Overview of adrenergic anorectic agents

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ABSTRACT Adrenergic anorectic agents of the amphetamine class suppress appetite and reduce body weight via activation of β-adrenergic and/or dopaminergic receptors within the perifornical hypothalamus (PFH). Although phenylpropanolamine (PPA) is often considered to be a member of the amphetamine class of anorexiants, this drug is an atypical adrenergic anorexiant. Unlike amphetamine, microinjection of PPA into the PFH does not suppress feeding. Moreover, PPA anorexia is not reversed by the dopamine antagonist haloperidol. The anorexic action of PPA may result, in part, from its interaction with α1-adrenergic receptors within the paraventricular medial hypothalamus (PVN). This hypothesis is supported by prior research, which documents that PPA is a direct-acting agonist predominantly at α1 adrenoceptors, that microinjections into the PVN of the α1-adrenoceptor agonists PPA and l-phenylephrine suppress feeding, and that injections of α1-adrenoceptor antagonists within the PVN enhance feeding behavior. Am J Clin Nutr 1992;55:1935–85.

KEY WORDS Adrenergic anorectic agents, hypothalamus, amphetamine, phenylpropanolamine, α1-adrenergic receptors

Introduction

Most research and clinical workers today recognize that an effective treatment for obesity will involve a variety of modalities including behavioral, exercise-based, pharmacologic, and perhaps surgical treatments. As we enter the 1990s, a limited number of prescription and over-the-counter (OTC) drugs are available in the United States to suppress appetite and reduce body weight. Table 1 summarizes the regulatory classification (Schedules 2–4 or OTC) and trade name for each of the appetite suppressants as well as an index of the relative effectiveness of each drug for the induction of weight loss (kg/wk) (3, 4). With the exception of fenfluramine, these anorexogenic drugs are viewed as sympathomimetic amines similar in neuropharmacologic action to the prototypical anorexiant, amphetamine. Although the amphetamine anorexigens generally produce a comparable degree of weight loss in double-blind clinical trials, these drugs exert differential effects with regard to propensity for abuse. Amphetamine, a Schedule 2 anorexiant, has marked abuse potential whereas phenylpropanolamine (PPA), an OTC drug, has no abuse potential.

The intent of the present overview is to describe the neurochemical mechanisms of action by which anorectic drugs such as amphetamine may act to suppress appetite, including adrenergic and/or dopaminergic activity within the lateral perifornical regions of the hypothalamus (PFH). Yet, not all adrenergic agents act via the lateral hypothalamus. As will be shown below, PPA represents an atypical adrenergic drug, which may suppress feeding, in part, via activation of postsynaptic α1-adrenergic receptors within the medial hypothalamic paraventricular nucleus (PVN).

Figure 1 depicts a schematic representation of the adrenergic synapse, including the synthesis and release of the transmitter norepinephrine (NE) into the synaptic cleft, its interaction with pre- and postsynaptic receptors, and the eventual reuptake and/or degradation of NE. Adrenergic receptors are divided into α-adrenergic and β-adrenergic classes. Each adrenergic receptor class is further subdivided into subtypes (α1 and α2, β1 and β2). The α receptor class is particularly relevant to an understanding of the neuropharmacological control of feeding within brain. Alpha-1-adrenergic receptors are most sensitive to the agonists phenylephrine and methoxamine and are antagonized by prazosin, whereas α2-adrenergic receptors are activated by clonidine and are antagonized by yohimbine. Alpha-1- and α2-adrenergic receptors are located on the postsynaptic membrane, whereas some α2-autoreceptors are located on the presynaptic membrane (these serve to inhibit NE release). Beta-1 and β2 receptors, in contrast, are differentially sensitive to dobutamine and salbutamol and are located within the heart and vasculature, respectively.

Adrenergically elicited feeding: the PVN

In 1960, Grossman (5) reported that local application of crystalline norepinephrine into the lateral hypothalamus elicited a marked eating response in food-satiated rats. Subsequent systematic mapping studies noted that, although the induction of feeding by NE was observed in both lateral and medial aspects of the hypothalamus, the medial and anterior aspects of the hypothalamus, especially the PVN, yielded the site of greatest sensitivity to NE (6). Moreover, the feeding response induced by NE was observed at doses (1–4 ng) approaching the physiological level (7), suggesting that NE was acting at endogenous receptors within the hypothalamus to enhance feeding.

