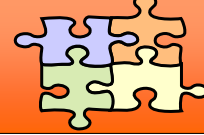


# Endojen $\beta$ -endorfin kökenli dipeptit glisil-glutamin'in nikotinin oluşturduğu koşullanmış yer tercihi ve yoksunluk üzerine etkisi

Dr. Gökhan Göktalay  
Uludağ Üniversitesi Tıp Fakültesi  
Farmakoloji ve Klinik Farmakoloji Anabilim Dalı

## Giriş



### Nikotin

- Kafeinden sonra en yaygın kullanılan ve sistimal edilen maddedir
- Nikotin bağımlılığı önlenbilir erken ölümler arasında ön sıradadır
- Her yıl ortalama 5.5 milyon kişi sigara kullanımı nedeniyle hayatını kaybetmektedir
- Tedavi için yapılan tıbbi harcamalar 75 milyar dolar
- Nikotin bağımlılığının tedavisine yönelik yapılan araştırmalar gelecekte başarılı tedavi programlarının geliştirilmesine katkı sağlayacaktır.

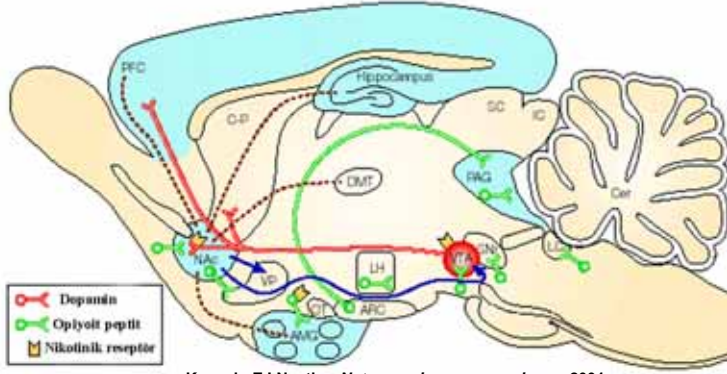


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## Giriş

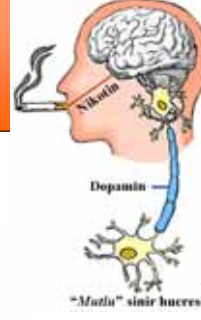
### Nikotin ve ödüllendirme yolları



Kaynak: EJ Nestler, *Nature reviews neuroscience*, 2001



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## Giriş

### Nikotin-opiyoiderjik sistem ilişkisi

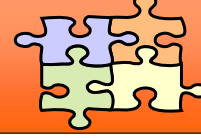
- Nikotin deney hayvanlarında endojen opiyoidlerin salınımını artırır
- Opiyoid reseptör antagonisti nalokson, nikotinin oluşturduğu,
  - Yer tercihi
  - Yoksunluk
  - Analjezik etkiyi engellemektedir
- $\mu$ -opiyoid reseptörleri nikotinin ödüllendirici etkilerinin oluşması için gereklidir.



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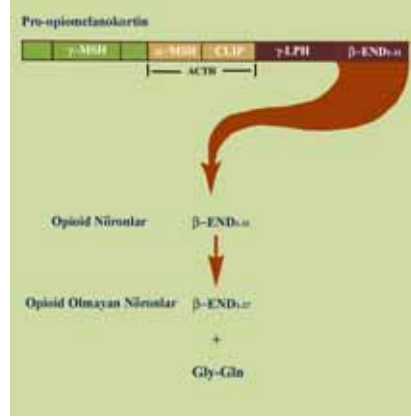


# Giriş



## Glisil-glutamin

- Gly-L-Gln, Gly-Gln,  $\beta$ -End<sub>30-31</sub>
- İlk defa 1983 yılında keşfedildi
- Endojen  $\beta$ -Endorfin kökenli dipeptit
- Biyolojik olarak aktif
- Nöronlarda inhibitör aktivite
- $\beta$ -End<sub>1-27</sub> opiyat antagonisti
- Farmakolojisi hakkındaki bilgiler sınırlı



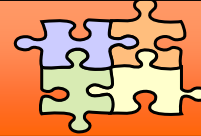
Resim 1.  $\beta$ -Endorfin<sub>1-31</sub>'den Gly-Gln oluşumunun şekilsel gösterimi



