Leptin as a Possible Modulator of Craving for Alcohol

Whereas the psychological construct and pathophysiological basis of craving for alcohol, a major risk for relapse in alcoholism, has been intensively evaluated in recent years, no measurable biological correlate exists.\(^1\) Neurobiological and psychological similarities between craving and appetite are well established since both are known to be influenced by the mesolimbic brain reward system and its endorphinergic inputs.\(^2\) Recently, leptin, the protein product of the obesity gene, was proposed to be a signal responsible for linking adipose stores with hypothalamic centers regulating energy homeostasis and body weight.\(^3\) In addition, leptin has been shown to alter the gene expression of corticotropin-releasing hormone and pro-opiomelanocortin in the hypothalamus, suggesting a role both in regulating the stress hormone axis and possibly in the endorphinergic modulation of the reward system.\(^4\) Leptin mutually interacts with other neuroendocrine systems involved in the regulation of appetite such as NPY (neuropeptide Y)\(^5\) or the newly discovered hypothalamic peptide CART (cocaine- and amphetamine-regulated transcript).\(^6\)

To prove the hypothesis that leptin is also associated with alcohol craving, we observed craving challenged by alcohol withdrawal and assessed plasma leptin levels (radioimmunoassay) in a consecutive sample of 20 subjects with alcohol dependency 1 and 14 days after onset of withdrawal and in 16 healthy volunteers. To control for mutual interactions of plasma leptin and pituitary-adrenocortical hormone secretion, which is regularly enhanced during withdrawal, plasma cortisol (radioimmunoassay) was also determined. Patients with alcohol dependency and without psychiatric comorbidity were diagnosed according to international classifications (DSM-IV criteria). Mean (SD) age was 43 (10.6) years; weight, 65 (9.1) kg; and body mass index (BMI) (calculated as weight in kilograms divided by the square of height in meters), 20.65 (3.10). Controls did not differ significantly in these data. Normally distributed data were tested for significance using Pearson product moment correlation coefficients, partial correlation coefficients, and \(t\) tests for group comparisons. In accordance with prior studies, leptin was highly correlated \((r=0.79, P<.001)\) with the BMI. In subjects with alcohol dependency, leptin levels as well as the leptin-BMI ratio decreased significantly \((P<.03)\) between day 1 and 14 but were significantly elevated at day 14 compared with controls \((P<.03)\). At the onset of withdrawal, self-rated craving for alcohol on a visual analog scale correlated with the leptin-BMI ratio \((r=0.68, P<.04)\). Dichotomization of the patient sample by the common median of BMI revealed an even stronger correlation of leptin plasma level and craving in patients with a BMI lower than 20.56 \((r=0.85, P<.005; n=10)\). During therapy, craving decreased significantly without being related to leptin at day 14, pointing not to a simple relation but to a more complex interaction of leptin with other regulatory systems. Plasma cortisol was positively correlated with clinically assessed withdrawal (Clinical Institute Withdrawal Assessment for Alcohol questionnaire) but without any relation to leptin, leptin-BMI ratio, or craving, suggesting that elevated plasma leptin was independent from withdrawal-induced activation of the pituitary-adrenocortical axis (Figure). This is also confirmed by calculation of the partial correlation of craving with the leptin-BMI ratio controlling for cortisol \((r=0.54, P<.02)\). According to prior results, no association between liver damage \((\gamma\text{-glutamyltransferase, aspartate transaminase, alanine transaminase})\) and leptin levels was seen. Fulton et al\(^7\) recently showed that the rewarding effect of lateral hypothalamic electrical stimulation in rats was attenuated by intracerebroventricular infusion of leptin. In line with their assumptions, our results may also reflect a comparative process underlying behavioral al-
location with reducing food reward while enhancing the value of competing behaviors such as craving. Taking into account the major role of ethanol in energy homeostasis in alcoholics and the suggestion that a leptin-induced modulation of the brain reward system may prime appetite for alcohol, our results give, to our knowledge, the first evidence that increased leptin may be involved in withdrawal-induced alcohol craving.

