. Zaczek, R., Culp, S., De Souza, E. B. 1991. Interactions of [^{3}H]amphetamine with rat brain synaptosomes. II. Active transport. *J. Pharmacol. Exp. Ther.* 257:830–35
139. Fischer, J. F., Cho, A. K. 1976. Properties of dopamine efflux from rat striatal tissue caused by amphetamine and p-hydroxyamphetamine. *Proc. West. Pharmacol. Soc.* 19:179–82
140. Zaczek, R., Culp, S., De Souza, E. B. 1990. Intrasynaptosomal sequestration of [^{3}H]amphetamine and [^{3}H]methylenedioxyamphetamine: characterization suggests the presence of a factor responsible for maintaining sequestration. *J. Neurochem.* 54:195–204
141. Zaczek, R., Culp, S., Goldberg, H., McCann, D. J., De Souza, E. B. 1991. Interactions of [^{3}H]amphetamine with rat brain synaptosomes. I. Saturable sequestration. *J. Pharmacol. Exp. Ther.* 257:820–29
142. Quinton, R. M., Halliwell, G. 1963. Effects of alpha-methyl DOPA and DOPA on the amphetamine excitatory response in reserpinized rats. *Nature* 200:178–79
143. Randrup, A., Munkvad, I. 1966. Role of catecholamines in the amphetamine excitatory response. *Nature* 211:540
144. Van der Schoot, J. B., Ariens, E. J., Van Rossum, J. M., Hurkmans, J. A. 1962. Phenylisopropylamine derivatives, structure and action. *Arzneim. Forsch.* 12:902–7
145. Weissman, A., Koe, B. K., Tenen, S. S. 1966. Antiamphetamine effects following inhibition of tyrosine hydroxylase. *J. Pharmacol. Exp. Ther.* 151: 339–52
146. Besson, M.-J., Cheramy, A., Feltz, P., Glowinski, J. 1971. Dopamine: spontaneous and drug-induced release from the caudate nucleus in the cat. *Brain Res.* 32:407–24
147. Besson, M. J., Cheramy, A., Feltz, P., Glowinski, J. 1969. Release of newly synthesized dopamine from dopamine-containing terminals in the striatum of the rat. *Proc. Natl. Acad. Sci. USA* 62:741–48
148. Glowinski, J. 1970. Effects of amphetamine on various aspects of catecholamine metabolism in the central nervous system of the rat. See Ref. 1, pp. 301–16
149. Callaway, C. W., Kuczenski, R., Segal, D. S. 1989. Reserpine enhances amphetamine stereotypies without increasing amphetamine-induced changes in striatal dialysate dopamine. *Brain Res.* 505:83–90
150. Chiueh, C. C., Moore, K. E. 1975. D-amphetamine-induced release of "newly synthesized" and "stored" dopamine from the caudate nucleus in vivo. *J. Pharmacol. Exp. Ther.* 192: 642–53
151. Parker, E. M., Cubeddu, L. X. 1986. Effects of d-amphetamine and dopamine synthesis inhibitors on dopamine and acetylcholine neurotransmission in the striatum. II. Release in the presence of vesicular transmitter stores. *J. Pharmacol. Exp. Ther.* 237:193–203
152. Knapper, S. M., Grunewald, G. L., Rutledge, C. O. 1988. Inhibition of norepinephrine transport into synaptic vesicles by amphetamine analogs. *J. Pharmacol. Exp. Ther.* 247:487–94
153. Philippu, A., Beyer, J. 1973. Dopamine and noradrenaline transport into subcellular vesicles of the striatum. *Naunyn Schmiedeberg's Arch. Pharmacol.* 278: 387–402
154. Ary, T. E., Komiskey, H. L. 1980. Phencyclidine: effect on the accumulation of ^{3}H-dopamine in synaptic vesicles. *Life Sci.* 26:575–78
155. Beers, M. F., Carty, S. E., Johnson, R. G., Scarpa, A. 1982. H+-ATPase and catecholamine transport in chromaffin granules. *Ann. NY Acad. Sci.* 402:116–33
156. Sulzer, D., Rayport, S. 1990. Amphetamine and other psychostimulants reduce pH gradients in midbrain dopaminergic neurons and chromaffin granules: a mechanism of action. *Neuron* 5:797–808
157. Rudnick, G., Wall, S. C. 1992. The molecular mechanism of "ecstasy" [3,4-methylenedioxymethamphetamine (MDMA)]: serotonin trasporters are targets for MDMA-induced serotonin release. *Proc. Natl. Acad. Sci. USA* 89:1817–21
