Nörolojik Hastalıkların Deneysel Hayvan Modelleri

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ÖNSÖZ

Geleceğin güvencesi eğitime, eğitim ise öğretmene dayalıdır. Öğretmen doğan güneşe benzer. Etrafını aydınlatarak karanlıklara meydan okur. Prof. Dr. Aysel AĞAR da bilim yolunda ışık olup pek çok öğrencinin ve eğitimcinin yolunu aydınlatmıştır. Bizler de bu mirası hocamızdan alıp gelecek nesillere aktarmak adına ve santral sinir sistemi hastalıkları üzerine çalışan veya çalışmak isteyen araştırmacılara yol göstermesi amacıyla bu kitabı hazırladık. Kitabımız, bölüm yazarları tarafından 04.03.2021 tarihinde emekliliğe ayrılmış olan değerli hocamız Prof. Dr. Aysel AĞAR'a ithaf edilmiştir.

Eserinin üzerinde imzası olmayan yegâne sanatkâr öğretmendir.

M. Kemal Atatürk

KİTAP HAKKINDA

Vücudun sinir sistemiyle ilgili hastalıklar, nörolojik hastalıklar olarak bilinmektedir. Beyin, omurilik ya da sinirlerin elektriksel yapısındaki anormallikler birçok soruna yol açtığı için nörolojik hastalıklar tüm vücut sistemlerini etkileyebilmektedir. Nörolojik hastalıklar, kalp hastalıklarından sonra ölümlerin ikinci önde gelen nedenidir ve dünya genelinde insidansı ve prevelansı oldukça yüksektir. Santral sinir sisteminin karmaşık yapısı ve kompleks sinyal yolakları, hastalıkların nörobiyolojisini ve patofizyolojisini anlamayı zorlaştırdığı gibi bu hastalıklara yönelik radikal tedavilerin geliştirilmesinin de önünü kapatmaktadır. Nörolojik hastalıkların mekanizmalarının anlaşılması, bu hastalıkların önlenmesi ve etkin tedavi yöntemlerinin uygulanmasında deneysel çalışmalar önemli rol oynamaktadır. Hayvan modelleri kullanılarak yapılan araştırmalar, bu hastalıkların mekanizmalarını aydınlatabilmek ve etkin tedavi stratejileri geliştirebilmek için hayati rol oynamaktadır. Bir tedavi yönteminin araştırılmasında, yeni tedavi protokollerinin geliştirilmesinde ve yeni ilaç moleküllerinin keşfedilmesinde kemirgenler (fare, sıçan, gerbil gibi) ve kemirgen olmayan memeliler (köpek, tavşan, kedi, domuz, şempanze gibi) sıklıkla kullanılmaktadır. Hayvan modellerinde hem normal hem de anormal beyin fonksiyonunun temel nöronal mekanizmaları araştırılmaktadır. Her modelin kendine özgü avantajları ve dezavantajları vardır. Bu nedenle araştırmacı, belirli bir model seçmeden önce bu avantajların ve kısıtlamaların farkında olarak çalışması için en uygun modeli tercih etmelidir. Nörolojik hastalıklar modellenirken büyük ölçüde kemirgen modelleri kullanılmaktadır. Çünkü; kemirgenlerin üretimi ve manipülasyonu kolaydır, boyutları küçüktür ve anatomileri insanlarınkine benzerdir. Bu kitapta Alzheimer, epilepsi, migren, nöropatik ağrı, Parkinson, serebral iskemi ve travmatik beyin hasarı deneysel modellerine ve bu modeller arasından çalışmalarda en sık kullanılan yöntemlere detaylı olarak yer verilmiştir. Kliniği yansıtan ve ilaç araştırmalarında en çok tercih edilen modellerin protokolleri de görseller ile zenginleştirilerek bölümler oluşturulmuştur. Kitap bölüm yazarları, daha önce bu alanda çalışmış olan bilgi ve tecrübe sahibi araştırmacılardan oluşmaktadır.