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Admixtiture Analysis of Age at Onset in Bipolar I Affective Disorder

Age at onset (AAO) has frequently been a key indicator in delineating disorder subtypes leading to gene identification. Thus far, differences in AAO have helped to separate genetic from sporadic cases in common illnesses such as breast cancer. Differences in AAO may also be used to identify different vulnerability genes, as in Alzheimer disease, or different mutations in the same gene, as in Duchenne-Becker muscular dystrophy. More recent findings have shown that AAO may also reflect differential expansion of an unstable DNA region at or near the disease locus, as in myotonic dystrophy and Huntington disease.

In bipolar I affective disorder (BPAD), clinical, familial, and biological differences have been reported according to AAO. Early-onset BPAD is associated with (1) higher frequency of affective disorders in relatives; (2) higher rates of comorbid conditions such as psychotic symptoms during affective episodes; lifetime panic disorder, conduct disorder, alcohol abuse, and drug addiction; and (3) more frequent suicidal behavior. Poor prognosis and poor lithium response are thought to be associated with early onset. Genetic studies also suggest differences as an association between the apolipoprotein E e4 allele and early-onset BPAD and the tyrosine hydroxylase gene polymorphism have been reported. In linkage studies, Baron et al suggest that X-linked BPAD is characterized by an early AAO, a high familial loading of affective disorder, and a high frequency of depressive relapses. In addition, AAO has been shown to be correlated in affected siblings, suggesting that some familial vulnerability factors may be age-specific.

Despite the large amount of data available, none of the various thresholds of AAO used in clinical, biological, and familial studies have been validated. The findings obtained to date raise several questions concerning AAO in BPAD: (1) Is AAO a clinical indicator that distinguishes different biological subtypes of BPAD? (2) Should patients with different AAOs be considered as a continuum, presenting with qualitatively similar forms of the same disorder but differences in severity? If AAO is a marker for biologically different subtypes of BPAD, then AAO subgroups should have separate normal distributions with different means, variances, and population proportions as well as different clinical characteristics. In contrast, if patients with different AAOs form a continuum, then they would be expected to form a single normal distribution with similar clinical characteristics. We explored these questions by performing an admixture analysis of AAO in a sample of prospectively recruited patients with BPAD.

Sampling Method. Consecutive inpatients and outpatients meeting DSM-IV criteria for BPAD were included. They were interviewed with a French version of the Diagnostic Interview for Genetic Studies. Written informed consent was obtained from patients. The clinicians who conducted the interviews were blind to the hypothesis tested.

Age at onset was defined as the age at which the patient first met DSM-IV criteria for either a major depressive episode or mania according to medical case notes and interviews. Age at onset was first assessed by the interviewer (F.B.) and then blindly rated by an independent psychiatrist (F.S.) according to medical case notes and the information collected by the Diagnostic Interview for Genetic Studies. Interrater reliability for AAO was high (r = 0.99).

Statistical Method. We used admixture analysis, a method for identifying the model that best fits the observed distribution of a continuous variable. This method was used to test whether the observed AAO distribution was a mixture of gaussian distributions. The number of components was determined using forward stepwise estimation and maximum likelihood ratio tests as criteria for adding a component. The criterion used for adding a component was the threshold value of a χ² distribution with 3 degrees of freedom at the .05 level. For each number of components, the weights, means, and variances of each component were estimated using the stochastic expectation maximization algorithm.

Results. Two hundred eleven patients (118 women, 93 men; mean [SD] age at interview, 42.4 [14.8] years) were included. The likelihood ratio criterion between the models with 3 and 2 distributions was χ²(3) = 23
(P<.001). No further improvement was obtained using the 4-component model. Thus, the model that best fit the observed AAO distribution was a mixture of 3 gaussian distributions (mean [SD] [proportion of the population]): 16.9 (2.7) years (41.4%), 26.9 (5.0) years (41.9%), and 46.2 (8.0) years (16.6%) (Table 1).

