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IN NEUROFARMACOLOGIA

IL PROMETEO

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La luce della scienza cerco e 'l beneficio

LUX SCIENTIAE

DOTTORATO
INTERNAZIONALE
DI
NEUROFARMACOLOGIA

Università degli Studi di Catania

Dipartimento di Biomedicina Clinica e Molecolare
Sezione di Farmacologia e Biochimica

Viale Andrea Doria, 6 - Catania

Tel.: +39 095 7384237
Tel.: +39 095.7384238

il_prometeo@email.it
http://www.unict.it/dfsc

Coinvolgimento dei recettori metabotropici del glutammato del sottotipo 5 nella fisiopatologia della Sindrome del Cromosoma X Fragile

di Elisabetta Aloisi

Studentessa al secondo anno del Dottorato di Ricerca Internazionale in Neurofarmacologia, coordinato dal prof. Filippo Drago, da circa otto mesi mi trovo a Bordeaux, graziosa città nel sud della Francia, per svolgere il periodo di formazione all'estero. Nel corso degli ultimi anni questa città è diventata una delle più grandi realtà scientifiche in Europa nel campo delle neuroscienze grazie alla sinergia tra diversi istituti di ricerca, quali INSERM, CNRS, IINS e l'Università di Bordeaux, che insieme costituiscono un istituto virtuale chiamato "Bordeaux Neuroscience Institute". La mia attività di ricerca si svolge presso il Neurocentre Magedie INSERM, fondato e diretto dal Prof. Pier Vincenzo Piazza. Il Neurocentre Magendie è un istituto di ricerca multidisciplinare dedicato allo studio delle neuroscienze, partendo dai meccanismi cellulari e molecolari dell'attività neuronale per arrivare fino alla comprensione delle patologie neurologiche e comportamentali.

Il mio progetto di ricerca riguarda il coinvolgimento dei recettori metabotropici del glutammato del sottotipo 5 (mGlu5) nella fisiopatologia della Sindrome del Cromosoma X Fragile (FXS). Questa sindrome è la forma più frequente di deficit cognitivo ereditario e la seconda causa di ritar-

do mentale dopo la sindrome di Down. La sindrome è causata dal silenziamento del gene Fmr1 che codifica per la proteina FMRP, un mRNA binding protein coinvolta nella regolazione della traduzione, del trafficking e della stabilità degli mRNAs target. E' plausibile pensare che nei neuroni la mancanza di FMRP possa interferire con i fenomeni di plasticità neuronale, proprietà che è alla base dei processi di memoria e di apprendimento. Esistono diverse evidenze che supportano il ruolo centrale dei recettori mGlu5 nella fisiopatologia della FXS. In particolare è stato dimostrato che nel modello animale della malattia, rappresentato dai topi Fmr1 KnockOut (KO), i recettori mGlu5 sono meno associati alle proteine Homer, una classe di scaffoldig proteins postsinaptiche importante per la regolazione dell'espressione superficiale e del trafficking del recettore mGlu5.

In accordo con queste evidenze, nel laboratorio del Dott. Andreas Frick, in collaborazione con la Dott.ssa Maria Vincenza Catania, stiamo studiando il trafficking del recettore mGlu5 sulla superficie di neuroni ippocampali ipotizzando un'alterazione nei topi Fmr1KO rispetto ai Wild Type (WT) e utilizzando come approccio il tracking di singole molecole sulla superficie cellulare basato sul "live cell quantum dot imaging". I quantum dots sono particelle di semiconduttori fluorescenti dalle dimensioni di alcuni nanometri (10-30 nm) le cui proprietà fisiche li rendono ottimi candidati per lo studio del trafficking molecolare di superfice e in particolare della diffusione laterale dei recettori di membrana. Questa tecnica rappresenta un nuovo approccio nell'ambito della ricerca nelle neuroscienze, offrendo una valida alternativa alla tradizionale immunocitochimica permettendo di visualizzare, tracciare e misurare le dinamiche delle traiettorie dei singoli recettori sulla superficie cellulare utilizzando un microscopio a fluorescenza collegato ad una videocamera digitale. Nei nostri esperimenti colture di neuroni ippocampali preparate da topi Fmr1KO e WT vengono incubate prima con un anticorpo primario specifico per la porzione extracellulare del recettore mGlu5 e successivamente con i quantum dots coniugati ad un opportuno anticorpo secondario. Le colture vengono poi incubate con un marcatore della sinapsi (Mitotracker) che permette di discriminare le traiettorie dei recettori nel compartimento sinaptico da quelle nel compartimento extrasinaptico. Una volta acquisite le immagini con l'appropriato sistema di rivelazione queste vengono analizzate con un sofisticato programma di analisi basato su complessi algoritmi e funzioni matematiche che analizzano le traiettorie tracciate dai singoli quantum dots sulla base della loro morfologia.