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DENEYSEL ALZHEİMER HASTALIĞI MODELLERİ

BÖLÜM 1

Betül DANIŞMAN[1]
Betül ÇİÇEK[2]

Giriş

Demansın en yaygın şekli olarak da bilinen Alzheimer hastalığı, dünya çapında yaklaşık 50 milyon kişiyi etkiyen ilerleyici, nörodejeneratif bir hastalıktır. Yıllar içinde Alzheimer hastalığı için çeşitli tedaviler geliştirilmiş olsa da bu hastalık için mevcut iyileştirici tedaviler henüz bulunamamış, sadece semptomlar hafifletilmiştir. Alzheimer hastalığı, çok sayıda biyolojik yolu etkileyen, çeşitli etiyolojik faktörlere atfedilebilen karmaşık bir durumdur. Deneysel modeller hastalığın patogenezini daha iyi anlayabilmek ve klinik öncesi yeni tedavileri test edebilmek için önemlidir. Alzheimer hastalığının karmaşıklığını tamamen kapsayan bir araştırma modeli geliştirmek zor olsa da çeşitli yönleriyle ilgili bilgi edinmek için birçok model geliştirilmiştir.

Alzheimer hastalığının deneysel hayvan modelleri, hem transgenik hayvanları hem de doğal, transgenik olmayan Alzheimer hastalığı modellerini içerir. Tüm bu modeller, Alzheimer hastalığı patolojisinin altında yatan temel mekanizmaların araştırılması ve ayrıca bu hastalığa karşı hedeflenen yeni tedavilerin test edilmesi için değerlidir.

Her bir modelin belirli sınırlamaları olsa da araştırmacılar uygun deneysel modelli kullanarak, Alzheimer hastalığı hakkında önemli bilgilere ulaşabilirler. Bu bölümde, güncel modellerin nasıl kullanılacağına ve bu modellerin insan hastalıklarıyla benzerlik ve farklılıklarına odaklanılarak, mevcut deneysel Alzheimer hastalığı modelleri özetlenmektedir.

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delleri için ek bilgi sağlayarak hücre dışı ortamların doğru ve tekrarlanabilir kontrolünü sağlar. Tüm bu modeller, AH'nin patofizyolojisini araştırmak ve potansiyel tedavileri değerlendirmek için uygundur. Her model belirli avantajlar ve belirli sınırlamalar sunar. Deneysel bir modelin seçilmesi, hem araştırma hedeflerine hem de çalışmanın temel amaçlarına bağlıdır.

Bir bütün olarak, bu bölümde tartışılan deneysel AH modelleri AH'yi anlamamıza katkıda bulunmuştur. Bununla birlikte, bu modellerin hiçbiri, AH alt tiplerinin büyük çoğunluğunda hastalık ilerlemesinin tüm yönlerini yeniden üretemez. Bu nedenle, mevcut modeller, insan AH'sinin karmaşık koşullarını tam olarak çoğaltmak için ek modifikasyonlar gerektirir. Kuşkusuz, deneysel modeller gelecekteki AH araştırmalarında hayati bir rol oynamaya devam edecektir.

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DENEYSEL EPİLEPSİ MODELLERİ

BÖLÜM 2

Güven AKÇAY[1]

Giriş

Epilepsi, beyindeki nöronların anormal ve aşırı elektriksel deşarjları sonucu ortaya çıkan ve tekrarlayan spontan kronik beyin hastalığı olarak tanımlanmaktadır. Epilepsinin başlıca nedenleri arasında inme, kafa travmaları, beyin damarlarındaki yapısal bozukluklar, beyindeki hemorajiler ve genetik faktörler yer almaktadır. Epilepsi, psikolojik, fiziksel sosyal ve ekonomik problemlere yol açmaktadır. Her yıl yaklaşık olarak 2.4 milyon kişide epilepsi hastalığı görülmektedir. Epilepsi dünyada % 1 prevelansa sahip olduğu öngörülen, yaygın ve ciddi nörolojik bir bozukluktur. Dünya Sağlık Örgütü'nün 2019 verilerine göre, dünyada yaklaşık 50 milyon epilepsili hasta olduğu rapor edilmiştir. Epilepsi çocukluk çağında ve yaşlılıkta en yüksek insidansa sahip iken erken erişkinlikte ise daha düşük düzeyde olduğu gözlenmiştir. Epilepsi nöbetleri beyindeki sinir hücreleri arasındaki inhibisyon ve eksitasyon dengesinin bozulması sonucu ortaya çıkmaktadır. Epileptik hastalarının yaklaşık olarak % 20-30'unun antiepileptik ilaçlara dirençli olduğu bilinmektedir. Epilepsi tedavisinde genellikle nöbet sıklığının kontrolü üzerine odaklanılmıştır. Epilepsinin oluşumuna sebep olan mekanizmaların ve yeni tedavi yöntemlerin anlaşılmasında deneysel modellerin kullanılması sıklıkla tercih edilmektedir. Bu yüzden çok sayıda deneysel epilepsi modelleri geliştirilmiştir. Bu deneysel modeller hayvanlarda elektrik uyarımı, kimyasal konvülzanlar, genetik modeller, yapısal lezyonlar, fiziksel uyaranlar (soğuk, basınç, hipertermi, elektriksel) ile oluşturulmaktadır.