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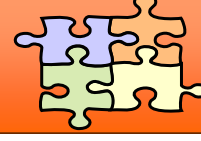
# Giriş



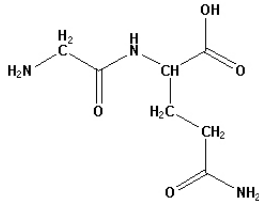
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# Giriş

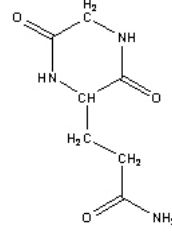


## Gly-L-Gln



Resim 2. Glisil-glutaminin kimyasal yapısı

## Siklo(Gly-Gln)



Resim 3. Siklik glisil-glutaminin kimyasal yapısı



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# Glisil-glutaminin Farmakolojisi



## ✚ Parish ve ark., 1983

- Nöronlarda ateşlenme sıklıkları
- Naloksan etkiyi geri çevirmiyor

## ✚ Hirsch ve ark., 1986

- β-Endorfinin oluşturduğu davranışlar

## ✚ McCain ve ark., 1987

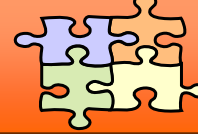
- β-Endorfinin oluşturduğu immun yanıtlar



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## Glisil-glutaminin Farmakolojisi



0022-3565/94/2712-0922\$05.00/0  
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JNET 27:1952-958, 1994

Vol. 271, No. 2  
Printed in U.S.A.

### $\beta$ -Endorphin-Induced Cardiorespiratory Depression is Inhibited by Glycyl-L-Glutamine, a Dipeptide Derived from $\beta$ -Endorphin Processing<sup>1</sup>

CAN B. UNAL, MEDGE D. OWEN and WILLIAM R. MILLINGTON

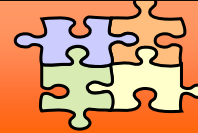
Division of Molecular Biology and Biochemistry (C.B.U., W.R.M.) and Department of Anesthesiology (M.D.O.),  
University of Missouri-Kansas City, Kansas City, Missouri  
Accepted for publication July 1, 1994



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## Glisil-glutaminin Farmakolojisi



*Am J Physiol Regulatory Integrative Comp Physiol*  
270: R1944-R1946, 2000.

### rapid communication

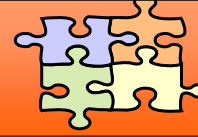
Glycyl-glutamine inhibits the respiratory depression,  
but not the antinociception, produced by morphine

MEDGE D. OWEN,<sup>1</sup> CAN B. UNAL,<sup>2</sup> MICHAEL F. CALLAHAN,<sup>3</sup> KAVITA TRIVEDI,<sup>1</sup>  
CATHERINE YORK,<sup>1</sup> AND WILLIAM R. MILLINGTON<sup>4</sup>  
Departments of <sup>1</sup>Anesthesiology and <sup>2</sup>Physiology and Pharmacology, Wake Forest University  
School of Medicine, Winston-Salem, North Carolina 27157; <sup>3</sup>Intek, Ltd., Bursa, Turkey;  
and <sup>4</sup>Albany College of Pharmacy, Albany, New York 12214  
Received 20 April 2000; accepted in final form 10 August 2000



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Alcohol, Vol. 16, No. 2, pp. 101-107, 1998  
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0741-8329/98 \$19.00 + .00

PII S0741-8329(97)00167-5

## Glycyl-L-Glutamine Injected Centrally Suppresses Alcohol Drinking in P Rats

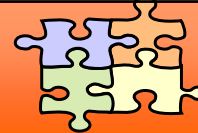
C. WAYNE SIMPSON,\* G. E. RESCH,\* W. R. MILLINGTON\* AND R. D. MYERS†

\*Division of Molecular Biology and Biochemistry, University of Missouri, Kansas City, MO  
†Departments of Pharmacology and Psychiatric Medicine, School of Medicine,  
East Carolina University, Greenville, NC

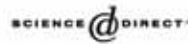
Received 1 July 1997; Accepted 29 October 1997



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Brain Research 1058 (2005) 73–81

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[www.elsevier.com/locate/brainres](http://www.elsevier.com/locate/brainres)