158. Rudnick, G., Wall, S. C. 1992. p-Chloroamphetamine induces serotonin release through serotonin transporters. *Biochemistry* 31:6710–18
159. Zetterstrom, T., Sharp, T., Ungerstedt, U. 1986. Further evaluation of the mechanism by which amphetamine reduces striatal dopamine metabolism: a brain dialysis study. *Eur. J. Pharmacol.* 132:1–9
160. O'Dell, S. J., Weihmuller, F. B., Marshall, J. F. 1991. Multiple methamphetamine injections induce marked increases in extracellular striatal dopa-

mine which correlate with subsequent neurotoxicity. *Brain Res.* 564:256–60
161. Carlsson, A. 1988. The current status of the dopamine hypothesis of schizophrenia. *Neuropsychopharmacology* 1: 179–86
162. Crow, T. J. 1982. Schizophrenia. In *Disorders of Neurohumoral Transmission,* ed. T. J. Crow, pp. 287–340. New York: Academic
163. Van Kammen, D. P. 1979. The dopamine hypothesis of schizophrenia revisited. *Psychoneuroendocrinology.* 4:37–46
164. Jones, G. H., Marsden, C. A., Robbins, T. W. 1990. Increased sensitivity to amphetamine and reward-related stimuli following social isolation in rats: possible disruption of dopamine-dependent mechanisms of the nucleus accumbens. *Psychopharmacology* 102: 364–72
165. Kelley, A. E., Delfs, J. M. 1991. Dopamine and conditioned reinforcement. II. Contrasting effects of amphetamine microinjection into the nucleus accumbens with peptide microinjection into the ventral tegmental area. *Psychopharmacology* 103:197–203
166. Lyon, M., Robbins, T. 1975. The action of central nervous system stimulant drugs: a general theory concerning amphetamine effects. In *Current Developments in Psychopharmacology,* ed. W. B. Essman, L. Valzelli, pp. 79–163. New York: Spectrum
167. Smith, C. B. 1963. Enhancement by reserpine and alpha-methyl dopa of the effects of d-amphetamine upon the locomotor activity of mice. *J. Pharmacol. Exp. Ther.* 142:343–50
168. Thornburg, J. E., Moore, K. E. 1972. A comparison of the locomotor stimulant properties of amantadine and l- and d-amphetamine in mice. *Neuropharmacology* 11:675–82
169. Grossman, S. P., Sclafani, A. 1971. Sympathomimetic amines. In *Pharmacological and Biophysical Agents and Behavior,* ed. E. Furchtgott, pp. 269–345. New York: Academic
170. Hoebel, B. G. 1977. The psychopharmacology of feeding. See Ref. 166, pp. 55–129
171. Holtzman, S. G., Jewett, R. E. 1971. The role of brain norepinephrine in the anorexic effects of dextroamphetamine and monoamine oxidase inhibitors in the rat. *Psychopharmacologia* 22:151–61
172. Houser, V. P. 1970. The effects of adrenergic and cholinergic agents upon eating and drinking in deprived rats. *Psychonomic Sci.* 20:153–55
173. Stark, P., Totty, C. W. 1967. Effects of amphetamines on eating elicited by hypothalamic stimulation. *J. Pharmacol. Exp. Ther.* 158:272–78
174. Hartmann, E. 1970. The D-state and norepinephrine-dependent systems. *Int. Psychiat. Clin.* 7:308–28
175. Oswald, I. 1968. Drugs and sleep. *Pharmacol. Rev.* 20:273–303
176. Oswald, I. 1970. Effects on sleep of amphetamine and its derivatives. See Ref. 1, pp. 865–71
177. Rechtschaffen, A., Maron, L. 1964. The effect of amphetamine on the sleep cycle. *Electroenceph. Clin. Neurophysiol.* 16:438–45
178. Barondes, S. H., Cohen, H. D. 1968. Arousal and the conversion of "short-term" to "long-term" memory. *Proc. Natl. Acad. Sci. USA* 61:923–29
179. Evans, W. O., Smith, R. P. 1964. Some effects of morphine and amphetamine on intellectual functions and mood. *Psychopharmacologia* 6:49–56