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yıcıların işlev bozukluğunun epilepsiye yol açtığı bildirilmiştir (61). Voltajla aktive olan potasyum kanalının KCNQ2/3 alt birimlerindeki mutasyon, bir tür neonatal epilepsi sendromu olan Brief Fear of Negative Evaluation Scale (BFNE)'ye neden olmaktadır (62, 63). BFNE'li yenidoğan vakaların çoğunda kendiliğinden geçen nöbetler yaşarlar; ancak yenidoğanların %10-15'i ileriki yaşamlarında epilepsi geliştirmeye devam ederler (64). KCNQ2 ve KCNQ3 homozigot mutant farelerde, spontan nöbetler görülmektedir (65, 66). Sodyum kanallarının SCN1A, SCN2A veya SCN1B alt birimindeki mutasyon, bir tür çocukluk çağı epilepsisi olan ateşli nöbetlerle birlikte genel epilepsiye sebep olmaktadır. Bebeklik döneminde şiddetli miyoklonik epilepsisi (SMEI veya Dravet sendromu) olan hastalarda da SCN1A'da mutasyon tanımlanmıştır (67).

Sonuç ve Öneriler

Epilepsi, her yaştan insanı etkileyen en yaygın nörolojik durumlardan biridir. Epilepsi, spontan tekrarlayan nöbetlerin ortaya çıkması ile karakterizedir. Halihazırda mevcut ilaçlar, epilepsili hastaların yaklaşık üçte birinde nöbetlerin kontrolünde etkisizdir. Ayrıca, bu ilaçlar yan etkilerle ilişkilidir ve bunların hiçbiri bir nöbet sonrasında epilepsi gelişimini önlemede etkili değildir. Epilepsi (epileptogenez) gelişim sürecine müdahale edebilecek etkili bir terapötik strateji geliştirilmesinde epilepsi öncesi ve sonrası beyinde meydana gelen değişiklikleri incelemek çok önemlidir. Deneysel epilepsi modelleri, epileptogenez mekanizmasının yanı sıra nöbet oluşumunun anlaşılmasına büyük ölçüde katkıda bulunur. İnsan epilepsisinin bazı özelliklerini temsil edebilecek birçok model vardır. Her modelin avantajları ve dezavantajları bulunur. Araştırmacıların çalışmalarına başlamadan önce kullanacağı terapötik ilaca uygun modeli seçerken iyi analiz etmesi gerekir. Bu bağlamda sizlere yardımcı olabilmesi adına deneysel epilepsi modelleri bu bölümde özetlenmiştir.

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DENEYSEL MİGREN MODELLERİ

BÖLÜM 3

Güven AKÇAY[1]

Giriş

Migren, genellikle tekrarlayan baş ağrısı atakları, nörolojik ve sistemik semptomlarla karakterize beyin hastalığıdır. Dünyada yetişkin ve genç nüfusta ilk sırada yer alan engellilik sebebidir. Migren insanların işlevselliğini yaşam kalitesini olumsuz etkiler. Fotofobi, fonofobi, kutanöz allodini, bulantı ve kusma migrenin en karakteristik semptomlarıdır. Migren baş ağrısı genellikle tek taraflı (% 60) ve zonklayıcıdır (% 50). Bu ağrılar fiziksel aktivite (% 90) veya baş hareketleri ile daha da kötüleşir. Migrenin primer semptomları, ağrı başlangıcından saatler veya günler önce başlar. En çok karşılaşılan uyarıcı semptomlar yorgunluk, bozulmuş konsantrasyon ve boyun sertliğini içerir. Stres, anksiyete, depresyon, fotofobi, esneme, artan idrara çıkma, bulantı, ishal ve yiyecek istekleri ise ağrı başlangıcından önce ortaya çıkar. Migren, etiyolojisi tam bilinmeyen, karmaşık, çok faktörlü, tipik olarak epizodik nörovasküler hastalık olarak bilinir. Migrenin patofizyolojisi hala tam olarak anlaşılmış değildir. Patofizyolojisinin anlaşılması geliştirilecek tedaviler adına yol gösterici olacaktır. Günümüzde, terapötik ilaç ve tedavilere olan ihtiyaçtan dolayı migren ilişkili ağrının nörobiyolojisinin nedenlerini anlamak için deneysel hayvan çalışmaları önemli rol oynar. Deneysel modeller migrenin altında yatan iyonik, nörokimyasal ve hücresel mekanizmaların anlaşılmasını mümkün kılar.