Comment. This study was designed to test the popular but unproven notion that AAO is a marker for different subtypes of BPAD. We demonstrated that the observed distribution of AAO in BPAD is a mixture of 3 gaussian distributions.

Gaussian mixture analyses applied to individual studies may have limited power because sample sizes are small. However, our sample of 211 patients with BPAD provides sufficient power, as several authors have recommended the use of samples of more than 100 for such analyses.19,20 To our knowledge, this is the first demonstration that AAO does not have a normal distribution in BPAD, suggesting that AAO may be of value for distinguishing between the various biological subgroups of BPAD. McMahon et al21 have already suggested that BPAD is heterogeneous in terms of AAO. Comparison of early- and late-onset patients with BPAD has repeatedly demonstrated clinical, therapeutic, and familial differences. Further evidence of the existence of 3 subgroups according to AAO is provided by our findings that these subgroups have different clinical profiles. Our results demonstrate the need to use a validated AAO cut-off in future studies to describe these bipolar subgroups further.

If confirmed, these results have important implications for the search for vulnerability factors underlying BPAD. In particular, AAO has been shown to be correlated in affected siblings, suggesting that some familial vulnerability factors may be age-specific.16 Thus, work-

Table 1. Description of the Age at Onset Distributions*

<table>
<thead>
<tr>
<th>Class</th>
<th>Mean (SD), y</th>
<th>Proportion of the Population, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.9 (2.7)</td>
<td>41.4</td>
</tr>
<tr>
<td>2</td>
<td>26.9 (5)</td>
<td>41.9</td>
</tr>
<tr>
<td>3</td>
<td>46.2 (8)</td>
<td>16.6</td>
</tr>
</tbody>
</table>

*Likelihood: χ², 23; P=.001.

Table 2. Clinical Characteristics of Patients Belonging to the 3 Distributions Identified by the Admixture Analysis of Age at Onset*

| Class | At Least 1 SA, %† | Number of SA, Mean (SD)‡ | At Least 1 Violent SA, %§ | Family History of Affective Illness, %|| | Psychotic Symptoms During Affective Episode, %¶ | Sex Ratio, % F# |
|-------|-------------------|--------------------------|--------------------------|-------------------------------|----------------|----------------------------------|----------------|
| 1     | 48.3              | 1.2 (1.9)                | 31.0                     | 70.4                          | 72.6          | 57.4                             |
| 2     | 37.9              | 0.57 (0.06)              | 34.5                     | 68.0                          | 69.7          | 57.4                             |
| 3     | 22.6              | 0.35 (0.8)               | 71.4                     | 51.0                          | 51.6          | 46.8                             |

*SA indicates suicide attempt.
†Univariate analysis, χ², 6.53; P = .038. Multiple regression, P = .015.
‡Analysis of variance, F = 18.18; P = .003.
§Univariate analysis, exact P = .18.
∥Univariate analysis, χ², 3.77; P = .15. Multiple regression, P = .06.
¶Univariate analysis, χ², 4.75; P = .09. Multiple regression, P = .03.
#Univariate analysis, χ², 1.25; P = .53. Multiple regression, P = .89.
ing with subgroups defined according to AAO may facilitate the identification of more familial (ie, genetic) subgroups, specific genetic vulnerability factors underlying each of the AAO subgroups, and/or vulnerability factors implicated in the onset of the disorder. Our results and those of previous studies on AAO in BPAD suggest that AAO is a strong candidate symptom that is relevant for genetic studies.