Research Report

## Glycyl-glutamine in nucleus accumbens reduces ethanol intake in alcohol preferring (P) rats

Garth E. Resch<sup>a,\*</sup>, Shyam Shridharani<sup>b</sup>, William R. Millington<sup>c</sup>,  
David R. Garris<sup>a</sup>, C. Wayne Simpson<sup>a</sup>

<sup>a</sup>Division of Molecular Biology and Biochemistry, School of Biological Sciences, University of Missouri-Kansas City,  
3007 Rockhill Road, Kansas City, MO 64110, USA

<sup>b</sup>Dept. Orthopedic Surgery, Mayo Clinic, Rochester, MN 55905, USA

<sup>c</sup>Department of Basic and Pharmaceutical Sciences, Albany College of Pharmacy, Union University, Albany, NY 12208-1492, USA

Accepted 27 July 2005



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# Glisil-glutaminin Farmakolojisi



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JPET 313:449-456, 2006

Vol. 313, No. 2  
0920394906  
Printed in U.S.A.

## Glycyl-Glutamine, an Endogenous $\beta$ -Endorphin-Derived Peptide, Inhibits Morphine-Induced Conditioned Place Preference, Tolerance, Dependence, and Withdrawal

Sinan Cavun, Gökhan Göktaş, and William R. Millington

Department of Basic and Pharmaceutical Sciences, Albany College of Pharmacy, Union University, Albany, New York (S.C., G.G., W.R.M.); Ion Technologies, Inc., Winston-Salem, North Carolina (G.G.); and Department of Pharmacology and Clinical Pharmacology, Uludağ University School of Medicine, Bursa, Turkey (S.C., G.G.)

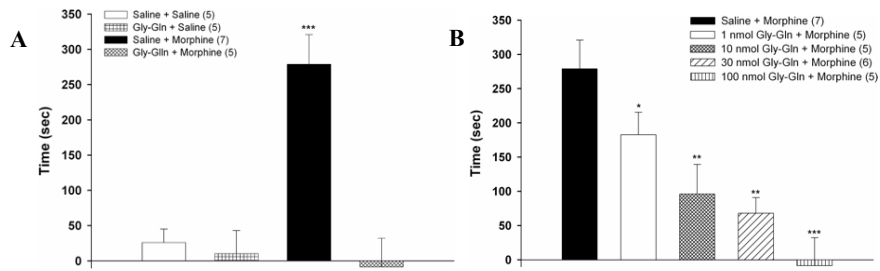
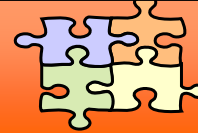
Received June 23, 2005; accepted July 28, 2005



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# Glisil-glutaminin Farmakolojisi



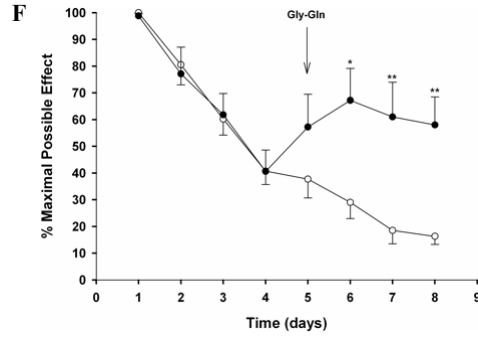
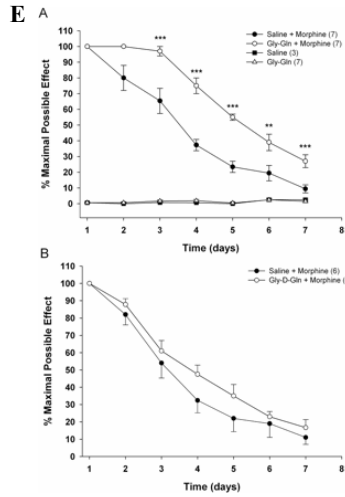
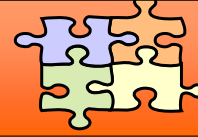
Çavun ve ark., 2005



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# Glisil-glutaminin Farmakolojisi