In conclusione, il nostro studio, grazie all'utilizzo di questa innovativa tecnologia, è volto a fornire per la prima volta delle informazioni sul trafficking di superficie dei recettori mGlu5 nella FXS nonché una maggiore comprensione della loro disregolazione in questa patologia.

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Abstract

Role of the endocannabinoid system in energy balance regulation and obesity

Dr. Daniela Cota

MD, CR1 INSERM, group leader, group "Energy Balance and Obesity", INSERM U862, University of Bordeaux

The discovery of the endocannabinoid system (ECS) and of its impact on the regulation of energy homeostasis represents a significant advance in the study of obesity and type 2 diabetes.
The ECS comprises two distinct membrane cannabinoid receptors, CB1 and CB2, specific ligands named endocannabinoids, such as anandamide (AEA) and 2-arachidonoylglycerol (2-AG), and enzymes for ligand biosynthesis and inactivation.
Over the past 10 years, we and others have critically contributed in demonstrating that the CB1-dependent signaling in particular has a role in the regulation of every aspect participating to the maintenance of energy balance.
This lecture will give an overview of the knowledge acquired over the years, which points to CB1 as a potential target for the therapy of obesity and type 2 diabetes.
In particular, it will be discussed the progress done in distinguishing between neuronal and non-neuronal roles of CB1 in energy balance, and the strategies used to dissect the role of the ECS within the central nervous system circuits known to regulate energy balance. Finally, the potential role of the ECS in human eating behavior and in the physiopathology of human obesity will be discussed.
Despite the withdrawal of the first generation of CB1 antagonists from the pharmaceutical market due to the occurrence of psychiatric adverse events, recent evidence suggests that peripherally restricted CB1 antagonists might be efficacious for the treatment of obesity and its associated metabolic disorders. Our recently published findings pointing to a potential role of peripheral AEA levels in meal initiation in humans, suggest that the use of combinatorial multi-target pharmacological approaches, including low doses of peripherally acting CB1 antagonists together with drugs altering other pathways impacting on food intake and energy balance, might represent a valid strategy to tackle obesity limiting undesired side effects.

Neurotrophins, neuronal plasticity and neuroprotection: Role of antidepressant drugs.

Prof. Eero Castren

Neuroscience Center, University of Helsinki

Neuronal plasticity is active during the early postnatal life, when neuronal networks are modified by environmental guidance, but plasticity is much more restricted in adult brain. Antidepressant treatments have been shown to promote different forms of neuronal plasticity, including neurogenesis, synaptogenesis and neuronal maturation in the hippocampus. We have shown that antidepressants activate signaling of TrkB, the receptor for the neurotrophin brain-derived neurotrophic factor (BDNF) in adult brain and BDNF-TrkB signaling appears critical for the behavioral effects of antidepressants in rodents. By using the well-characterized developmental plasticity of the mammalian visual cortex as a model in collaboration with Prof. Maffei's lab, we recently showed that chronic antidepressant treatment reactivates the critical period-like plasticity in the visual cortex adult rats. Furthermore, we have showed that the impaired vision brought about by a closure of one eye throughout development (amblyopia) was completely rescued in adult rats if adult antidepressant treatment was combined with the opening of the amblyopic eye and patching of the better eye in rats in adulthood. These effects were associated with increased BDNF and cold be inhibited by blocking BDNF signaling through TrkB receptors, emphasizing the important role of BDNF in adult plasticity. Very recently, we have observed that antidepressant fluoxetine reactivates a developmental-like state also in the fear-conditioning circuitry including amygdala and that a combination of fluoxetine treatment and fear extinction training leads to a long-term erasure of the conditioned fear response. Our data suggest that pharmacological agents, such as antidepressants, can reactivate developmental-type cortical plasticity and help to repair malfunctioning neuronal networks brought about by imbalanced early experiences, when antidepressant treatment is combined with environmental rehabilitation. These findings open up a novel view of antidepressant drug action where the drug treatment does not work alone, but act by relaxing neuronal plasticity facilitates the effects of psychotherapy and other types of rehabilitation.