180. Consolo, S., Garattini, S., Ghielmetti, R., Valzelli, L. 1965. Concentrations of amphetamine in the brain in normal or aggressive mice. *J. Pharm. Pharmacol.* 17:666
181. Miczek, K. A., Gold, L. H. 1983. Ethological analysis of amphetamine action on social behavior in squirrel monkeys (*Saimiri sciureus*). *Prog. Clin. Biol. Res.* 131:137–55
182. Welch, B. L., Welch, A. S. 1966. Graded effect of social stimulation upon d-amphetamine toxicity, aggressiveness and heart and adrenal weight. *J. Pharmacol. Exp. Ther.* 151:331–38
183. Bignami, G. 1966. Pharmacologic influences on mating behavior in the male rat. Effects of d-amphetamine, LSD-25, strychnine, nicotine and various anticholinergic agents. *Psychopharmacologia* 10:44–58
184. Bohdanecky, Z., Jarvik, M. E. 1967. The effect of D-amphetamine and physostigmine upon acquisition and retrieval in a single trial learning task. *Arch. Int. Pharmacodyn. Ther.* 170:58–65
185. Carr, G. D., White, N. M. 1984. The relationship between stereotypy and memory improvement produced by amphetamine. *Psychopharmacology* 82: 203–9
186. Doty, B. A., Doty, L. A. 1966. Facilitative effects of amphetamine on avoidance conditioning in relation to age and problem difficulty. *Psychopharmacologia* 9:234–41

187. Rech, R. H. 1966. Amphetamine effects on poor performance of rats in a shuttle-box. *Psychopharmacologia* 9: 110–17
188. Evangelista, A. M., Gattoni, R. C., Izquierdo, I. 1970. Effect of amphetamine, nicotine and hexamethonium on performance of a conditioned response during acquisition and retention trials. *Pharmacology* 3:91–96
189. Clark, F. C., Steele, B. I. 1966. Effects of D-amphetamine on performance under a multiple schedule in the rat. *Psychopharmacologia* 9:157–69
190. Dews, P. B., Morse, W. H. 1961. Behavioral pharmacology. *Annu. Rev. Pharmacol.* 1:145–74
191. Laties, V. G., Weiss, B. 1966. Influence of drugs on behavior controlled by internal and external stimuli. *J. Pharmacol. Exp. Ther.* 152:388–96
192. Glatt, M. M. 1968. Abuse of methylamphetamine. *Lancet* 2:215–16
193. Kramer, J. C., Fischman, V. S., Littlefield, D. C. 1967. Amphetamine abuse. Pattern and effects of high doses taken intravenously. *J. Am. Med. Assoc.* 201:305–9
194. Schuster, C. R., Thompson, T. 1969. Self administration of and behavioral dependence on drugs. *Annu. Rev. Pharmacol.* 9:483–502
195. Cole, S. O. 1967. Experimental effects of amphetamine: a review. *Psychol. Bull.* 68:81–90
196. Cole, S. O. 1978. Brain mechanisms of amphetamine-induced anorexia, locomotion, and stereotypy: a review. *Neurosci. Biobehav. Rev.* 2:89–100
197. Robinson, T. E., Becker, J. B. 1986. Enduring changes in brain and behavior produced by chronic amphetamine administration: a review and evaluation of animal models of amphetamine psychosis. *Brain Res.* 396:157–98
198. Robbins, T. W. 1981. Behavioural determinants of drug action: rate-dependency revisited. In *Theory in Pychopharmacology,* ed. S. J. Cooper, 1:1–63. New York: Academic
199. Kelleher, R. T., Morse, W. H. 1968. Determinants of the specificity of behavioral effects of drugs. *Ergeb. Physiol.* 60:1–56
200. Nathanson, M. H. 1937. The central action of beta-aminopropylbenzene (benzedrine): Clinical observations. *J. Am. Med. Assoc.* 108:528–31
201. Goetzl, F. R., Stone, F. 1948. The influence of amphetamine sulfate upon olfactory acuity and appetite. *Gastroenterology* 10:708–13
202. Harris, S. C., Ivy, A. C., Searle, L. M. 1947. The mechanism of amphetamine induced loss of weight. *J. Am. Med. Assoc.* 134:1468–75
