

# Neural degeneration following chronic stimulant abuse reveals a weak link in brain, fasciculus retroflexus, implying the loss of forebrain control circuitry

Gaylord Ellison\*

*Department of Psychology, UCLA, 405 Hilgard Ave, Los Angeles, CA 90024, USA*

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## Abstract

There is increasing evidence that the fasciculus retroflexus (FR) represents a ‘weak link’ following the continuous administration of drugs of abuse. A variety of drugs which predominantly potentiate dopamine, including D-amphetamine, methamphetamine, MDMA, cocaine, and cathinone, all induce degeneration in axons from lateral habenula, through the sheath of FR, to midbrain cells such as SN, VTA, and raphe. For some drugs, such as cocaine, this is virtually the only degeneration induced in brain. Continuous nicotine also selectively induces degeneration in FR, but in the other half of the tract, i.e. in axons from medial habenula through the core of the tract to interpeduncular nucleus. This phylogenetically primitive tract carries much of the negative feedback from forebrain back onto midbrain reward cells, and the finding that these descending control pathways are compromised following simulated drug binges has implications for theories of drug addiction but also psychosis in general.

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## 1. Introduction

The development of a convincing animal model always presages an increased understanding of the disease. Unfortunately, animal models of psychiatric disorders such as schizophrenia or mania have generally remained only limitedly successful. The most convincing come from pharmacological models, for they are based not only on those drugs which can treat the disorder, but also on the conversely-acting drugs which induce states strikingly similar to the disorder itself. This is clear in the case of the dopaminergics, with the dopamine blockers and antipsychotics representing the therapies versus opposed amphetamine and cocaine paranoid psychosis models. In this paper I will describe a series of studies in which animal models of stimulant psychosis were developed and which have led to the discovery of a highly unexpected

neural tract in brain which is especially vulnerable to damage following amphetamine or cocaine binges. The anatomic and neural effects of damage to this pathway have highly interesting theoretical implications, certainly for drug addiction but also perhaps for psychoses in general.

A crucial aspect of this research is the ‘weak link’ strategy, where drugs must be given in the proper drug regimen and at the lowest effective doses, so that not only can the behaviors of the animals be studied, but also any long-lasting effects are only observed in the most highly affected neuropil. The discovery of the most vulnerable circuits in these drug models may not only shed light upon the pharmacology and neuroanatomy of progressive drug addiction, but could also have more general implications for biological psychiatry, and the neurosciences in general. The discovery of those circuits in brain which prove most vulnerable to neural failure in drug models of psychosis would seem to be prime candidates for the ‘weak links’ in brain involved in other affective and psychiatric disorders.

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\*Tel.: +1-310-398-4854; fax: +1-310-206-5895.

E-mail address: [ellison@psych.ucla.edu](mailto:ellison@psych.ucla.edu) (G. Ellison).

## 2. Monoaminergic reward circuits in brain

The most important brain circuits underlying control over affect are mediated by reward pathways which follow an ascending circuit from cell bodies in midbrain to various forebrain structures. Most significant are the dopamine projections from substantia nigra and VTA, and the serotonergic projections from the raphe nuclei. Each of these cell collections has distinctively specific anatomical innervations of the forebrain, but there are also other ascending pathways from cholinergic and other axons from the midbrain reticular formation. All these pathways represent the multiple types of pharmacologically distinct circuits by which these phylogenetically more primitive midbrain cells exert a degree of control over higher forebrain circuitry in the integrated brain.

These ascending pathways have proved to be of major importance in the pharmacological treatment of various psychiatric and mood disorders, and they also mediate the major modes of action of a variety of drugs of abuse. It is from chronic drug models, and especially those based upon dopaminergic stimulant addictions, that particularly clear correlations can be made between human and animal models. This is because these syndromes have been so extensively studied, and also because the effects of these drugs on behavior are so distinctive.

There is now an extensive literature on drug addiction which primarily focuses upon the actions of dopamine in structures directly innervated by DA axons, especially nucleus accumbens, and the dopaminergic projections to higher structures, especially those to amygdala, frontal cortex and other forebrain structures. Predominant in this literature is the significance, for the process of addiction, of the learning-like, progressive sensitization process which occurs following repeated, intermittent injections of dopaminergics whereby the drug becomes increasingly more potent in increasing activity and reward mechanisms. Recent examples are the reviews by Wise (2000) and Berke and Hyman (2000). This literature represents an attempt to understand the process of progressive addiction via a forward-based, mechanistic framework.

This present paper presents a review of the converse strategy: that of attempting to understand the effects of addiction, and how to devise treatments, by modeling the 'end-stage' behaviors of stimulant addicts, then working backwards in time to understand what led to these behaviors, and the correlated alterations in brain.

## 3. The stages of amphetamine and cocaine stimulant addiction

The most well-understood models of stimulant addiction are based upon the amphetamine and cocaine syndromes (Ellinwood, 1967; Ellison, 1991; Satel et al., 1991). It is well established that both drugs markedly increase dopa-

mine levels, mood, activity levels and self-stimulation in rats, leading eventually to repeated motor stereotypies. But both also have a notable characteristic. Repeated daily doses of either drug leads to tolerance for some effects, such as anorexia, but also leads to a fundamentally important 'sensitization' process whereby the drug becomes increasingly more potent in inducing hyperactivity, and also hedonically more reinforcing, with each repeated administration when the drug is given once each day (Robinson and Becker, 1986). This effect leads to the initial stages of the addictive process, whereby those reward circuits stimulated by the drug become progressively more potent. As a result, drug intake gradually increases.