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kilde anlaşılmasına yol açmıştır. KYD modelini deney hayvanlarında; mekanik (iğne batırılması) , kimyasal (potasyum, glutamat, asetilkolin, yoğun foto-oksidasyon) ve elektriksel (tetanik yada galvanik) uyaranlar ile oluşturulabildiği gösterilmiştir (53, 54). KYD modelinin en basit modeli, hücre dışı K^+ artışı ile KYD'nin başlatılmasıdır.

3.5.1. KCl ile KYD Metodu

Anestezisi altına alınan hayvanlar stereotaksik çerçeveye yerleştirilerek, kafatasına 0.5 mm yarı çaplı bir delik açılıp (Bregmaya göre, 2 mm anterior ve 1 mm lateral) bu noktaya kalıcı bir kılavuz kanül yerleştirilerek 1M KCl ile bulaştırılmış bir insülin enjektörü ile pin-prick tatbik edilir (55). Akut KYD grubu genellikle birer saat ara ile 2 defa pin-prick uygulanarak 24. saatte deneyler sonlandırılır. Kronik KYD grubu ise her gün birer saat ara ile 2 defa 1M KCl uygulanarak, deney süresince tekrarlanarak uygulama yapılmalıdır. Uygulama gün sayısı deney protokolünüze göre değişiklik gösterebilir.

Sonuç ve Öneriler

Migren, yaşam kalitesini bozabilecek, değişen duyusal algı ile ilişkili, güçten düşürücü bir baş ağrısı hastalığıdır. Migren hastalığının patogenizi halen tam olarak anlaşılamamış ve sınırlı sayıda terapötik tedavi yöntemleri mevcuttur. Yeni terapötik ajanları geliştirilmesinde kimyasal, fiziksel veya genetik modifikasyonlu deneysel hayvan modelleri önemli rol oynar. Migren hastalığının altında yatan nedenleri anlamak amacıyla hayvan modelleri geliştirilmiş, ancak bunların hepsi dezavantajlara sahiptir. Hayvan modellerinin güvenilir olarak kabul edilmesi için insan migrenine benzer bir etiyoloji ve fenotip sergilemesi gerekir. Bu hastalığın değişken bir fenotiple karmaşık olduğu düşünülse de, şu anda tüm özelliklerini modelleyebilecek bir hayvan modeli bulunmamaktadır. Bu kitap bölümünde, migren hastalığı araştırmalarında sıklıkla tercih edilen kemirgen migren modelleri özetlendi.

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DENEYSEL MULTİPLE SKLEROZ MODELLERİ

BÖLÜM 4

Betül DANIŞMAN[1]

Giriş

Multiple skleroz, dünya çapında 2,5 milyondan fazla insanı etkilediği tahmin edilen, demiyelinizasyona yol açarak motor, görsel, duyusal ve otonom sistemlerde bozulmayla birlikte nöronal kaybının gerçekleştiği otoimmün bir hastalıktır. MS her hasta için farklı klinik bulgular ve ilerleyiş göstermesi nedeniyle öngörülemez bir durumdur. Sinir lifleri, koruyucu miyelin kılıf ile kaplıdır ve sağlıklı bir sinirde miyelin kılıf oluşan potansiyellerin daha hızlı iletilmesini sağlar. MS hastalığında ise bağışıklık sisteminin hücreleri beyin ve omuriliğindeki sinir liflerine saldırarak miyelin kılıfa zarar verir ve sinir hücrelerinin normal işlevi bozulur. MS'in hayvan modelleri, hastalığın patolojik mekanizmalarını ve tedavilerinin nasıl hedeflenebileceklerini tahmin etmede önemli rol oynar. Merkezi sinir sisteminde inflamasyon, demiyelinizasyon, remiyelinizasyon ve nörodejenerasyonun farklı yönlerini incelemek için oldukça yararlı olduğu kanıtlanan birçok farklı model mevcuttur. Mevcut modeller, MS patolojisinin karmaşıklığını ve heterojenliğini tam olarak yansıtmasa da, MS hastalarının tedavisi için ilaç geliştirilmesinde kullanılmaktadır. En çok kullanılan deneysel hayvan modelleri otoimmün ensefalomiyelit (EAE) ve toksin ve/veya virüs kaynaklı demiyelinizasyondur. Deneysel modeller, EAE, MS sırasında meydana gelen inflamasyon, MSS penetrasyonu, demiyelinizasyon, aksonopati ve bağışıklık hücrelerinin aracılık ettiği nöronal kayıp dâhil olmak üzere çeşitli patolojik süreçleri aydınlatmada etkili olmuştur. Bu bölümde MS araştırmalarında farklı hayvan modellerinin kullanımına ilişkin bilgiler özetlenecektir.