203. Schwartz, S., Johnson, J. H. 1981. *Psychopathology of Childhood.* New York: Pergamon
204. Wender, P. H. 1974. Some speculations concerning a possible biochemical basis of minimal brain dysfunction. *Life Sci.* 14:1605–21
205. Dews, P. B. 1955. Studies on behavior. II. The effects of pentobarbital, methamphetamine, and scopolamine on performances in pigeons involving discriminations. *J. Pharmacol. Exp. Ther.* 115:380–89
206. Brill, H., Hirose, T. 1969. The rise and fall of a methamphetamine epidemic: Japan 1945–1955. *Semin. Psychiat.* 1:179–94
207. Inghe, G. 1969. The present state of abuse and addiction to stimulant drugs in Sweden. In *Abuse of Central Stimulants,* ed. F. Sjoqvist, M. Tottie, pp. 187–219. Stockholm: Almqvist, Wiksell
208. Jonsson, L.-E., Gunne, L.-M. 1970. Clinical studies of amphetamine psychosis. See Ref. 1, pp. 929–36
209. Ellinwood, E. H. 1967. Amphetamine psychosis: I. Description of the individuals and process. *J. Nerv. Ment. Dis.* 144:273–83
210. Ellinwood, E. H., Stripling, J. S., Kilbey, M. M. 1977. Chronic changes with amphetamine intoxication: underlying processes. In *Neuroregulators and Psychiatric Disorders,* ed. E. Usdin, D. Hamburg, J. Barchas, pp. 578–87. New York: Oxford Univ. Press
211. Griffith, J. D., Fann, W. E., Oates, J. A. 1972. The amphetamine psychosis: experimental manifestations. In *Current Concepts on Amphetamine Abuse,* ed. E. H. Ellinwood, S. Cohen, pp. 185–91. Washington, DC: US Govt. Printing Off.
212. Schiorring, E. 1981. Psychopathology induced by "speed drugs". *Pharmacol. Biochem. Behav.* 14 (Suppl. 1):109–22
213. Connell, P. H. 1958. *Amphetamine Psychosis.* London: Inst. Psychiatry. 133 pp.
214. Snyder, S. H. 1972. Catecholamines in the brain as mediators of amphetamine psychosis. *Arch. Gen. Psychiatry* 27:169–79
215. Ellinwood, E. H., Sudilovsky, A., Nelson, L. M. 1973. Evolving behavior in the clinical and experimental amphetamine (model) psychosis. *Am. J. Psychiatry* 130:1088–93
216. Freedman, A. M., Kaplan, H. I. 1967.

Comprehensive Textbook of Psychiatry. Baltimore: Williams & Wilkins. 1665 pp.
217. American-Psychiatric-Association. 1987. *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC: Am. Psychiatr. Assoc. 567 pp.
218. Nahmias, J., Karetzky, M. S. 1989. Current concepts in narcolepsy. *NJ Medicine* 86:617–22
219. Zarcone, V. 1973. Narcolepsy. *N. Engl. J. Med.* 288:1156–66
220. Rechtschaffen, A., Dement, W. 1969. Narcolepsy and hypersomnia. In *Sleep: Physiology and Pathology: A Symposium,* ed. A. Kales, pp. 119–30. Philadelphia: Lippincott
221. Shafik, E. N., Aiken, S. P., McArdle, J. J. 1991. Regional catecholamine levels in brains of normal and ethanol-tolerant long-sleep and short-sleep mice. *Brain Res.* 563:44–48
222. MacPhail, R. C., Seiden, L. S. 1976. Effects of intermittent and repeated administration of d-amphetamine on restricted water intake in rats. *J. Pharmacol. Exp. Ther.* 197:303–10
223. Pearl, R. G., Seiden, L. S. 1976. The existence of tolerance to and cross-tolerance between d-amphetamine and methylphenidate for their effects on milk consumption and on differential-reinforcement-of-low-rate performance in the rat. *J. Pharmacol. Exp. Ther.* 198:635–47
224. Leibowitz, S. F. 1975. Amphetamine: possible site and mode of action for producing anorexia in the rat. *Brain Res.* 84:160–67
225. Leibowitz, S. F. 1975. Catecholaminergic mechanisms of the lateral hypothalamus: their role in the mediation of amphetamine anorexia. *Brain Res.* 98:529–45