## 4. Binge intake appears

This leads to increasingly more frequent drug intake, for the addictive process alters the drug regimen, and this appears crucial. Chronic amphetamine and cocaine addicts do not continue in a once per day drug regimen, but begin to go on drug binges whereby the drug is taken repeatedly round the clock. These binges can last for days, for once the binge has begun it will be ended by the crash, which can only be delayed by heightened drug intake. This eventually induces a very distinctive effect: a paranoid psychosis with many symptoms very similar to those in paranoid schizophrenics (Bell, 1965; Connell, 1958; Ellinwood, 1967). This was even documented in controlled studies conducted in the 1970s in which human volunteers were kept in hospitals, given hourly doses of amphetamine, and observed until the paranoid psychosis which reliably developed occurred (Angrist et al., 1974; Griffith et al., 1972). Distinctive stages in behavior were observed, with an initial stage in which the subjects were socially forceful. Then they became somewhat hypochondriacal, eventuating after several days in a 'distinct prepsychotic phase' in which the subjects isolated themselves in their rooms. When they then emerged they spoke freely about their paranoid delusions, the command voices they heard, and of hallucinations in virtually every sensory modality.

My students and I initially studied animal models of simulated amphetamine binges using slow-release drug pellets implanted in rats housed in enriched colony environments (Ellison et al., 1978a). We observed distinctive stages of behavior similar in many ways to those observed in the humans in the hospital studies. In the rats there was initial hyperactivity, gradually evolving into a period of incessant and prolonged motor stereotypies. During this time the amphetamine animals showed minimal social interactions but were never in the burrows. But then, at day 3, they retreated to the burrows for almost a day, and when they emerged showed a variety of 'late-stage' behaviors, including behaviors normally suppressed by acute amphetamines but elicited by hallucinogens (limb-flicks, wet dog

Table 1  
Stages of continuous amphetamines in humans, monkeys, and rats

|                | Human                                                                                           | Monkey                                                                                       | Rat                                                                                                                                                          |
|----------------|-------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Initial stages | Euphoria and exhilaration                                                                       | Increased activity<br>Fixed staring<br>Motor stereotypy                                      | Increased activity<br>Motor stereotypy                                                                                                                       |
| Crash stage    | Increased irritability<br>Anhedonia<br>Intellectual flattening<br>Depression and self-isolation | General activity, hunched posture<br>Motor dyskinesias, including tongue protusions, tremors | Retreat to burrows<br>Heightened startle                                                                                                                     |
| Late stage     | Paranoid delusions<br>Parasitosis<br>Hallucinations                                             | Hallucinatory-like behaviors<br>Parasitosis<br>Sudden orient and fleeing 'wet-dog' shakes    | Parasitosis<br>Hallucinogen-like behavior (limb flick, 'wet-dog' shakes)<br>Sudden startle<br>Abnormal social behavior, fixations, fight or flight behaviors |

shakes), 'pop-corn' behavior (sudden startle responses), parasitotic grooming behavior (like a dog infected by fleas), and a sudden increase in fight or flight behaviors. Some of these social interactions were quite amazing, for the amphetamine rats paired off in stereotyped fighting, whereby the same two rats would constantly seek out the other one to fight. This is a cardinal characteristic of the paranoid fixation (Table 1).

We also observed monkeys implanted with slow-release amphetamine pellets (Ellison et al., 1981). The stages were roughly similar, although the motor stereotypies and the 'hallucinatory' behaviors in the monkeys were much more complex. But the monkeys also eventually showed a 'late stage' with explosive startle or escape episodes and pronounced parasitotic grooming, with frantic episodes of slapping at various areas of the skin. Parasitotic delusions are a very distinctive characteristic of amphetamine psychosis (de Leon et al., 1992). From these experiments we had a good idea of when to look for neurochemical correlates of the 'late-stage'.

## 5. The neuroanatomy of the stages of stimulant addiction

We then began to search for what changes in brain were responsible for the 'late-stage' and soon found that continuous amphetamines had a distinctive neurotoxic effect on dopaminergic innervations of caudate, inducing their degeneration (Ellison et al., 1978b). This effect has been replicated extensively, and seems to be due to the reuptake of a toxic compound into dopamine terminals in caudate (but not accumbens) during continuous amphetamine administration (Hanson et al., 1987).

One aspect of this finding was especially striking. In these studies we gave the amphetamine for 5 days continuously at a dose which had substantial behavioral effects. In another group of animals, the same total dose of amphetamine was given but in five daily injections, given once each 24 h. While these rats received five massive injections, inducing very much higher transient plasma levels of amphetamine, no neurotoxicity in caudate was observed (Fig. 1). We have found this to be true with a number of other drugs of abuse: incessant drugs are especially neurotoxic. Apparently the nervous system can deal much more effectively with repeated transient insults, if then given time to recover (and sleep), than with constant low-level stimulation.