Dopamine D3 receptors as therapeutic targets, focus on antagonists for improving cognition in schizophrenia and other CNS disorders.

Prof. Mark J. Millan

Institut de Recherches Servier, Centre de Recherches de Croissy, France

Dopamine is well known to fulfill important roles in the control of mood, motor function and cognition, all of which are affected in disorders of the CNS. Dopamine exerts its actions via five classes of receptor: D1 and D5 receptors are coupled positively to adenylyl cyclase, while D2, D3 and D4 receptors couple negatively. Much interest has focused on D2 sites, and their blockade and stimulation is important for treatment of schizophrenia and Parkinson's disease, respectively. The present talk focuses on D3 sites which fulfill different and even opposite roles vs their closely-related D2 counterparts. These contrasting roles of D3 sites have become clear with the availability of mice genetically deprived of D3 receptors, of agonists preferentially recruiting D3 receptors, and of antagonists selective for these sites. Surprisingly, there is an impressive convergence of data from genetic and pharmacological studies that activating D3 receptors compromises cognitive performance whereas their blockade is pro-cognitive. This represents a role very different from not only of D2 but also D1/D5 receptors. This negative and positive influence of D3 receptor stimulation and blockade upon cognition is expressed both in rodents and in primates. The cellular substrates still require elucidation but actions in frontal cortex appear to be of particular importance, despite the low density of D3 sites in this region. In this region, D3 receptor inactivation activates signals like c-fos and most importantly, mTOR, which may directly compromise cognition. Further, enhanced frontocortical cholinergic transmission and, possibly, increased release of D-Serine from astrocytes may improve cognition. Importantly, blockade of D3 receptors favours many different domains of cognition including attention, working memory, executive function, social cognition, declarative memory and possibly speed of processing. All these domains are compromised in schizophrenia and, supporting the use of D3 antagonists, they reverse cognitive deficits associated with two developmental models of schizophrenia, isolation rearing and neonatal treatment with PCP. In addition, pro-cognitive effects are seen in older animals, consistent with the use of D3 antagonists for the cognitive deficits of Parkinson's disease and Alzheimer's disease. Frustratingly, some 20 years after their discovery we still have no clear clinical feedback on the effects of dopamine D3 receptor blockade on cognition or other functions. However, the development of the D3 agonist PHNO as a PET radioligand will help define drug doses to be used in clinical studies, and data with a D3 antagonist on various cognitive domains in human subjects should soon become available.

Pharmacological approaches to the management of alcohol addiction

Prof. Giovanni Addolorato

Department of Internal Medicine, Catholic University of Rome, Italy

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Neurobiology of impulse-control disorders: implications for the treatment

Prof. Stefano Pallanti

Dipartimento di Psichiatria Università degli Studi di Firenze

Impulsivity may be defined as “a predisposition toward rapid, unplanned reactions to internal or external stimuli with diminished regard to the negative consequences of these reactions to the impulsive individual or to others”. In the “impulsive circuit”, a striatal component (ventral striatum/nucleus accumbens shell) may drive impulsive behaviors and a prefrontal component (anterior cingulated/ventromedialprefrontal cortex) may exhertinhibitory control. Hyperactivity within the striatal components or abnormalities (presumably hypoactivity) in the prefrontal components may thus results in an increased automatic tendency for executing impulsive behaviors during engagement in reward-related behaviors. The identification of the brain circuits implicated in the different ICDs (impulse control disorders), may represent the base for the development of a “circuit-targeted” treatment. This purpose is suitable only with the use of the neuroscience instruments (such as neuoroimaging, neurophysiology, translational research etc.).

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