226. Leibowitz, S. F., Rossakis, C. 1978. Analysis of feeding suppression produced by perifornical hypothalamic injection of catecholamines, amphetamines and mazindol. *Eur. J. Pharmacol.* 53:69–81
227. Teitelbaum, P., Wolgin, D. L. 1975. Neurotransmitters and the regulation of food intake. *Prog. Brain Res.* 42:235–49
228. Erinoff, L., MacPhail, R. C., Heller, A., Seiden, L. S. 1979. Age-dependent effects of 6-hydroxydopamine on locomotor activity in the rat. *Brain Res.* 164:195–205
229. Heffner, T. G., Heller, A., Miller, F. E., Kotake, C., Seiden, L. S. 1983. Locomotor hyperactivity in neonatal rats following electrolytic lesions of mesocortical dopamine neurons. *Brain Res.* 285:29–37
230. Miller, F. E., Heffner, T. G., Kotake, C., Seiden, L. S. 1981. Magnitude and duration of hyperactivity following neonatal 6- hydroxydopamine is related to the extent of brain dopamine depletion. *Brain Res.* 229:123–32
231. Shaywitz, B. A., Klopper, J. H., Yager, R. D., Gordon, J. W. 1976. Paradoxical response to amphetamine in developing rats treated with 6-hydroxydopamine. *Nature* 261:153–55
232. Heffner, T. G., Seiden, L. S. 1982. Possible involvement of serotonergic neurons in the reduction of locomotor hyperactivity caused by amphetamine in neonatal rats depleted of brain dopamine. *Brain Res.* 244:81–90
233. Seevers, M. H. 1936. Opiate addictions in the monkey. I. Methods of study. *J. Pharmacol. Exp. Ther.* 56:147–56
234. Balster, R. L., Schuster, C. R. 1973. A comparison of d-amphetamine, l-amphetamine, and methamphetamine self-administration in rhesus monkeys. *Pharmacol. Biochem. Behav.* 1:67–71
235. Deneau, G., Yanagita, T., Seevers, M. H. 1969. Self-administration of psychoactive substances by the monkey. *Psychopharmacologia* 16:30–48
236. Pickens, R., Harris, W. C. 1968. Self-administration of d-amphetamine by rats. *Psychopharmacologia* 12:158–63
237. Pickens, R., Thompson, T. 1971. Characteristics of stimulant drug reinforcement. In *Stimulus Properties of Drugs,* ed. T. Thompson, R. Pickens. New York: Appleton-Century-Crofts
238. Pickens, R., Meisch, R. A., Dougherty, J. A. 1968. Chemical interactions in methamphetamine reinforcement. *Psychol. Rep.* 23:1267–70
239. Harris, R. T., Balster, R. L. 1968. Discriminative control by dl-amphetamine and saline of lever choice and response patterning. *Psychon. Sci.* 10: 105–6
240. Huang, J.-T., Ho, B. T. 1974. Discriminative stimulus properties of d-amphetamine and related compounds in rats. *Pharmacol. Biochem. Behav.* 2:669–73
241. Kuhn, D. M., Appel, J. B., Greenberg, I. 1974. An analysis of some discriminative properties of d-amphetamine. *Psychopharmacologia* 39:57–66
242. Overton, D. A. 1967. Differential responding in a three choice maze controlled by three drug states. *Psychopharmacologia* 11:376–78
243. Schechter, M. D., Rosecrans, J. A. 1973. D-amphetamine as a discrimina-

tive cue: drugs with similar stimulus properties. *Eur. J. Pharmacol.* 21:212–16

244. Schechter, M. D., Cook, P. G. 1975. Dopaminergic mediation of the interoceptive cue produced by d-amphetamine in rats. *Psychopharmacologia* 42:185–93
245. Munkvad, I., Pakkenberg, H., Randrup, A. 1968. Aminergic systems in basal ganglia associated with stereotyped hyperactive behavior and catalepsy. *Brain Behav. Evol.* 1:89–100
246. Randrup, A., Munkvad, I. 1965. Special antagonism of amphetamine-induced abnormal behaviour. Inhibition of stereotyped activity with increase of some normal activities. *Psychopharmacologica* 7:416–22
247. Sato, M., Chen, C.-C., Akiyama, K., Otsuki, S. 1983. Acute exacerbation of paranoid psychotic state after long-term abstinence in patients with previous methamphetamine psychosis. *Biol. Psychiatry* 18:429–40