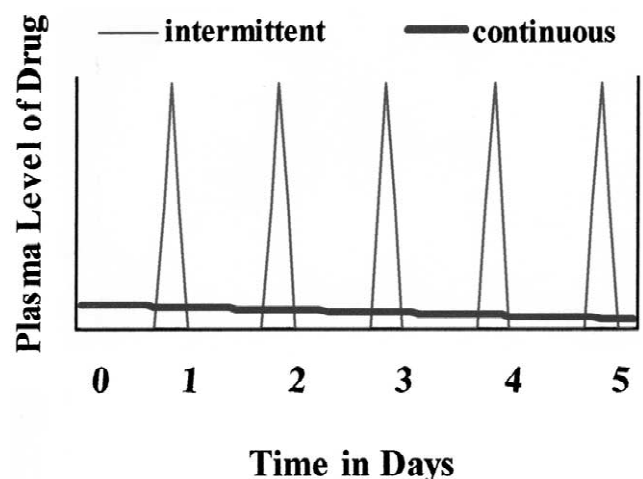


Fig. 1. Schematic comparison of plasma drug levels during continuous versus intermittent (daily) injections of the same total amount of drug. Only the continuous intake is neurotoxic.

## 6. Fasciculus retroflexus degenerates after many dopaminergic stimulants

But the damaged dopaminergic innervations of caudate, it developed, were not solely responsible for the paranoid psychosis. This became apparent when we studied the neurotoxic effects of continuous cocaine. Cocaine also increases dopamine stimulation, leads to a binge intake regimen, and eventually induces paranoia. However, continuous cocaine induced absolutely no degeneration in caudate, as assessed using sensitive silver stains (Switzer, 2000) although it did induce pronounced ‘late-stage’ behaviors in rats. But we had silver-stained the entire brain to identify degeneration, and discovered (Ellison, 1992) that there was degeneration in both the continuous amphetamine and continuous cocaine animals in a completely unexpected part of brain: fasciculus retroflexus (‘FR’). The degeneration following each of these dopaminergic drugs showed the same distinctive anatomical pattern: axons from lateral habenula, traveling ventrally in the outside border, or sheath of FR, until they dispersed in ventral mesencephalon. Stained axons with characteristic features of degenerating axons were present, such as a corkscrew shape or segmentation, in which the axon has begun to disintegrate. This pattern of degeneration can best be seen in a sagittal section (Fig. 2).

In further studies we found that intermittent injections of cocaine again did not induce this degeneration and we have now tested a number of other dopaminergics, including methamphetamine, MDMA, and cathinone, and found that they all induce identical degeneration in fasciculus retroflexus (Carlson et al., 2000). While some of these drugs also induce degeneration in other parts of brain as well (amphetamines in caudate terminals, MDMA in serotonergic terminals), for some drugs, such as cocaine, the degeneration in fasciculus retroflexus is virtually the only degeneration induced in brain. This tract appeared to be a ‘weak link’ for binge-like intake of dopaminergic stimulants, and this suggested that degeneration in FR might underlie, in part, the progressive effects which develop with repeated binges. It is well established that with repeated bingeing, addicts report that the paranoia appears earlier with each binge, and this implies progressive changes in some part of brain.

## 7. The lateral habenula and fasciculus retroflexus (FR)

This is an extremely interesting observation, for fasciculus retroflexus is part of a rather poorly understood and anatomically strange circuit in brain. While this circuit carries much of the descending control from forebrain back onto midbrain reward circuits, such as DA and 5HT cell bodies, it takes a very convoluted course (Ellison, 1994). A variety of structures in forebrain project, via GABA

axons in stria medullaris, to the habenula, which is located in the dorsal-most part of diencephalon, just above the thalamus. After synapsing in habenula, a massive pathway, fasciculus retroflexus, descends to innervate various midbrain cells (Herkenham and Nauta, 1979). There are other, much more direct feedback pathways for this reciprocal innervation and descending control, such as along the medial forebrain bundle. However, this circuitous pathway through habenula has remained in higher vertebrates a major source of descending control by forebrain over midbrain monoaminergic cell bodies, representing the major input of all of brain to the raphe nuclei, and a major source of input to dopamine cell bodies.

This circuit clearly seems to be an evolutionary throw-back, for the habenula evolved as the stalk of the pineal gland and the lizards’ ‘third eye’. While in higher vertebrates the pineal gland broke free from direct neural contact with habenula, the neural pathway had been established, and this “dorsal descending conduction system” (Sutherland, 1982) became a major pathway by which forebrain, in reciprocal innervation, could control midbrain reward circuits.

This descending circuit has two medial-lateral halves in habenula, only one of which degenerates after continuous amphetamines or cocaine: the axons projecting ventrally in FR from cells in the lateral habenula. The lateral habenula nucleus receives a majority of its input from dopamine-rich regions such as caudate, accumbens, and frontal cortex, and sends projections which descend in the sheath of the FR tract to dopaminergic cells in SN and VTA and serotonergic cells in the raphe nuclei (Fig. 3).