Receptor-binding studies revealed the presence of both α1- and α2-adrenergic receptor subtypes in the medial hypothalamus of rat brain (8, 9). Pharmacologic studies revealed that the elici...
TABLE 1
Appetite suppressant drugs available in the United States

<table>
<thead>
<tr>
<th>Drug</th>
<th>DEA schedule</th>
<th>Tradename</th>
<th>Dose</th>
<th>Average weight loss* (less placebo)</th>
<th>Duration</th>
<th>Weight loss</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphetamine</td>
<td>II</td>
<td>Benzedrine, Biphentine</td>
<td>5 mg tid</td>
<td>2.8</td>
<td>12</td>
<td>0.23</td>
</tr>
<tr>
<td>Phenmetrazine</td>
<td>III</td>
<td>Preludin</td>
<td>75 mg</td>
<td>1.2</td>
<td>6</td>
<td>0.2</td>
</tr>
<tr>
<td>Benzphetamine</td>
<td>III</td>
<td>Didrex</td>
<td>75-150 mg</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Chlorphentermine</td>
<td>III</td>
<td>Voranil</td>
<td>50 mg</td>
<td>0.7-1.1</td>
<td>4</td>
<td>0.28</td>
</tr>
<tr>
<td>Clortermine</td>
<td>III</td>
<td>Pre-Sate</td>
<td>65 mg</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Phendimetrazine</td>
<td>III</td>
<td>Bontril, Plegine</td>
<td>105 mg</td>
<td>2.9</td>
<td>12</td>
<td>0.24</td>
</tr>
<tr>
<td>Diethylpropion</td>
<td>IV</td>
<td>Tenuate, Tepanil</td>
<td>25 mg tid</td>
<td>2.6</td>
<td>12</td>
<td>0.22</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>IV</td>
<td>Pondimine</td>
<td>20 mg tid</td>
<td>4.1</td>
<td>12</td>
<td>0.34</td>
</tr>
<tr>
<td>Mazindol</td>
<td>IV</td>
<td>Mazoran, Sanorex</td>
<td>2 mg</td>
<td>3.7</td>
<td>12</td>
<td>0.31</td>
</tr>
<tr>
<td>Phentermine</td>
<td>IV</td>
<td>Adipex, Fastin, Ionamin</td>
<td>30 mg</td>
<td>4.8</td>
<td>14-16</td>
<td>~0.32</td>
</tr>
<tr>
<td>Phenylpropanolamine</td>
<td>OTC</td>
<td>Dextrim</td>
<td>75 mg</td>
<td>4.62</td>
<td>20</td>
<td>0.23†</td>
</tr>
</tbody>
</table>

* The weight loss data are derived, except where noted, from reference 1.
† Data derived from reference 4.

Iontophoretic application of NE generally induces inhibition of nerve cells and it has been suggested that exogenous NE infusion into the PVN may serve to inhibit a descending satiety control system (13). Further, endogenous NE rhythms within the PVN have been related to diurnal rhythms of feeding and to hunger induced by deprivation. Microdialysis experiments revealed an endogenous rhythm for the release of NE within the PVN with a peak in extracellular NE level at the start of the dark phase of the diurnal cycle. At that time rats exhibit vigorous feeding bouts (14). This peak in NE corresponds to an increase in the density of α2 adrenoceptors within the hypothalamus at the start of the dark cycle as determined by receptor-binding studies (15). The latter result may explain why NE injections into the PVN produce a greater enhancement of feeding at the start of the dark cycle than at other times during the diurnal cycle. Moreover, extracellular NE levels within the PVN increase by 215% after 24-h food deprivation but rapidly return to baseline upon refeeding (14). These experiments, when considered with those described earlier, suggest that an endogenous NE system within the PVN acts via postsynaptic α2 adrenoceptors to modulate feeding behavior.

Adrenergic suppression of feeding: the PFH

In contrast to the relative insensitivity of the lateral regions of the hypothalamus to NE (13), direct injection of certain phenylethylamine drugs into the perifornical region of the lateral hypothalamus suppressed feeding in hungry rats. These data are clearest for the phenylethylamine amphetamine (AMP). Direct injections of AMP into the PFH suppressed feeding at dosages as low as 6.25 nmol (16, 17). The neuropharmacologic basis by which AMP suppresses feeding was soon traced to two distinct effects on catecholamine activity within the PFH. AMP anorexia was mimicked by direct injection into the PFH of various β-
adrenergic agonists (NE, isoproterenol, epinephrine) or the transmitter dopamine (DA, 17). Pharmacologic antagonism of β-adrenergic receptors or DA receptors within the PFH reversed the anorexic activity of AMP (17). The hypothesis that systemic amphetamine acts within the PFH to suppress feeding was further supported by experiments in which electrolytic lesions of the lateral hypothalamus antagonized the anorexic activity of AMP (18). Moreover, destruction of ascending adrenergic and noradrenergic fibers which innervate the PFH attenuated the anorexic activity of amphetamine (19, 20).