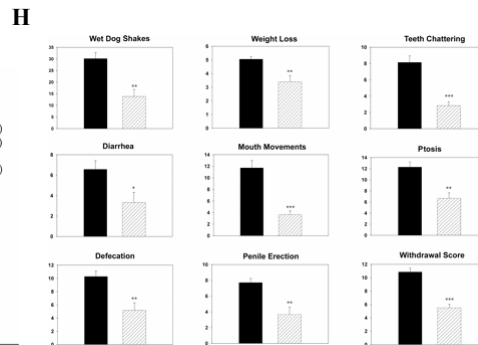
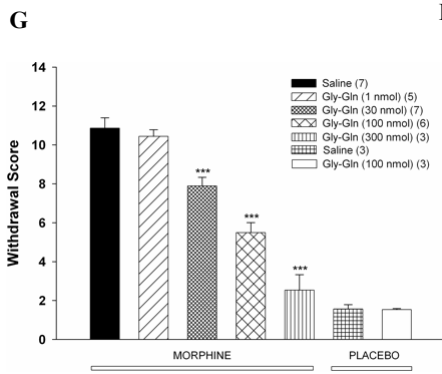
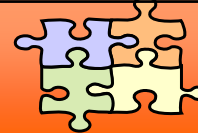


Çavun ve ark., 2005

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# Glisil-glutaminin Farmakolojisi



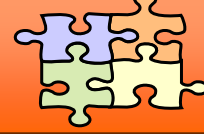
Çavun ve ark., 2005

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## Hipotez



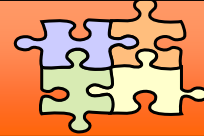
- ✚ Bağımlılık patofizyolojisinde *nucleus accumbens*teki DA sistem aktivasyonunun ortak bir mekanizma olması ve glisil-glutaminin morfin ve alkol bağımlılığında yararlı etkilerinin gösterilmesi, beta-endorfin kaynaklı bu dipeptidin diğer bağımlılık modellerinde de yararlı etkilerinin olabileceğini düşündürmüştür.



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## Hipotez



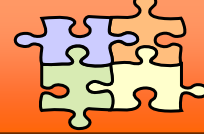
- ✚ Bu düşünceden hareket edilerek yapılan bu çalışmada, nikotinin oluşturduğu koşullanmış yer tercihi ve yoksunluk belirtileri üzerine glisil-glutaminin etkili olup olmadığı test edilmiştir.



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## Gereç ve yöntem



### ✚ Kullanılan Hayvanlar ve Cerrahi

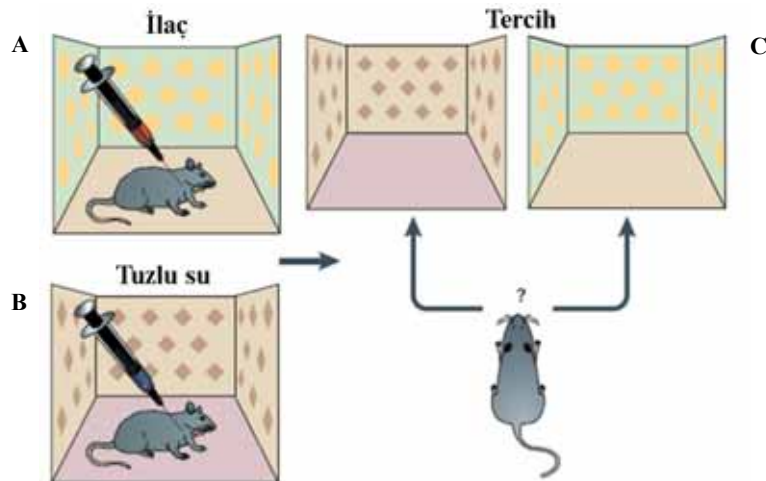
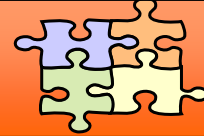
- Sprague-Dawley (250-300 g)
- Halotan anestezisi altında isv klavuz kanül (P; 0.9 mm, L;1.3 mm; D: 4 mm)
- Cerrahi iyileşme 1 hafta
- Bütün peptitler % 0.9 tuzlu su içerisinde çözüldü
- Kullanılan ilaçlar ve dozları
  - Nikotin (0,6 mg/kg, sk)
  - Gly-L-Gln (3-100 nmol, isv)
  - Gly-D-Gln (100 nmol, isv)
  - Siklo[(Gly-Gln) 100 nmol, isv]
  - Siklo[(Gly-Gln) 25 mg/kg, ip]
  - Mekamilamin (1 mg/kg, sk)
  - U50,488 (1 mg/kg, sk)