This an important pathway, for FR carries major inputs from forebrain onto midbrain monoaminergic nuclei, and this consists largely of an inhibitory control. The connections from lateral habenula through FR to dopamine cell bodies have been shown to mediate a large part of the negative feedback between dopamine-receiving forebrain cells and dopamine-releasing midbrain cells. It is well known that the systemic administration of a dopamine agonist leads to an inhibition of firing of dopamine cells in SN, due to a negative feedback circuit from the receiving cells back onto the dopamine cells. It turns out that a most of this negative feedback circuitry is mediated through FR, for this effect is markedly attenuated after lesions of stria medullaris, or lateral habenula, or FR (Sasaki et al., 1990). FR also appears to have a predominantly inhibitory influence on the raphe nuclei.

Thus, with all of these continuous stimulant drug models, lateral habenula and FR seemed to be a common weak link, and we speculated that “these model connections may lead to a new, more complex theory of dopamine dysregulation in psychosis. If the axons which are degenerating due to continuous stimulants prove to be those from lateral habenula which mediate the negative feedback from forebrain dopamine-rich and limbic structures onto midbrain dopamine-secreting cells, an interest-

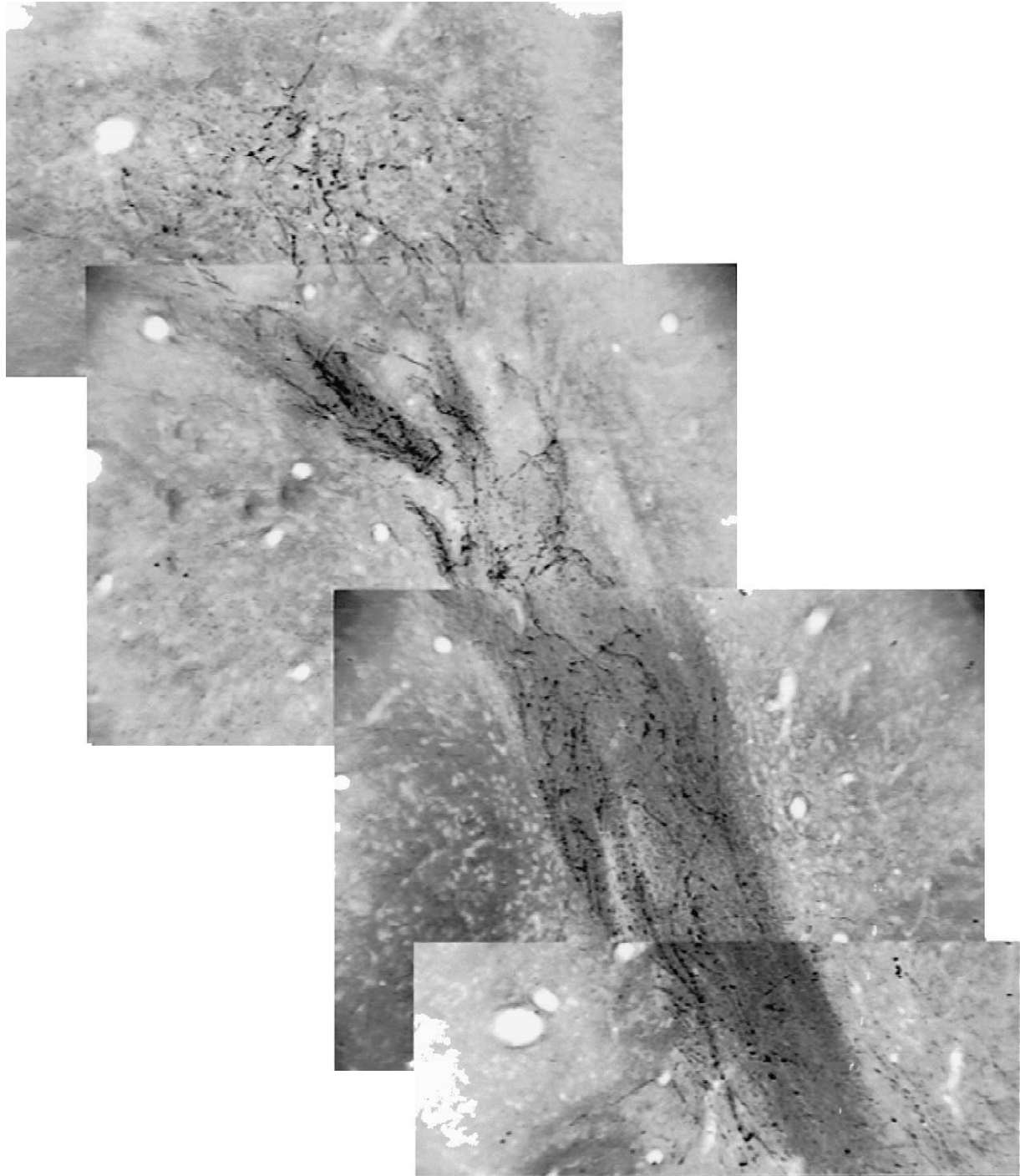


Fig. 2. Saggital section from the brain of a rat given 5 days of continuous cocaine. Multiple long darkly stained degenerating axons and swollen varicosities can be traced through FR.

ing theory about psychosis would follow. This would involve the failing of important inhibitory feedback control over dopamine release by forebrain, and the loss of inhibitory control by forebrain circuitry over serotonin neurons” (Ellison, 1994).