These studies suggested a general model of the adrenergic control of feeding (13, Fig 2). In this model, a medial noradrenergic mechanism functions to increase feeding (presumably by α2-adrenoceptor-mediated inhibition of a descending satiety control), whereas a β-adrenergic/dopaminergic mechanism within the PFH functions to suppress food intake. The inhibitory action on feeding of serotoninergic agonists such as fenfluramine after injection into the PVN is accounted for in Figure 2 by the hypothesized action of serotonin (5-HT) on the PVN noradrenergic mechanism (13).

PPA: an atypical adrenergic anorectic

PPA is a racemic mixture of the enantiomers d- and l-norephedrine (NEP), which are only slightly different from amphetamine in structure (see Fig 3). The l-NEP molecule is a more potent appetite suppressant than is the d-NEP enantiomer (21, 22). In the periphery, PPA is known to act primarily as a mixed agonist at α2-adrenergic receptors, but the drug does have a slight effect at α1-adrenergic receptors (23). Although PPA only weakly penetrates into brain because of its poor lipid solubility (24), systemic administration of PPA does alter brain catecholamine activity (25–27).

Although PPA structurally resembles amphetamine, PPA does not act on β-adrenergic/dopaminergic receptors within the PFH to suppress appetite. Wellman and Cockroft (28) compared the effects on feeding of microinjection of d-amphetamine and PPA (40, 80, and 160 nmol) within the PFH. Although amphetamine induced a dose-dependent suppression of feeding, PPA was without effect on feeding. In a complementary experiment, systemic administration of the dopaminergic receptor antagonist haloperidol was found to reverse the anorexic effect of amphetamine, but not that induced by the l-NEP enantiomer of PPA (29).

In yet another experiment, Wellman and Davies (30) compared the effect on feeding of local injection of d-amphetamine and PPA within the PVN (see Fig 4). Both drugs suppressed appetite when injected into the PVN at a dose of 160 nmol/L. This experiment suggested that PPA might act via the PVN to suppress appetite. The locus was somewhat surprising given that prior research by Leibowitz (6, 8) had documented that α2-adrenergic stimulation within the PVN enhanced rather than suppressed feeding and that PPA is known to have weak activity as an α2-adrenergic agonist (23).

Two distinct adrenergic mechanisms were identified by us as possibly explaining the anorexic action of PPA within the PVN. The first explanation drew its inspiration from the assertion of Leibowitz (31) that reduced feeding might result from a manipulation that suppresses noradrenergic function in the PVN. We took note of the fact that most tests of PPA anorexia involved fasting states in which PVN NE levels are likely to be high and

![FIG 2. Schematic of adrenergic mechanisms that modulate feeding within the medial and lateral regions of the hypothalamus. Paraventricular nucleus (PVN); third ventricle (IIIv); perifornical hypothalamus (PFH); fornix (F); dopaminergic (DA); β-adrenergic (β-ADR); norepinephrine (NE); serotonin (5-HT); phenylpropanolamine (PPA). (Adapted from reference 13)](https://academic.oup.com/ajcn/article-abstract/55/1/193S/4715206)
FIG 4. Percent suppression of feeding induced by 160 nmol PPA injected into various sites within the paraventricular hypothalamic nucleus. (Reprinted with permission from reference 28).
ADRENERGIC ANOREXIC AGENTS

Our recent results suggest a simple explanation for the seemingly paradoxical suppression of feeding noted after intra-PVN
injection of PPA. The explanation (diagrammed in the upper portion of Fig 2) proposes that α₂-adrenergic receptor activation
within the PVN enhances the activity of the putative PVN satiety
mechanism. This explanation takes into account the known
pharmacologic activity of PPA and is in accord with an earlier
study from Goldman et al (10), which reported that injection of
the α₂-adrenergic receptor antagonist yohimbine enhanced
feeding induced by NE within the PVN. Whether the α₂-adrenergic
activity of PPA plays a role in its anorexic activity remains
to be established in future experiments.

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Fig 5. Effects of feeding during a 60-min test period for rats after
administration of various adrenergic drugs (dose in nanomoles) into the
PVN. The drug injections were: vehicle (VEH), norepinephrine (NE),
clonidine (CL), l-phenylephrine (PN), and phenylpropanolamine (PPA).
The lines above each bar represent the standard error of the mean. (Re-
printed with permission from reference 31).