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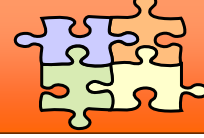
## Koşullanmış yer tercihi



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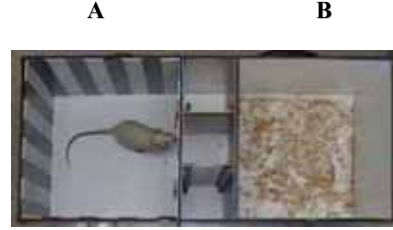


## Materyal ve metod



### Koşullanmış Yer tercihi Aparatı

- Koşullanma odacıkları (30 x 30 x 35 cm)
  - A. Odacığı, tabanı beyaz, duvarlar siyah beyaz çizikli
  - B. Odacığı, tabanı beyaz üzerinde talaş, duvarlar beyaz
- Orta odacık (nötral odacık) (30 x 12 x 35 cm)



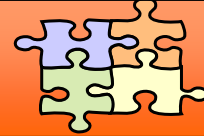
Resim 3. Koşullanmış yer tercihi aparatı



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## Koşullanmış yer tercihi



### Koşullanmış yer tercihi iki şekilde incelenebilmektedir

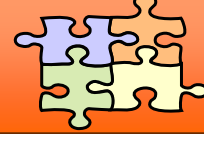
- Kazanım (acquisition)
  - Test edilen maddenin yer tercihi gelişimine etkisi
- Açığa çıkma (expression)
  - Test edilen maddenin yer tercihi oluştuktan sonraki etkisi



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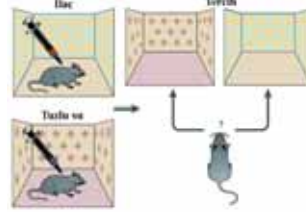


## Koşullanmış yer tercihi



### Kazanım

- Alıştırma ve ön test
- Koşullandırma
- Asıl test



Cerrahi  
(isv kanül)



İyileşme

+

Alıştırma

Ön Test



Koşullandırma

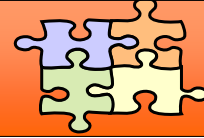
Asıl test



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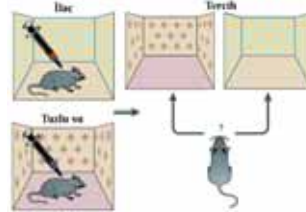


## Koşullanmış yer tercihi



### Açığa çıkma

- Alıştırma ve ön test
- Koşullandırma
- Asıl test



Cerrahi  
(isv kanül)



İyileşme

+

Alıştırma

Ön Test



Koşullandırma

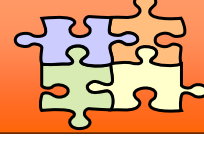
Asıl test



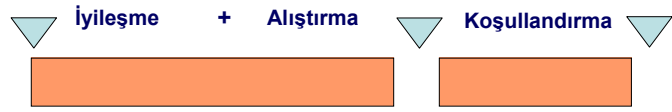
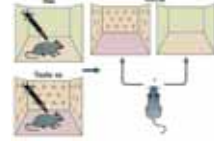
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## Koşullanmış yer sakınması



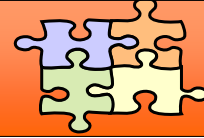
Cerrahi  
(isv kanül + ozmotik pompa)



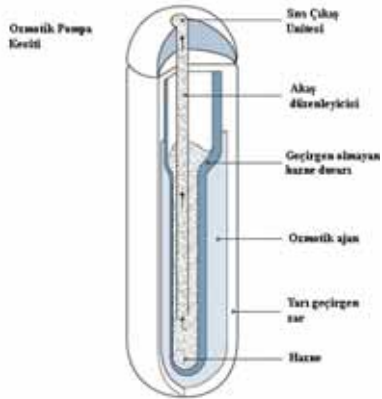
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## Ozmotik pompa