These results do not necessarily imply irreversible damage in chronic stimulant addicts, for these studies used appreciable doses administered to previously drug-naïve

rats. However, they do clearly indicate that FR is a tract especially vulnerable to binge-like stimulant action. While frank degeneration might represent the extreme case, it is likely that this particular pathway would be especially compromised in the confirmed addict. These results have interesting implications. They suggest stages in the addictive process to stimulants which have distinct anatomical correlates.

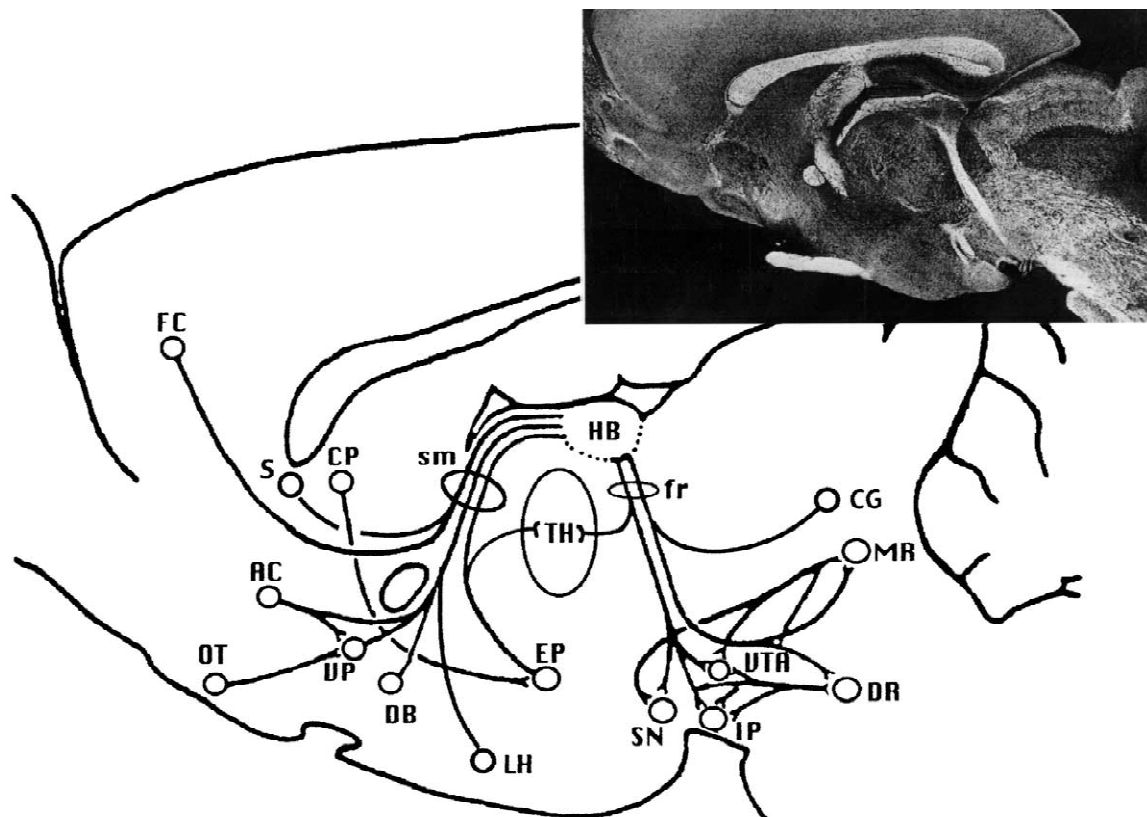


Fig. 3. Schematic diagram of the connections of the habenula. Insert shows sagittal section with myelin stain, demonstrating FR. The two major tracts are sm (stria medullaris), ascending into habenula, and fr (fasciculus retroflexus, descending from habenula). AC, nucleus accumbens; CP, caudate-putamen; DB, nucleus of the diagonal band; DR, dorsal raphe nucleus; EP, entopeduncular nucleus; FC, frontal cortex; fr, fasciculus retroflexus; HB, habenula; IP, interpeduncular nucleus; MR, medial raphe nucleus; OT, olfactory tubercle; sm, stria medullaris thalami; SN, substantia nigra; TH, thalamic nuclei, including dorsomedial, ventral anterior, and ventral lateral; VP, ventral pallidum; VTA ventral tegmental area.

### 7.1. Stage 1: The initial addictive process

During initial experimentation with the drug, as the ascending circuitry becomes sensitized, the drug becomes progressively more reinforcing. This is a consequence of the intermittent, 'sensitization' process. Drug intake gradually increases. This effect appears to be mediated principally in nucleus accumbens, caudate, and frontal cortex.

### 7.2. Stage 2: Nearly continuous, or binge intake

The drug is taken increasingly more frequently and over prolonged periods. Drug addicts report that the 'high' lasts a few minutes, but the paranoia lasts much longer. This is correlated with 2DG studies in rats. Single doses of amphetamine induce a relatively brief increase in glucose metabolism in primary dopamine targets such as caudate, but the habenula circuitry is much more sluggish in its response (Brown and Wolfson, 1983). This means that frequently repeated drug intake induces virtually constant metabolic alterations in the habenular circuitry.

