Bölüm 10

ALZHEIMER HASTALIĞINA KARŞI İLAÇ KEŞFİNDE NİTROJEN BİLEŞİKLERİNİN ROLÜ

Mehtap TUĞRAK SAKARYA[1]

1. GİRİŞ

Alzheimer hastalığı (AD), dünya çapında yaklaşık 50 milyon kişiyi etkileyen, ilerleyici bunamanın en yaygın şeklidir (1, 2). AD'nin önemli bir klinik semptomu, ciddiyetine göre dört kategoride sınıflandırılan (hafif, orta, şiddetli, çok şiddetli) kademeli hafıza kaybıdır. AD patolojisi, özellikle kolinerjik olan nöronların kaybı, amiloid-β (Aβ) dolu plakların ve distrofik nöritlerin birikmesi ve temporal lobda belirgin nörofibriler yumakların (NFY'ler) varlığı ile karakterize edilir (3-6). Bugüne kadar FDA tarafından AD semptomlarını tedavi etmek için dört ilaç onaylanmıştır. Bu dört ilaçtan üçü asetilkolinesteraz inhibitörleri olan donepezil, rivastigmin ve galantamin ve biri rekabetçi olmayan bir *N*-metil-D-aspartat (NMDA) reseptör antagonisti ve dopamin agonisti olan memantin'dir (7-9). Bu ilaçlar, hafif ila orta şiddette AD için birinci basamak tedaviler olarak kabul edilmektedir. FDA, 1993 yılında takrini de (güçlü bir asetilkolinesteraz inhibitörü) onaylamıştır, ancak olumsuz yan etkileri nedeniyle 2013 yılında bu ilacın kullanımı durdurulmuştur (10, 11). Anti-AD ilaçları, bilişsel işlev bozukluğu için semptomatik rahatlama sağlar, ancak hastalığın ilerlemesini yavaşlatma yönünde etki göstermez. AD'yi ilaçlarla önlemenin veya tedavi etmenin bilinen bir yolu bulunmamaktadır, bu nedenle etkili tedaviler bulmak için acil ihtiyaç hali söz konusudur. Potansiyel hedeflere karşı geliştirilen Tau proteini, amiloid, asetilkolinesteraz (AChE) ve butirilkolinesteraz (BChE), tirozin kinazlar, glikojen sentaz kinaz-3, γ-sekretaz, β-sekretaz, fosfodiesterazlar, monoamin oksidaz (MAO), kalsitonin geniyle ilişkili peptit, NMDA reseptörü, muskarinik asetilkolin reseptörü, dopamin 2 reseptörü, γ-aminobütirik asit-A (GABA-A) reseptörü, 5-hidroksi triptamin (5-HT6) reseptörü gibi birkaç yeni preklinik ve klinik aday vardır (12-16).

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sahip yeni ilaçları keşfetmek oldukça zordur. Ayrıca, medisinal kimyacılar AD ilaçlarını keşfetmeye çalışırken çok sayıda zorlukla karşılaşmaktadırlar. Süreç; hedef ajanın tanımlanmasını, bağlanma afinitesinin iyileştirilmesini, potent ve/veya seçicilik sorunlarını, güvenlik endişelerini, fizikokimyasal, farmakokinetik ve farmakodinamik özelliklerini iyileştirmeyi veya ayarlamayı gerektirmektedir. Bu çalışmada, nitrojen içeren heterosiklik bileşiklerin yanı sıra bu bileşiklerin tasarım stratejilerini, gerekçelerini, SAR ve farmakolojik profillerini araştırmak amaçlanmıştır. Bu çalışma ile, medisinal kimyacılara ve araştırmacılara, bu süreçte mevcut boşlukları ele almalarının ve bildirilen stratejilerden yararlanmalarının yanı sıra, güçlü, daha güvenli, seçici ve uygun maliyetli olan anti-AD ajanlarının geliştirilmesinde yardımcı olmak umut edilmektedir.

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