A



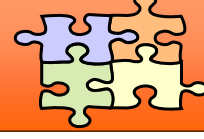
B



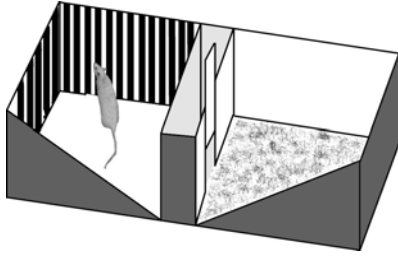
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## Deney düzeneđi



Kamera



Koşullanmış yer tercihi aparatı



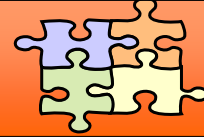
Videolu TV



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## Bulgular



### Koşullanmış yer tercihi

 Kazanım

 Açıđa çıkma

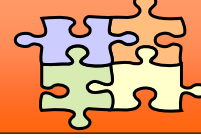
### Koşullanmış yer sakınması



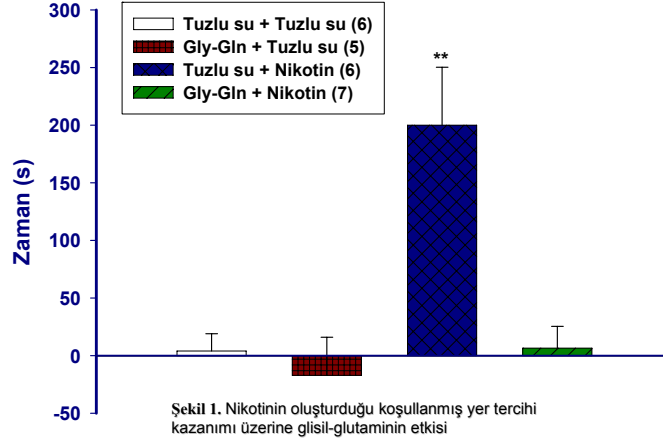
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## Koşullanmış yer tercihi



### A. Kazanım

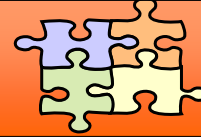


Şekil 1. Nikotinin oluşturduğu koşullanmış yer tercihi kazanımı üzerine glisil-glutaminin etkisi

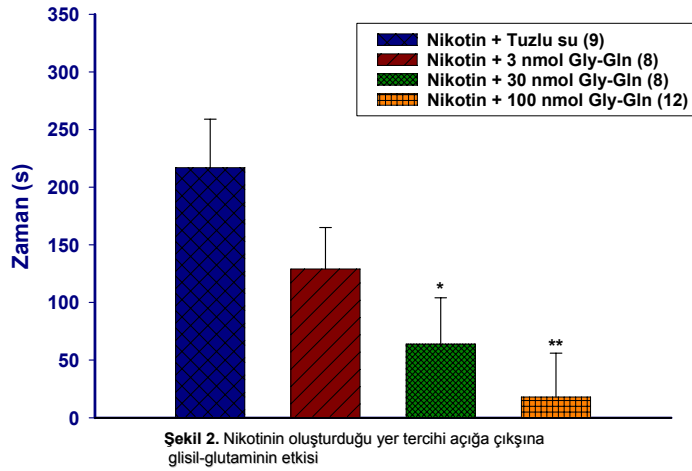
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## Koşullanmış yer tercihi



### B. Açığa çıkma

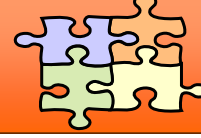


Şekil 2. Nikotinin oluşturduğu yer tercihi açığına glisil-glutaminin etkisi

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## Koşullanmış yer tercihi



Tablo 1.

Tedavi	Zaman (s)
Tuzlu su + Tuzlu su	9 ± 16
Nikotin + Tuzlu su	217 ± 42 <sup>a</sup>
Tuzlu su + Gly-Gln	7 ± 17
Nikotin + Gly-Gln	18 ± 38
Tuzlu su + Gly-D-Gln	6 ± 36
Nikotin + Gly-D-Gln	207 ± 25 <sup>a</sup>

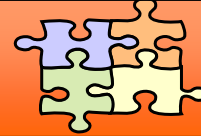
Tablo 1. Nikotinin oluşturduğu yer tercihi açığa çıkışına glisil-D-glutaminin etkisi