### 7.3. Stage 3: The degenerative stage

Due to the increasingly disrupted axonal circuitry in FR, the forebrain loses control over one of its major regulatory pathways to midbrain reward circuitry. Once this stage is reached, therapeutic strategies for treating drug addiction must change, as different cognitive therapy strategies must be used to counteract the loss of this major descending pathway.

## 8. Further validation of the 'weak link' hypothesis: degeneration in medial habenula and FR induced by nicotine

We have continued to screen other drugs of addiction for where they induce degeneration in brain. Continuous PCP (phencyclidine) and other NMDA antagonists induced degeneration in various limbic cells, but none in FR (Carlson et al., 2000). We could find no degeneration in FR (or, remarkably, in any of brain) after substantial continuous doses of LSD. But when we tested nicotine, at a dose

which we had previously found to induce persisting behavioral alterations, such as increases in sucrose intake compared to fats or proteins (Jias and Ellison, 1990), or increases in alcohol intake (Pothoff et al., 1983), or improved performance in the eight-arm maze cognitive test for rats (Levin et al., 1990), we found that the degeneration induced by continuous nicotine was the most selectively confined degeneration we had ever encountered in brain (Fig. 4).

Nicotine given continuously has an extraordinarily selective degeneration profile in brain: at least 95% of the degeneration in brain is confined to the other half the fasciculus retroflexus: the cholinergic axons descending from the medial habenula through the core of the tract to the interpeduncular nucleus. Medial habenula predominantly receives limbic inputs, including the septal region, diagonal band of Broca, and nucleus accumbens. However, this highly localized degeneration in FR might not have been entirely unexpected, for this cholinergic half of FR is one of the largest cholinergic pathways in rat brain (Herkenham and Nauta, 1979; Woolf and Butcher, 1989) and contains one of the highest concentrations of nicotinic receptors in all of brain (London et al., 1985; Perry and Kellar, 1995). But even at very high, extreme doses, the degree of selectivity of this neurotoxicity is extraordinary, and this was rather surprising because nicotine is generally a very toxic substance. In further studies, we found that degeneration in FR could also be observed at lower doses, including one which induces plasma levels of nicotine and its metabolites which approximate those of heavy smokers (Carlson et al., 2000).

The addition of the nicotinic neurotoxic effect on FR to the previous findings dramatically amplifies this neuro-anatomical model of stimulant drug additions. That two major classes of addictive drugs would attack the same

pathway in brain implies a common link between stimulant and nicotinic addictions, but also clearly establishes FR as a ‘weak link’ in brain for addictions. Because stimulants which primarily potentiate dopamine are, besides PCP, among the best drug models of psychosis, this pathway through FR should also be a prime candidate for mediating other psychiatric disorders.

#### **9. Why are the pathways synapsing in habenula so susceptible to continuous stimulant or nicotinic administration?**

These experiments raise the question of why it is that this tract, of all pathways in brain, is so vulnerable, and what are the mechanisms which mediate this neurotoxicity. There are two unusual characteristics of this degeneration in FR which may make this question solvable. One is the unusual microanatomy of this degeneration. It may be a major clue to the neurotoxicity produced in FR by various drugs of abuse that it involves axons exclusively, with no staining of cell bodies or terminals, for the analysis of which neuronal parts are primarily affected by various neurotoxins often provides an important clue as to the mechanisms involved in the toxicity. Thus, the neurotoxic effects of continuous amphetamines on dopamine terminals in caudate are widely thought to be due to the uptake into dopamine terminals of a neurotoxic substance (Fleckenstein et al., 1997; Hanson et al., 1987) and this correlates well with the observation that this degeneration is concentrated in synaptic terminals and axon endings. Similarly, NMDA antagonists such as PCP or MK-801 induce limbic degeneration which may involve an excitotoxic mechanism, perhaps produced by hyperactivity at the non-blocked AMPA receptors (Ellison et al., 1999; Sharp et al.,

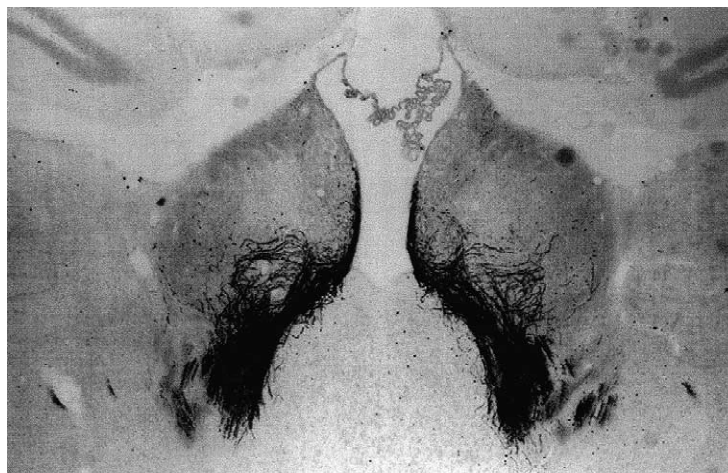


Fig. 4. Section through habenula following a high dose of nicotine. The intense degeneration can be seen bilaterally exiting from most medial aspects of habenula and projecting down into fasciculus retroflexus.

1995), and this correlates with the observation from silver degeneration stains that this neurotoxicity involves entire neuronal cells, with the complete cell body, including all processes, stained. This raises the question of what kind of neurotoxic mechanisms would involve only axons.