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**Fish Consumption, Depression, and Suicidality in a General Population**

A recent double-blind, placebo-controlled trial of 30 patients with bipolar affective disorder demonstrated a significant benefit of ω3 fatty acid supplements on reducing episodes of severe mania and depression.1 ω3 Polyunsaturated fatty acids (PUFAs) are now regarded as a promising but untested treatment as mood stabilizers.2 Consistent with these observations, several studies of patients with depression have reported depletions of ω3 PUFAs in plasma or cell membranes.3 Previously, a cross-national comparison revealed a 50-fold lower annual prevalence of major depression, which was strongly predicted by higher fish consumption.4 Since fish is the major source of ω3 fatty acids in the human diet, the frequent consumption of fish could lead to a high intake of ω3 PUFAs, thus decreasing the risk of depression.

Data was gathered on fish consumption, depression, and suicidality among a general population in Kuopio, Finland. A random sample of subjects (N = 3004) aged 25 to 64 years was drawn from the National Population Register. The study questionnaires were mailed in spring 1999, and 1767 subjects responded (59%). An ethical review board of the Kuopio University approved the study.

Depression was estimated with the 21-item Beck Depression Inventory (BDI). A person was considered depressed if the BDI score was greater than or equal to 10.
One of the BDI items screens the severity of suicidal tendencies. Suicidality was considered to be present if there were any thoughts of harming oneself. Fish consumption was estimated with a food-frequency questionnaire, which has been reported to be comparable with a 7-day food record. A subject was regarded as a frequent fish consumer if fish were consumed twice a week or more often.

Both the risk of being depressed (odds ratio, 0.63; 95% confidence interval, 0.43-0.94; P=.02) and the risk of having suicidal ideation (odds ratio, 0.57; 95% confidence interval, 0.35-0.95; P=.03) were significantly lower among frequent lake-fish consumers compared with more infrequent consumers in a multiple logistic model even after adjustment for sex, age, marital status, education, employment status, work ability, area of living, financial status, general health, smoking, alcohol intake, coffee drinking, and physical activity. These results are also consistent with a study of 265,000 Japanese subjects followed for 17 years, which found a decreased risk of suicide among subjects with daily fish consumption compared with nondaily consumption.

Consequently, fish oils may alleviate depression and suicidal tendencies. However, large-scale intervention trials are needed before dietary recommendations to increase fish consumption or ω-3 PUFA intake could be applied to depressed patients or people in the general population.

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In reply

Tanskanen and colleagues report that higher consumption of fish is associated with a reduced risk of major depression and suicidal ideation in a large, community-based sample in Finland. The authors mailed surveys that screened for major depression using the self-rated 21-item Beck Depression Inventory to 304 randomly chosen individuals. The survey also asked about fish consumption, using a validated food frequency questionnaire.

This study has flaws inherent in this type of epidemiological survey (eg, association does not imply causation), and the strength of the statistical differences in depression risk and suicide risk were of a relatively low magnitude (P=.02 and P=.03, respectively). However, this data is consistent with the growing body of literature regarding ω-3 fatty acids and major depression.

For example, a recent study reported that Icelanders have far lower rates of seasonal mood shifts than would be expected from countries of a similar latitude. A separate interpretation of this Icelandic data suggests that greater seafood consumption may prevent depressive symptoms by increasing dietary and thus brain ω-3 fatty content.

In addition, the current report hints at possibly specific antisuicide effects, perhaps similar to the effects of lithium. This preliminary finding should be followed up in controlled studies. The emerging data on ω-3 fatty acids in mood disorders is remarkable. However, we must await the results of well-controlled studies in both bipolar and unipolar mood disorders before reaching a definitive conclusion on the role of the ω-3 fatty acids in mood disorders.