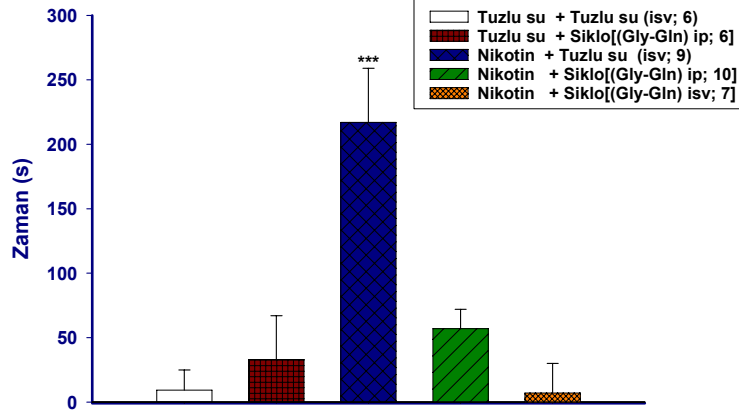
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## Koşullanmış yer tercihi



### Siklo(Gly-Gln)



Şekil 3. Nikotinin oluşturduğu koşullanmış yer tercihinin açığa çıkmasına siklik-glisil-glutaminin etkisi

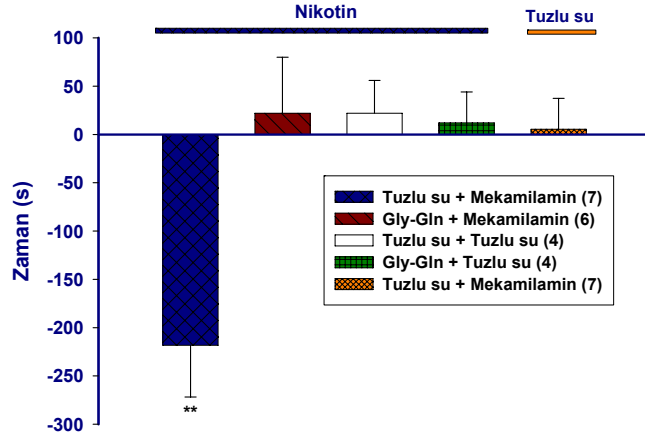


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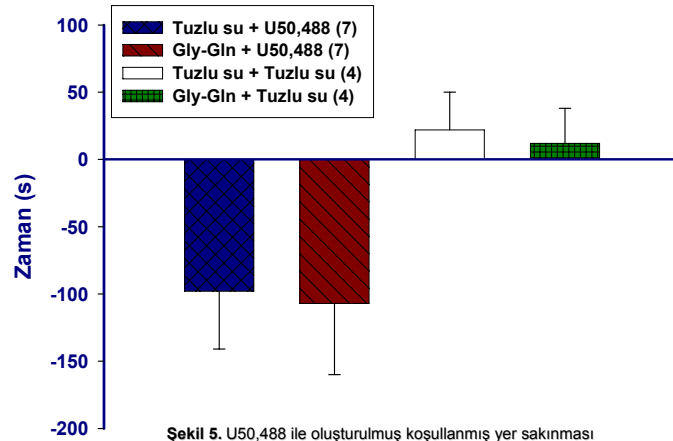
## Koşullanmış yer sakınması



Şekil 4. Nikotin bağımlı hayvanlarda mekamilaminin oluşturduğu yer sakınmasına glisil-glutaminin etkisi

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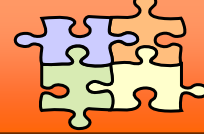
## Koşullanmış yer sakınması



Şekil 5. U50,488 ile oluşturulmuş koşullanmış yer sakınması üzerine glisil-glutaminin etkisi

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## Sonuç



Bu çalışmadan elde edilen bulgular ile glisil-glutamin;

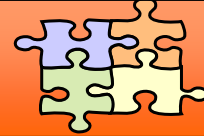
- + Nikotinin ödüllendirici ve pozitif pekiştirici etkisini engellemektedir.
- + Nikotin yoksunluğunun negatif motivasyon oluşturucu etkisini engellemektedir.
- + Ancak, glisil-glutaminin kendisi, tercih ya da sakınma davranışlarına neden olmamaktadır.