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modelleri, demiyelinizasyon ve remiyelinizasyon hakkında oldukça değerli bilgiler sağlar, ancak sonuçları doğrudan uygulanabilir değildir. Bir modelin veya diğerinin seçilmesi, çalışmanın özel amaçlarına bağlıdır.

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DENEYSEL NÖROPATİK AĞRI HAYVAN MODELLERİ

BÖLÜM 5

Büşra CESUR[1]

Giriş

Nöropatik ağrı (NA), primer lezyon ya da bir hastalık sonucunda gelişebilen teşhisi ve tedavisi konusunda hala aşılması gereken zorlukları olan, devamlı nosiseptif uyarının görüldüğü karmaşık bir ağrı çeşididir (1). NA klinikte sıklıkla görülen bir hastalıktır (2). NA'nın, santral ve periferik mekanizmalardan kaynaklandığı bilinmektedir. Bunlar travma, sinir hasarı, enfeksiyonlar, kemoterapötikler, toksinler, vitamin eksiklikleri gibi periferik ya da inme, tümör, multiple skleroz gibi santral rahatsızlıklar olabilmektedir. NA, sıklıkla kronik olup ciddi epidemiyolojik bir sorun olarak karşımıza çıkmaktadır. NA'da hiperaljezi, allodini ve hiperpati gibi bulgular görülmektedir. NA duygu durumu bozukluklarına yol açar ve hastanın yaşam kalitesini düşürür (3). Antikonvülzanlar, antidepresanlar, opioidler ve non opioidler NA tedavisinde kullanılsa da tam olarak etkinliği kanıtlanmış bir ilacın olmayışı, bu ağrının henüz aydınlatılmamış farklı mekanizmalardan meydana geldiğini düşündürmektedir. NA'nın, mekanizmasının yeterince aydınlatılamaması ve etkin bir tedavisinin olmayışı gibi sorunların aşılması için daha az yan etkili ve etkinliği yüksek ilaçların geliştirilmesine ihtiyaç duyulmaktadır. Bu nedenle, güncel bir problem haline gelen NA'nın anlaşılabilmesi yeni tedavi stratejilerinin geliştirilebilmesi için deneysel hayvan modellerine ihtiyaç duyulmaktadır (4). NA'nın patofizyolojisindeki farklılıklar nedeniyle pek çok NA modeli geliştirilmiştir. Bu modelleri periferik sinir hasarı, santral sinir sistemi hasarı, ilaçlara bağlı modeller, hastalık kaynaklı modeller ve geriye kalanlarını da diğer nöropati modelleri olarak sınıflandırmak mümkündür. Bu kitapta literatürde sıklıkla kullanılan deneysel nöropatik hayvan modelleri anlatılmıştır.

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DENEYSEL PARKİNSON HASTALIĞI HAYVAN MODELLERİ

BÖLÜM 6

Dilara NEMUTLU SAMUR[1]

Giriş

Parkinson hastalığı (PH); dopaminerjik sistemde meydana gelen nörodejenerasyon sonucu istirahat tremoru, rijidite ve bradikinezi gibi klasik üçlü motor belirti ile karakterize bir hareket hastalığı olarak tanımlanmaktadır (1). Ancak, günümüzde serotonerjik, kolinerjik ve noradrenerjik sistemler gibi diğer nörotransmitter sistemlerin de bu nörodejeneratif süreçten etkilendiği ve motor olmayan belirtilerin de hastalık tablosuna eşlik ettiği bilinmektedir (2). PH'nin prevalansının genellikle 100.000 kişide 100 ile 200 arasında değiştiği kabul edilmektedir ve yıllık insidansın 15/100.000 olduğu düşünülmektedir (3). Durmuş ve ark. tarafından yapılan Türkiye'de PH prevalansını belirlemeye yönelik ilk büyük popülasyon tabanlı çalışmada, PH prevalansı 202/100.000 bulunmuştur (4). PH'nin karakteristik özellikleri, SNpc'de nöromelanin pigmenti içeren nöronlarda meydana gelen nöron kaybı ve yaygın hücre içi protein (α-sinüklein) birikimi ile meydana gelen yuvarlak, hiyalin nöronal sitoplazmik inklüzyonların (Lewy cisimcikleri) varlığıdır (2). Değişen başlangıç yaşı, semptomlar ve ilerleme hızına sahip heterojen bir hastalık olan PH'de, hastalığın farklı yönlerini incelemek için çeşitli hayvan modellerinin kullanılması gerekir (5). PH'yi deney hayvanlarında modellemek için üç ana yaklaşım kullanılır: (i) nörotoksinler, (ii) genetik manipülasyonlar ve (iii) transkripsiyon faktörlerini hedef alan stratejiler (5). Bu kitap bölümünde PH'nin motor ve motor olmayan semptomlarını taklit etmede başarılı modeller olarak kullanılan nörotoksin modelleri ele alınmıştır.