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Low Salivary Cortisol Levels and Aggressive Behavior

In their article “Low Salivary Cortisol and Persistent Aggression in Boys Referred for Disruptive Behavior,” McBurnett et al report a relationship between low (ie, below the group median) salivary cortisol levels and aggressive behavior in boys. They conclude that low hypothalamic-pituitary-adrenal axis activity may be a correlate of severe and persistent aggression in male children and adolescents. Their interesting finding raises another consideration. Is it possible that some of these boys could have had a readily treatable endocrine disorder, namely a form of late-onset congenital adrenal hyperplasia with disturbed cortisol production as a result of inherited enzyme deficiency, resulting in abnormally high serum levels of androgenic intermediaries of cortisol synthesis that might contribute to the development of aggressive behavior? A case in point follows.

Report of a Case. A 13-year-old boy had refractory, disabling anxiety and maladaptive behaviors, especially
outbursts of anger and aggression, since age 7 to 8 years. There was little response to trials of various forms of psychotropic medication treatment, including methylphenidate, hydrochloride, pemoline, carbamazepine, amitriptyline hydrochloride, and clonazepam. His birth history was remarkable for late-term maternal toxemia necessitating cesarean delivery. There was fetal distress at birth requiring resuscitation. He was hyperactive. Physical and language development were normal, but social interactions were delayed. Findings from physical examination were remarkable for left-body hemiatrophy and left-sided dystonic posturing on testing stressed gait. Magnetic resonance cranial imaging showed right hippocampal atrophy with gliosis. Electroencephalogram showed right frontotemporal slowing and spikes. His aggressive behavior prompted a screen for hyperandrogenism. The DHEA-S (dehydroepiandrosterone-sulfate) level was elevated at 13.0 µmol/L (reference range, 5.4-9.0 µmol/L). Cortisol levels were in the low to normal range (9 AM, 303 nmol/L; 4 PM, 138 nmol/L). Corticotropin levels were 10.3 pmol/L (reference range, 3.3-12.1 pmol/L). Corticotropin stimulation test findings were consistent with a diagnosis of late-onset congenital adrenal hyperplasia, secondary to nonclassic 21-hydroxylase enzyme deficiency. A treatment regimen of ketoconazole that normalized the serum level of DHEA-S along with the levels of some other elevated excitatory neuroactive steroids, while raising the serum levels of inhibitory neurohormones improved behavioral symptoms. The case is intriguing because the endocrine profile shows that stable differences in hormonal output are influenced by numerous determinants, including breeding strain, age, genetics, and epigenetics.

**Adrenal Hormone Data and Associated Anxiety and Maladaptive Behavior Scores in a 13-Year-Old Boy During Low- and High-Dose Ketoconazole Treatment**

<table>
<thead>
<tr>
<th>Hormone</th>
<th>Ketoconazole, Baseline</th>
<th>Ketoconazole, 100 mg, Twice Daily</th>
<th>Ketoconazole, 200 mg, Twice Daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Excitatory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DHEA-S, 5.4-9.0 µmol/L</td>
<td>13.0 (†)</td>
<td>6.1</td>
<td>9.2 (†)</td>
</tr>
<tr>
<td>17-OH pregnenolone, 40-450 ng/dl</td>
<td>1450 (†)</td>
<td>340</td>
<td>1087 (†)</td>
</tr>
<tr>
<td>Estradiol, &lt;147 pmol/L</td>
<td>253 (69) (†)</td>
<td>143 (39)</td>
<td>209 (57) (†)</td>
</tr>
<tr>
<td>Inhibitory</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deoxycorticosterone, 3.5-11.5 ng/dl</td>
<td>4.8</td>
<td>23.4 (†)</td>
<td>26.0 (†)</td>
</tr>
<tr>
<td>17-OH progesterone, 0.2-1.8 units ng/L</td>
<td>0.6</td>
<td>3.2 (†)</td>
<td>3.7 (†)</td>
</tr>
<tr>
<td>Progestosterone, 0.92-3.18 nmol/L</td>
<td>3.18</td>
<td>3.82 (†)</td>
<td>4.13 (†)</td>
</tr>
<tr>
<td>Clinical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>10</td>
<td>2.3</td>
<td>7.1</td>
</tr>
<tr>
<td>Maladaptive behaviors</td>
<td>10</td>
<td>2.0</td>
<td>6.9</td>
</tr>
</tbody>
</table>

*SDHEA-S indicates dehydroepiandrosterone-sulfate; †, increase in; and ↑, increase in; and 17-OH, 17-hydroxycorticosteroids.