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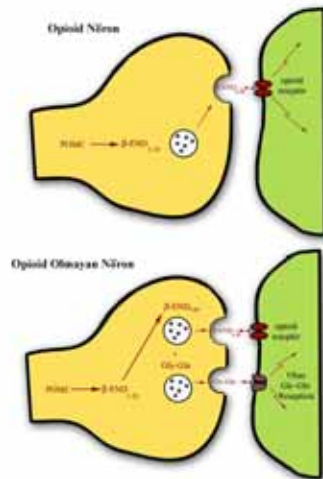


## Tartışma



Olası mekanizmalar?

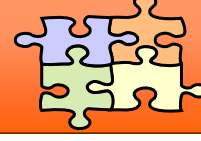
- + Opiyoit ?
- + Nikotin ?
- + Hidroliz ürünleri ?
- + Dopamin ? ✓
- + Kendisine ait reseptör ?



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## Devam eden ve gelecekte yapılması planlanan çalışmalar



### Devam eden çalışmalar

- ✚ Glisil-glutaminin, *nucleus accumbens*'te morfinin indüklediği dopamin çıkışı üzerine etkisi  
Çavun ve ark., Tubitak SBAG-3400 (106S152)

### Ne planlıyoruz?

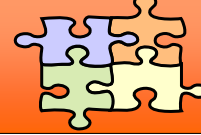
- ✚ Glisil-glutaminin psikostimulanlar (amfetamin, kokain vb) üzerine etkisi
- ✚ Glisil-glutaminin davranış profilleri üzerine etkisi çıkartılması
- ✚ İn vitro modellerde nörotransmitter çıkışı üzerine etkisi



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## Sonuç



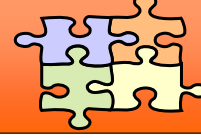
- ✚ Sonuç olarak elde ettiğimiz bulgular, morfin ve alkol bağımlılığında etkili olduğu daha önce gösterilen glisil-glutaminin nikotin bağımlılığı üzerine de etkili olduğunu göstermektedir.



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## Sonuç



✚ Glisil-glutamin ve gelecekte moleküler modelleme tekniği ile üretilebilecek analoglarının pek çok bağımlılık oluşturan maddenin tedavisinde kullanılabilme potansiyeli mevcuttur.



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### Glycyl-glutamine inhibits nicotine conditioned place preference and withdrawal

Gökhan Göktaş<sup>a,b,c</sup>, Sinan Cavun<sup>a,c</sup>, Mark C. Leventusky<sup>a</sup>,  
Jonathan R. Hamilton<sup>a</sup>, William R. Millington<sup>a,b,\*</sup>

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## Endorphin Derivative Inhibits Reward From Morphine and Nicotine in Rats

Recent studies on the pharmacology of glycyl-glutamine suggest therapeutic potential for opiate and nicotine addiction.

BY SARAH TEAGLE,  
NIDA Notes Contributing Writer

**A**naturally occurring brain chemical has shown early promise as a treatment for addiction. NIDA-funded researcher Dr. William Millington and colleagues at Albany College of Pharmacy demonstrated that gly-

**GLY-GLN BLOCKS THE REWARDING EFFECTS OF NICOTINE AND MORPHINE**  
Rats trained to associate nicotine or morphine infusions with a particular chamber showed a clear preference for the drug-linked chamber when later allowed to roam freely between it and a second chamber. Rats that were pretreated with Gly-Gln prior to receiving nicotine or morphine—as well as rats that received only saline—spent little or no time in the drug-linked chamber.

### SAFE ANALGESIA, TOO?

In separate studies, Dr. Millington and colleagues found evidence that Gly-Gln has potential for improving pain treatment by slowing the development of morphine tolerance. The investigators treated rats with morphine twice daily for 7 days and, each day, measured their reaction to pain with tail-flick latency tests. They observed that the pain-relieving effects of morphine declined 20 percent by the second day, an indication that tolerance had developed rapidly. However, rats pretreated with Gly-Gln did not begin showing evidence of morphine tolerance until the fourth day of treatment. Their level of pain relief had dropped to 75 percent of the maximum by day 4, compared with 39 percent for rats that were not pretreated.

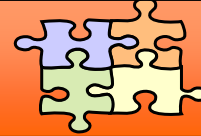
These findings offer new hope for making



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## Teşekkür



**Prof. Dr. William R. Millington**

**Doç. Dr. Sinan Çavun**

**Mark Levendusky**

**Jonathan Hamilton**



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