The second unusual characteristic, related to the first, is that two anatomically parallel yet neurochemically completely distinct FR systems show the same distinctive pattern of only axonal degeneration. It seems likely that there would be similarities in the mechanisms underlying degeneration in the two axonal systems, and that hypotheses developed from studies of one system could also be tested on the other, and similarities sought.

#### **10. Possible mechanisms underlying continuous stimulant-induced degeneration in the sheath of the tract**

In most cases of neurotoxicity induced by drugs of abuse, the neurotoxic effects are observed in brain regions where glucose metabolism is markedly heightened by the drug. The neurotoxic effects of continuous cocaine and amphetamine in axons from lateral habenula in FR are unusual in that they are so strongly correlated with a *decrease* in glucose metabolism in the habenula induced by these drugs. A number of studies of glucose utilization have consistently shown that while virtually all dopamine agonists increase glucose metabolism in dopamine-rich regions such as caudate nucleus, nucleus accumbens, substantia nigra, and VTA, they markedly decrease glucose metabolism in the habenula (cf. Ellison, 1994). Dopamine antagonists conversely increase glucose metabolism in lateral habenula. Yet dopamine agonists induce c-Fos expression in lateral habenula cells, leading to the hypothesis (Wirtshafter et al., 1994) that the GABA efferents in stria medullaris are strongly inhibited by the dopamine agonists. Thus, forebrain structures with rich dopaminergic innervations induce, via synaptic pathways through stria medullaris (some of which are mediated through entopeduncular nucleus—the rat globus pallidus) a chronic inhibitory influence on lateral habenula cells. During continuous stimulants, the reduced activity in the terminals of these GABA projections to lateral habenula results in both the reduction of 2DG uptake and the disinhibition of lateral habenular cells, leading to their continuous hyperactivity and c-Fos induction. An important finding is that these effects in habenula are mediated via stria medullaris, rather than due to other, direct effects in the nucleus, for 6-OHDA lesions of the nigrostriatal pathway eliminate the c-Fos induction in lateral habenula produced by dopamine agonists (Wirtshafter et al., 1994).

These findings suggest that the neurotoxicity induced by continuous amphetamine or cocaine in the FR axons may be due to the prolonged hyperactivity in the lateral

habenula cells produced by the removal of GABAergic inhibitory influences, leading to a prolonged overstimulation of these cells and an eventual neurotoxicity. Further evidence for this hypothesis comes from other studies (Keys and Ellison, 1999) in which rats were given continuous cocaine, a 14-day recovery period, and then sacrificed for autoradiographic studies using a variety of ligands for GABA, muscarinic, AMPA, serotonergic, and other receptors, as well as for the dopamine transporter. The largest change in receptor density for any ligand and any brain region was GABA receptors in habenula. Electron microscopic studies (Meshul et al., 1998) confirmed that continuous cocaine selectively induces changes in GABA junctions in lateral habenula.

This evidence suggests an excitotoxic effect on cells in lateral habenula. But were this true, why are there no degenerating cell bodies? Some cellular degeneration would eventually be expected, particularly with repeated bouts with the drug, and surely some time after continuous high doses of dopaminergics, or nicotine, decreased cell counts would be found. We have found that further bouts of cocaine induce further axonal degeneration, that frequently repeated bouts are especially neurotoxic, and that repeated bouts of cocaine induce a pale silver staining of a few cells in lateral habenula (Ellison et al., 1996). But the silver staining technique clearly indicates that the primary neurotoxic target of continuous dopaminergics is selectively the axons in the sheath of FR.

#### **11. Possible mechanisms underlying continuous nicotine-induced degeneration in the core of the tract**

However, a very different picture emerges from the studies related to the nicotine-induced neurotoxicity. There are a number of interesting correlates of this degeneration. That it is so anatomically selective is surprising, but that it occurs in the medial habenula–FR–interpeduncular system is not, for this system contains the highest concentrations of nicotinic receptors in brain (London et al., 1985; Perry and Kellar, 1995). Yet FR is an axonal tract. The labeling of this tract by nicotine, as well as the more selective nicotinic agonist epibatidine (Plenge and Møllerup, 1998), indicates receptors within the tract. And these may not just be vesicularly encapsulated nicotinic receptors being transported down this tract, for acute nicotine injections increase glucose metabolism in FR (London et al., 1988).

Receptors in axons have also been observed in other systems, such as opioid receptors in caudate and there are suggestions that stimulation can make these receptors move to the plasma membrane when the neuron is stimulated (Meshul and McGinty, 2000). In the case of nicotinic receptors and FR, this would lead to the opening of ion channels along FR due to the nicotinic brain plasma levels.

## 12. Effects of lesions of habenula or fasciculus retroflexus

These results with FR, taken as a whole, constitute strong evidence that alterations in this pathway, descending from forebrain, and exerting important control over lower midbrain structures, may constitute a ‘weak link’ in brain for chronic drug effects, including addiction and relapse. This descending system appears to have rather diffuse effects, for a wide variety of effects on behavior, sleep stages, and seizures are reported following lesions or stimulation of habenula or FR.