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Sonuç ve Öneriler

Nörotoksin modelleri hem uygulamaları hem de önceki çalışmalarla karşılaştırmaları kolay olduğu için oldukça değerlidir. 6-OHDA ve MPTP, deney hayvanlarında dopaminerjik nigrostriatal yolakta seçici ve etkili dejenerasyonunu indüklemek için en sık kullanılan modellerdir. Bunun yanı sıra rotenon gibi pestisit modelleri de hem nigral hem de ekstranigral patolojiyi kolaylıkla taklit edebildiği için değerlidir. Bir başka pestisit ve herbisit modeli olan parakuat/maneb etki mekanizması tam olarak aydınlatılamamış ve daha az sıklıkta kullanılan modellerdendir. Nörotoksin modellerinin her gibi çeşitli avantajlara sahip olmakla birlikte bu nörotoksin modellerinin hiçbiri PH'nin tüm patolojik özelliklerini taklit edemez. Bu nedenle test edilmek istenen hipoteze uygun avantajları olan nörotoksin PH modeli oluşturmak için seçilmelidir. Nörotoksin modelleri ile yapılan çalışmalar nöroprotektif tedavilerin geliştirilmesine veya PH patogenezinin aydınlatılmasına katkıda bulunabilir.

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DENEYSEL SEREBRAL İSKEMİ MODELLERİ

BÖLÜM 7

Güven AKÇAY[1]

Giriş

Beynimiz, görme, koklama, yürüme, koşma, düşünme, hissetme, akıl yürütme, dikkat ve hafıza gibi tüm bilinçli ve bilinçaltı fizyolojik fonksiyonlardan sorumlu organımızdır. Beyin uyku, uyanıklık, bilişsel ve fiziksel aktiviteleri yerine getirebilmek için gerekli düzeyde sürekli olarak oksijene ve enerjiye ihtiyaç duymaktadır. Beyin, vücut ağırlığının % 2'i kadarı olmasına karşın kardiyak kalp debisinin yaklaşık % 20'sini kullanmaktadır. Beyin beslenmesinde serebral kan akımı hayati önem taşımaktadır. Beynin bir bölgesinde veya tümünde serebral kan akımının azalması sonucu serebral iskemi meydana gelmektedir. Serebral iskemi, beyni besleyen damarların tıkanması veya kanaması sonucu oluşmaktadır. Dünyada her yıl yaklaşık 17 milyon inme vakası görülürken, ülkemizde de yaklaşık olarak 132.000 inme vakası görülmektedir. Her geçen yıl inme vakaları artmakta ve gelecekte bu durumun sağlıkla ve ekonomiyle ilgili ciddi sorunlara yol açacağı öngörülmektedir. Bundan dolayı inmenin önlenmesi ve etkin tedavi yöntemlerinin uygulanması hayati önem taşımaktadır. Bu tedavi yöntemlerinin araştırılmasında yeni tedavi protokollerinin geliştirilmesi ve yeni ajanların keşfedilmesinde deneysel hayvan modelleri sıklıkla tercih edilmektedir. Klinikteki serebral iskemik vakalarının fizyopatolojisinin araştırılmasında sıklıkla sıçan ve fare gibi kemirgenler üzerinde yapılan geçici global serebral iskemi, geçici fokal serebral iskemi ve geçici ön beyin iskemi modelleri kullanılmaktadır. Bu kitapta; serebral iskeminin epidemiyolojisi, patofizyolojisi ve deneysel serebral iskemi hayvan modelleri arasında en çok kullanılan orta serebral arter oklüzyon yöntemi ile ilgili bilgiler sunulmuştur.