248. Kokkinidis, L., Anisman, H. 1981. Amphetamine psychosis and schizophrenia: a dual model. *Neurosci. Biobehav. Rev.* 5:449–61
249. Segal, D. S., Kuczenski, R. 1987. Individual differences in responsiveness to single and repeated amphetamine administration: behavioral characteristics and neurochemical correlates. *J. Pharmacol. Exp. Ther.* 242:917–26
250. Segal, D. S., Mandell, A. J. 1974. Long-term administration of d-amphetamine: progressive augmentation of motor activity and stereotypy. *Pharmacol. Biochem. Behav.* 2:249–55
251. Segal, D. S., Janowsky, D. S. 1978. Psychostimulant-induced behavioral effects: possible models of schizophrenia. In *Psychopharmacology: A Generation of Progress,* ed. M. A. Lipton, A. DiMascio, K. F. Killam, pp. 1113–23. New York: Raven
252. Anden, N.-E., Butcher, S. G., Corrode, H., Fuxe, K., Ungerstedt, U. 1970. Receptor activity and turnover of dopamine and noradrenaline after neuroleptics. *Eur. J. Pharmacol.* 11:303–14
253. Creese, I., Burt, D. R., Snyder, S. H. 1978. Biochemical actions of neuroleptic drugs: focus on the dopamine receptor. See Ref. 19, pp. 37–89
254. Snyder, S. H. 1973. Amphetamine psychosis: a "model" schizophrenia mediated by catecholamines. *Am. J. Psychiatry* 130:61–67
255. Randrup, A., Munkvad, I. 1968. Behavioral stereotypies induced by pharmacological agents. *Pharmakopsychiatr. Neuro-Psychopharmakol.* 1: 18–26
256. Rebec, G. V., Bashore, T. R. 1984. Critical issues in assessing the behavioral effects of amphetamine. *Neurosci. Biobehav. Rev.* 8:153–59
257. Costall, B., Naylor, R. J. 1977. Mesolimbic and extrapyramidal sites for the mediation of stereotyped behaviour patterns and hyperactivity by amphetamine and apomorphine in the rat. In *Cocaine and Other Stimulants,* ed. E. H. Ellinwood, M. M. Kilbey, pp. 47–76. New York: Plenum
258. Joyce, E. M., Iversen, S. D. 1984. Dissociable effects of 6-OHDA-induced lesions of neostriatum on anorexia, locomotor activity and stereotypy: the role of behavioural competition. *Psychopharmacology* 83:363–66
259. Kelly, P. H., Saviour, P. W., Iversen, S. D. 1975. Amphetamine and apomorphine responses in the rat following 6-OHDA lesions of the nucleus accumbens septi and corpus striatum. *Brain Res.* 94:507 -22
260. Creese, I., Iversen, S. D. 1974. The role of forebrain dopamine systems in amphetamine-induced stereotyped behavior in the rat. *Psychopharmacologia* 39:345–57
261. Pijnenburg, A. J. J., Honig, W. M. M., Van Der Heyden, J. A. M., Van Rossum, J. M. 1976. Effects of chemical stimulation of the mesolimbic dopamine system upon locomotor activity. *Eur. J. Pharmacol.* 35:45–58
262. Fink, J. S., Smith, G. P. 1980. Relationships between selective denervation of dopamine terminal fields in the anterior forebrain and behavioral responses to amphetamine and apomorphine. *Brain Res.* 201:107–27
263. Makanjuola, R. O. A., Dow, R. C., Ashcroft, G. W. 1980. Behavioural responses to stereotactically controlled injections of monoamine neurotransmitters into the accumbens and caudate-putamen nuclei. *Psychopharmacology* 71:227–35
264. Staton, D. M., Solomon, P. R. 1984. Microinjections of d-amphetamine into the nucleus accumbens and caudate-putamen differentially affect stereotypy and locomotion in the rat. *Physiol. Psychol.* 12:159–62
265. Costall, B., Naylor, R. J., Olley, J. E. 1972. Stereotypic and anticataleptic activities of amphetamine after intracerebral injections. *Eur. J. Pharmacol.* 18:83–94
266. Kelley, A. E., Lang, C. G., Gauthier, A. M. 1988. Induction of oral stereo-