Lesions of habenula or FR disrupt a number of complex behaviors; these effects have been reviewed (Sutherland, 1982; Sandyk, 1991; Ellison, 1992). There are numerous reports that lesions of the habenular complex produce disruptions in a variety of behaviors, including mating behavior, avoidance learning, maze learning, feeding behavior, and hormonal response to stress. Thornton and Bradbury (1989) and Thornton et al. (1994) found deficits in avoidance behavior after small lesions confined to the habenula. Thornton and Davies (1991) found that lesions of the habenula resulted in impairments of learning in a water maze. Lee and Huang (1988) reported that lesions of the lateral habenula increased exploratory behavior in several paradigms. Haun et al. (1992) reported that lesions of fasciculus retroflexus disrupted normal sleep patterns; this is predominantly a suppression of REM sleep (Valjakka et al., 1998). Deficits in maternal behavior occur following habenular lesions in rats (Corodimas et al., 1992; Felton et al., 1998), as do deficits in spontaneous alternation in a t-maze. Electrical stimulation of lateral habenula causes an increase in epileptiform activity in hippocampus induced by local penicillin (Sabatino et al., 1991); this appears to be mediated by inhibitory effects on raphe. Carvey et al. (1988) found that bilateral lateral habenula lesions induced by kainic acid resulted in hyperactivity and a long-lasting potentiation of hyperactivity induced by low doses of apomorphine. Food intake is altered following habenular lesions (Wolinsky et al., 1994).

The habenula is involved in reward mechanisms. Rats will press levers to get stimulation in the dorsal diencephalic bundle within or just adjacent to the stria medullaris (Blander and Wise, 1989); this appears to be mediated through habenula’s connections with raphe (Sutherland and Nakajima, 1981). Boyd and Celso (1970) found that lesions of fasciculus retroflexus suppress self-stimulation from electrodes in the septum, and when Routtenberg et al. (1971) traced degeneration patterns after lesions placed at self-stimulation sites dorsal to the medial forebrain bundle, they reported degeneration most predominantly in lateral habenula. Brown et al. (1992) suggest an important role of lateral habenula in conditioned effects of cocaine, which they propose may be related to craving for the drug.

Habenula is also involved in pain inhibition. It mediates

aspects of the analgesia induced by electrical stimulation in brain, for lesions of LH or FR abolish part of stimulation-produced analgesia. Injections of naloxone into the habenula antagonize the analgesia elicited by morphine injected in the periaqueductal gray (Ma et al., 1992) or accumbens (Yu and Han, 1990), and electrical stimulation of periaqueductal gray results in C-fos immunoreactivity in lateral habenula (Sandner et al., 1992). Electrical stimulation of habenula results in a naloxone-reversible analgesia (Mahieux and Benabid, 1987). The majority of cells in lateral habenula respond to peripheral noxious stimulation (Benabid and Jeaugey, 1989).

Alterations in habenula have been reported in schizophrenics by Sandyk (1991) and Scheibel (personal communication).

## 13. Is FR a weak link for other psychiatric disorders?

The degeneration induced in FR by continuous stimulants has a unique feature which makes it especially appealing as a model of other, endogenous psychoses. Most neurotoxic effects of drugs of abuse are due to pharmacologically local (i.e. direct) neurotoxic effects of the drugs on neuronal elements. Examples are continuous amphetamines on caudate terminals, MDMA on serotonin terminals, PCP on limbic neurons. However, the effects of amphetamine or cocaine on FR are much more intriguing in that they appear to be mediated by a complex, multisynaptic circuitry, as the normal inhibitory GABAergic input to lateral habenula is chronically inhibited. A profound implication of this is that any other endogenous disorder which might also induce incessant dopaminergic hyperstimulation would be expected to similarly attack this phylogenetically compromised tract. During the psychotic break there is often a prolonged period of sleeplessness, anorexia, and a compulsive focusing (Bowers, 1968); these are all amphetamine-like symptoms. The implication is any chronic hyperdopaminergic state would similarly lead selectively to a compromised lateral habenula–FR projection.

The addition of the nicotinergergic neurotoxic effect in FR dramatically amplifies this neuroanatomical model of stimulant drug addictions. That two major classes of addictive drug would attack the same pathway in brain implies a common link between stimulant and nicotinic addictions. This link is very well documented, for there is a very high rate of nicotine intake in schizophrenics, as well as indications of decreased incidence of dopamine-related disorders such as Parkinson’s disease in smokers.

The medial and lateral habenula have a complex microanatomy, but there is minimal direct axonal communication between the two nuclei. With other paired structures in brain, such as the lateral versus medial hypothalamus and feeding behavior, there is often a balance between the

two halves, with damage to one nucleus producing an imbalanced output, which can only be corrected by a similar action on the other half. More attention needs to be paid to this habenula–FR system in studies of drug addiction, and also in the investigation of relations between various psychiatric disorders and nicotine<sup>1</sup>.

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<sup>1</sup>There is an interesting historical note relevant to these results. Rene Descartes hypothesized that the pineal gland was the ‘seat of the soul’ based upon its anatomical location and unitary (unpaired) structure at the center of the brain. If one believes that the confirmed, end-stage amphetamine or cocaine addict has ‘lost their souls’ to the drug, Descartes was only off by a few millimeters in his conclusion.

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