Simposio Internacional / *International Symposium*:

**Patología del Sueño: de la Neurobiología a las manifestaciones sistémicas**
***Sleep disorders: from Neurobiology to Systemic Consequences***

**Madrid, 18 y 19 de enero de 2018 / *January 18-19, 2018***

**ABSTRACT**

## Modelos animales en Medicina del Sueño
*Animal models in sleep medicine*

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Obstructive sleep apnea (OSA) is a prevalent condition characterized by repetitive occlusions of the upper airway during sleep resulting in intermittent hypoxia (IH), increased respiratory efforts and sleep fragmentation (SF). Over the last several decades, epidemiological, clinical and experimental evidence has provided significant support to the contention that OSA operates as an independent risk factor for cardiovascular, cognitive and metabolic morbidities. More recently, a potential link between OSA and cancer incidence and mortality has also emerged.

However, this pathology is conditioned by other factors such as obesity, age, sex or smoking. These confounding factors make difficult to know the potential contribution of OSA in the development of the aforementioned consequences and the mechanisms involved. On the other hand, the complexity of the functionality of the airway structure makes difficult to study the pathophysiology of the disease. To this end, during the last years, different in vitro and in vivo experimental models capable of mimicking OSA have been developed. The translational or preclinical research has allowed the study of the pathophysiology of the airway as the molecular mechanisms involved in the development of the different pathologies associated with OSA. The basic research has been essential to fully understand the clinical observations and has contributed to bring new concepts inspiring the design and execution of new clinical studies.

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Both forward (phenotype to genetics) and reverse ( genetic modifications, e.g. knockout(KO), transgenic to phenotype) have been used to study RLS. MEIS1 and BDBT9 genes have provided the strongest risk allelic variations to RLS and have been the most studied for relation to phenotype. Homozygous MEIS1 is lethal and the studies have focused mostly on heterozygous MEIS1 animals. These demonstrate hyperactivity considered analogous to restless phenotype of RLS. Data from caenorhabditis elegans indicate role for MEIS1 in ion regulation. Knock-out studies of Btbd9 (mouse homolog of

human BTBD9) mice compared to the wild type (WT) showed increased activity in the open field test, increased wheel running activity and decreased tail flick response to warm stimuli during the rest but not the active period which was reversed by a dopamine agonist (ropinirole) used to treat RLS. These mice compared to the WT also showed decreased sleep time with no difference in REM sleep and enhanced counterclockwise circling behavior. These differences match significant aspects of the RLS phenotype and the circling behavior may reflect dopamine dysfunction. Further studies demonstrate a significant role for Btbd9 in iron management in both mice and flies consistent in part with the brain iron deficiency seen in RLS.

Forward genetic studies led to identification of a murine strain in which dietary iron restriction produced significant decrease in ventral midbrain iron with little decrease in peripheral iron measurement. Further studies showed the experimental iron deficiency in these animals produced increased activity at the transition from active to sleep phase that was reversed by treatment with dopamine agonists. This matches well with the RLS behavioral phenotype and also the RLS treatment response to dopamine agonists.

These studies not only expand our knowledge about the neurobiology of RLS but also provide models for testing development of new treatments for RLS. Particularly noteworthy is one pre-clinical study of IV iron treatment using the inbred mouse strain identified by the VMB iron decreases. The iron treatment increased the iron in the critical brain areas with reduced iron, but it had no effect on iron in other brain areas. These results are reassuring regarding efficacy and safety of IV iron treatments.