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reperfüzyon aşaması oluşturmakta ve tedavi yöntemleri reperfüzyon hasarını önlemeye yönelik olmalıdır. Serebral iskeminin tedavi yöntemlerinin gelişmesinde özellikle deneysel çalışmalar büyük katkı sağlamaktadır. Yapılan deneysel patofizyolojik çalışmaların çoğu iskemi sonrası reperfüzyon hasarını önlemek, hastaların iyileşmesini hızlandıracak tedavi yöntemlerin geliştirilmesi üzerine yapılmaktadır İskemi reperfüzyonun tedavisi için yeni ajanların keşfedilmesi ve yeni tedavi protokollerinin geliştirilmesi için deneysel geçici serebral iskemi hayvan modelleri sıklıkla tercih edilmektedir. Bu nedenle deneysel geçici orta serebral oklüzyon modeli serebral iskemi araştırmalarında hayati önem arz etmekte ve yeni tedavi yöntemleri için daha fazla deneysel araştırmalar yapılmalıdır.

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DENEYSEL TRAVMATİK BEYİN HASARI MODELLERİ

BÖLÜM 8

Güven AKÇAY[1]

Giriş

Travmatik beyin hasarı, dünya çapında önde gelen mortalite ve morbidite nedenidir. Travmatik beyin hasarı sonrası kişilerde sıklıkla motor, bilişsel ve sensoriyel fonksiyon kaybı görülür. Travmatik beyin hasarı, ölüm, sakatlık ve ruhsal bozukluklar gibi önemli sağlık sorunlarına yol açar. Travmatik beyin hasarı, tüm dünyada giderek artan sağlık sorunu olmaya devam etmektedir. Her yıl yaklaşık 1,7 milyon insanın kafa travması geçirdiği ve bu bireylerden yaklaşık 50.000 kişinin hayatını kaybettiği tahmin edilmektedir. Travmatik beyin hasarı her yaşta ve popülasyonda görülmesine rağmen, vakanın en yüksek olduğu yaş popülasyonunu çocuklar ve yaşlılar oluşturur. Düşme, sportif faaliyetler ve motorlu araç kazaları travmatik beyin hasarının en büyük risk faktörü olarak karşımıza çıkar. Travmatik beyin hasarına yönelik teşhis ve tedavi yöntemlerinin geliştirilmesi için nöropatolojisinin altında yatan moleküler ve hücresel mekanizmaların bilinmesi gerekir. Bundan dolayı farklı modellerde tanımlanmış hafif, orta ve şiddetli deneysel travmatik beyin hasarı modelleri kullanılır. Travmatik beyin hasarının hayvan modellerini genel olarak fokal, difüz ve karışık hasar olarak sınıflandırılır. Travmatik beyin hasarı deneysel araştırmalarında sıvı perküsyon, kontrollü kortikal etki, ağırlık düşürme ve patlama dalgası en sık tercih edilen modellerdir. Bu bölümde, travmatik beyin hasarı için mevcut kemirgen modellerinin güçlü ve zayıf yönleri açıklanacaktır.

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için bir puan verilir: 13–18, şiddeti hasar; 7–12, orta orta hasar; 1-6, hafif hasar. Deneysel çalışmalarda nörolojik şiddet skoru ve motor fonksiyon testleri gibi davranış değişiklikleri değerlendirilmesinin yanında kilo kaybı ve kafa içi basınç artışı gibi fizyolojik değişiklikler; enfarktüs hacmi ve nöronal kayıp gibi histolojik değişiklikler de kullanılır (8, 79, 80).

Sonuç ve Öneriler

Travmatik beyin hasarı, ölüm ve sakatlığın önde gelen nedenlerinden biridir. TBH beyin dokusunun mekanik olarak bozulmasına neden olan dış gücün ve hasarı şiddetlendiren gecikmiş patojenik olayların sonucudur. Bu patojenik yaralanma süreçleri yeterince anlaşılmamıştır ve bu nedenle şimdiye kadar etkili nöroprotektif tedavi mevcut değildir. Deneysel modeller, TBH'nin fizyolojik ve patofizyolojik mekanizmalarının araştırması, yeni terapötik ajanları test edilmesi, klinik denemelerin güvenli ve başarılı olmasını sağlamak için hayvan modelleri gereklidir. İnsan TBH ile ilişkili farklı yaralanma mekanizmalarını modellemek için çeşitli kemirgen TBH modelleri geliştirilmiştir. Travmatik beyin hasarının kemirgen modelleri arasında en sık kullanılanları sıvı perküsyon, kortikal kontüzyon etki, ağırlık düşürme ve patlama dalgası modelleridir. Travmatik beyin hasarında meydana gelebilecek olayların tamamı tek bir kemirgen modeliyle kapsanamayacağından, belirli bir modelin tasarımı ve seçimi sinirbilimciler için büyük bir zorluk teşkil etmektedir. Bu bölümde, travmatik beyin hasarı için mevcut kemirgen modellerinin güçlü ve zayıf yönleri açıklanmıştır.