We recently reported that longitudinal measures of cortisol and aggression were inversely correlated and that low cortisol levels were correlated with early onset of aggression. We hesitated to speculate on mechanisms underlying these associations because of the bidirectional possibilities and the many degrees of freedom within the hypothalamic-pituitary-adrenal (HPA) axis.

Herzog and colleagues report that a 13-year-old boy with severe anxiety and aggression had low to normal cortisol levels but high levels of the adrenal androgen DHEA-S (dehydroepiandrosterone sulfate) along with 21-hydroxylase enzyme deficiency. Treatment that lowered DHEA-S and other excitatory neurohormones improved behavioral symptoms. The case is intriguing because the endocrine profile took the opposite direction from that reported in eating disorders. Second, treatment that returned endocrine concentrations to normal ranges reversed the behavioral disturbance. The curvilinear dose-response relationship highlights the importance of titrating dose to hormonal and behavioral criteria in this case.

We hope that neither this case nor our study is taken out of context. Effective treatment was discovered only after careful workup and failure of frontline treatments, and the clinical presentation was atypical. Our own work with clinic-referred disruptive children remains at the correlative level. It does not support inferences of causality or mechanism, and it does not justify changing clinical practice.

Delineating mechanisms of the cortisol-aggression relationship in typical cases of conduct disorder will be complicated, given the many sources of individual variability at every level of the HPA. Experimental work with animals shows that stable differences in hormonal output are influenced by numerous determinants, including breeding strain.

Comment. We have previously published findings from a series of 12 adults with refractory anxiety and/or maladaptive behaviors that were associated with late-onset congenital adrenal hyperplasia who responded favorably to treatment of the endocrine disorder.² The exciting new findings of McBurnett and colleagues and our experience with a 13-year-old boy suggest that we consider adrenal endocrine disorders in the assessment of childhood as well as adult anxiety and maladaptive behavioral disorders.

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timing and/or duration of stressors and deprivations, and drug exposure. Even under highly controlled conditions, the same early environmental stress can have directionally opposite effects on hormones, depending on genetic history.3

Moreover, future work may not be as fortuitous as that of Herzog and coauthors. Their case neatly fits the classic psychiatric-medical model in which an underlying disease process accounts for behavioral symptoms. In group samples, we may find relatively few cases with grossly abnormal hormone values. Altering an individual’s hormone ratios may have little effect on aggression, and to do so when the concentrations are within normal ranges would involve additional ethical considerations.

The chief contributions of our work to date lie in validation of the childhood-onset type of conduct disorder, implication of persistently low cortisol concentration as a risk factor for persistence, and specification of aggression (rather than any symptom of antisocial behavior) as the key early behavioral sign.

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Correction

Error in Author Order. In the letter titled “Deliberate Seizure Induction With Repetitive Transcranial Magnetic Stimulation in Nonhuman Primates,” published in the February issue of the ARCHIVES (2001;58:199-200), the order of authors listed in the signature block is incorrect. The correct order should have been as follows: Sarah H. Lisanby, MD, Bruce Luber, PhD, A. D. Finck, MD, Charles Schroeder, PhD, Harold A. Sackeim, PhD.
REFERENCES


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Correction

In the letter titled “Leptin as a Possible Modulator of Craving for Alcohol,” published in the May issue of the ARCHIVES (2001;58:509-510), the order of the authors in the signature block was incorrect. The correct order follows: Falk Kiefer, MD; Holger Jahn, MD; Michael Kellner, MD; Dieter Naber, MD; Klaus Wiedemann, MD.