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IN VİVO VOLTAMETRİ İLE NÖROTRANSMİTTER ÖLÇÜMLERİ

BÖLÜM 9

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Giriş

Merkezi Sinir Sistemi (MSS)'nde bulunan sinirler arasında iletiyi ve iletişimi sağlayan nörotransmitterlerin düzey değişimlerinin Parkinson, epilepsi, şizofreni, ilaç bağımlılığı ve birçok beyin hastalığında rollerinin olduğu birçok çalışmayla gösterilmiştir. Son 20 yıldır çok yaygın şekilde kullanılan mikrodiyaliz metodlar, nörotransmitterlerin dakika başı ölçümlerini vermiştir. Fakat nörotransmitterlerin hızlı dinamikleri, saniye temelinde ölçüm yapan bir tekniğe ihtiyaç doğurmuştur. In vivo voltametri sayesinde nörotransmitterlerin yaşayan canlıda miktar ölçümleri yüksek özgünlükte ve seçicilikte artık ortaya konabilmektedir. Bu teknikte elektrik akımını algılama ve iletme özelliğine sahip beyin elektrotları kullanılmaktadır. İstenen nörotransmitterlerin ölçülebilmesi için seçici bariyerlerle ve özel enzimlerle elektrotlar kaplanmaktadır. Bu teknikte uygulanan voltaj, ortamdaki nörotransmitterin enzimle reaksiyona girerek akım oluşturabilen maddelere dönüşümünü sağlamaktadır. Sonuçta sistemde algılanan elektrik akım miktarı ortamdaki nörotransmitter miktarıyla birebir ilişkili bulunmaktadır. Ayrıca beyine sokulan elektrot uçlarının hasar vermemesi yine mikrodiyaliz problarının ölçümlerine göre in vivo voltametri tekniğine önemli bir üstünlük sağlamaktadır. Şu an mevcut sistemler içinde anestezi altında veya serbest hareket edebilen hayvanlarda o bölgede en net nörotransmitter ölçümünün in vivo voltammetri tekniği ile yapılabileceği iddia edilebilir.

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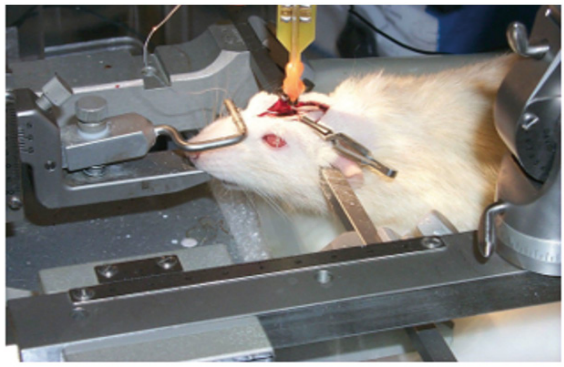

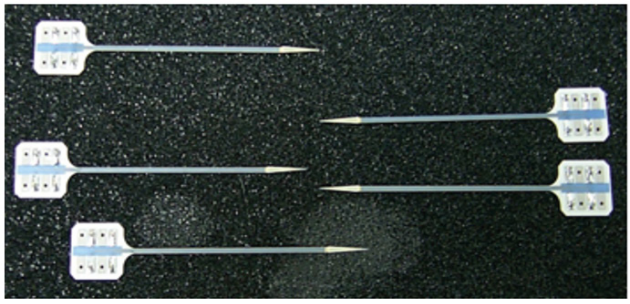

Şekil 14. Etik izinleri alınmış, deney hayvanlarında yapılan deneysel bir çalışma

7.2.İMPLANTASYONUN HİSTOPATOLOJİSİ

Kronik olarak implante edilen L-glutamat elektrodların çevre beyin dokusunda ya çok az ya da hiç beyin hasarına yol açmadığı gösterilmiştir. Sıçanlara 2, 4 veya 8 hafta süresince kronik olarak mikroelektrotlar implante edilmiş ve bu sürelerin sonunda sıçanların beyinleri çıkarılmış, kesitlere ayrılmış ve hem astrositler hem de mikroglialar boyanmıştır. Boyama sonucunda her üç zaman periyodu içinde implant çevresinde kontrol ile kıyaslanınca astrositlerin sayısında ve mikroglia aktivasyonunda kontrole göre istatistiksel bir fark görülmemiştir.

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