



Morvan's syndrome and the sustained absence of all sleep rhythms for months or years: An hypothesis

Claude Touzet

► To cite this version:

Claude Touzet. Morvan's syndrome and the sustained absence of all sleep rhythms for months or years: An hypothesis. Medical Hypotheses, 2016, 10.1016/j.mehy.2016.06.011 . hal-01337972

HAL Id: hal-01337972

<https://amu.hal.science/hal-01337972>

Submitted on 28 Jun 2016

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Morvan's syndrome and the sustained absence of all sleep rhythms for months or years: an hypothesis

Dr. Claude Touzet

Integrative and Adaptive Neurosciences (UMR CNRS 7260), Aix-Marseille Univ, 13331 Marseille, France.

Address for correspondence:

Claude Touzet, NIA UMR 7260, Case B, Pôle 3C, Faculté Saint Charles, Aix-Marseille Université, 13331 Marseille, France – Mobile: +337 8291 0319 – Email: claudetouzet@univ-amu.fr

Acknowledgment

We greatly thank Dr Marc Rey for helpful comments and Elise Millet for proofreading the manuscript.

ABSTRACT

Despite the predation costs, sleep is ubiquitous in the animal realm. Humans spend a third of their life sleeping, and the quality of sleep has been related to co-morbidity, Alzheimer disease, etc. Excessive wakefulness induces rapid changes in cognitive performances, and it is claimed that one could die of sleep deprivation as quickly as by absence of water. In this context, the fact that a few people are able to go without sleep for months, even years, without displaying any cognitive troubles requires explanations. Theories ascribing sleep to memory consolidation are unable to explain such observations. It is not the case of the theory of sleep as the hebbian reinforcement of the inhibitory synapses (ToS-HRIS). Hebbian learning (Long Term Depression) guarantees that an efficient inhibitory synapse will lose its efficiency just because it is efficient at avoiding the activation of the post-synaptic neuron. This erosion of the inhibition is replenished by hebbian learning (Long Term Potentiation - LTD) when pre and post-synaptic neurons are active together – which is exactly what happens with the travelling depolarization waves of the slow-wave sleep (SWS). The best documented cases of months-long insomnia are reports of patients with Morvan's syndrome. This syndrome has an autoimmune cause that impedes – among many things – the potassium channels of the post-synaptic neurons, increasing LTP and decreasing LTD. We hypothesize that the absence of inhibitory efficiency erosion during wakefulness (thanks to a decrease of inhibitory LTD) is the cause for an absence of Slow-Wave Sleep (SWS), which results in the absence of REM sleep.

Predation during sleep

Predation during sleep is important, and correlates with the duration of sleep [1]. An evolutionary increase in sleep exposure is associated with an evolutionary decrease in SWS time. In other words, when phylogeny is controlled, birds that sleep in riskier locations have low SWS times, while birds in safer sleeping locations have greater amounts of SWS. The conclusion is that sleep (in both birds and mammals) is related to the risk of predation associated with sleeping sites.

Ubiquity of sleep in the animal kingdom

All species of animals exhibit sleep, including cubomedusan jellyfish [2], tree frogs [3], lizards [4], drosophilas [5,6], zebrafish [7], birds [8,9], and all mammals [10] (starting with the platypus [11]).

Sleep may be “particular” such as dolphins [12] which sleep with only one hemisphere at a time – since breathing is a deliberate action for them. The same unihemispheric sleep has been co-evolved by several species of birds [13].

Unihemispheric slow-wave sleep is extremely interesting in the context of a theory of sleep. It demonstrates that evolution can alter sleep (one hemisphere at a time), but its presence sustains the notion that it must be essential [14].

A further evidence is provided by the northern fur seal (*Callorhinus ursinus*), which can alternate between bilateral and unilateral SWS depending on its location while sleeping. While on land, 69% of SWS occurs bilaterally; however, when sleep takes place in water, 68% of all SWS is found with interhemispheric EEG asymmetry, indicating unihemispheric SWS (reported in [13]).

Human sleep durations

The average sleep duration in adulthood is between 7 and 8 hours per day. Sleep duration varies through life: babies sleep more than children, who sleep more than teenagers, who sleep more than adults, who sleep more than older adults (> 65 years old). There is also a large variation of sleep duration among the population: some people are satisfied with only 4 hours of sleep, when others require 10 hours [15].

Sleep quality

The quality of sleep appears to be more and more essential for health, as demonstrated by the implication of SWS in the pathogenesis of Alzheimer's disease [16], long sleep with mortality [17], and sleep disturbances with suicide [18].

Sleep restriction

A number of conditions are impacted by sleep deprivation, starting with increases of blood pressure and stress hormone levels. Sleep deprivation makes it difficult for the body to process blood sugar and reduces levels of leptin, an appetite-depressing hormone. These two changes could lead to diabetes and weight gain [19]. Lack of sleep also increases inflammation, thought to be a key element in the development of heart disease.

Experiments on sleep restriction demonstrate that excessive wakefulness quickly impacts cognitive performances – such as those measured by the classical PVT [20]. The fact that a debt of sleep must be slept away is also a good indication that sleep is necessary [21]. A further proof is offered by the fact that a total lack of sleep kills initially healthy rats in less than a month [22].

Total insomnia

Total insomnia without impact on the cognitive function exists. The first one that received all the modern medical scrutiny has been reported by Jouvet [23], the famous French sleep specialist.

At the age of 27, the patient started to have acute insomnia, which was confirmed 6 months later by polysomnography at the hospital. There, his total insomnia duration was 4 months (after what the patient died) – but during this time period, he did not show any sign of cognitive impairment. The evaluation of his cognitive functions was considered normal (attention, short-term memory, learning, etc.). His lack of sleep was continuously monitored and controlled by the medical staff. He was diagnosed with Morvan's syndrome. Severe insomnia, including total insomnia, is the most reported symptom in Morvan's syndrome.

Total insomnia and sleep theories

All theories of sleep that advocate a crucial role of sleep in memorization [24-28] are unable to explain the lack of impact of severe (even total) insomnia on cognitive performances. In fact, these patients are “living” proof that sleep-dependent memory consolidation theories are wrong.

The case of the synaptic homeostasis hypothesis [29] is different since sleep (SWS) is supposed to downscale (excitatory) synaptic strength to a baseline level that is energetically sustainable. Cognitive performance could be maintained if downscaling was provided in a different way – or made unnecessary.

The theory of sleep as the hebbian reinforcement of the inhibitory synapses [30] offers a hypothesis compatible with total insomnia.

Theory of sleep as the hebbian reinforcement of the inhibitory synapses (ToS-HRIS)

This theory is based on several observations. Firstly, as long as the brain stays awake, hebbian learning guarantees that efficient inhibitory synapses lose their efficiency [31] – just because they are efficient at avoiding the activation of the targeted neurons. Secondly, since hebbian learning is the only known mechanism of synapse modification [32] that operates within the required time frame (hours) [33], it is necessary that in order to replenish the inhibitory synapses efficiency [34,35], source and targeted neurons must be activated together [36]. Thirdly, a travelling wave of depolarization [37] is exactly what is needed to ensure the strengthening of local inhibitory synapses.

ToS-HRIS states that it is exactly the purpose of the “slow-wave sleep” (SWS). It also states that the purpose of the REM sleep (Random Eye Movements sleep, also named paradoxical sleep), which follows each session of SWS, is to counteract the eroding effect of SWS on the excitatory long distance connections coding the events of the previous day. Indeed REM activity resembles that of the awake state, except that it is played much faster and not in the same order [38]. ToS-HRIS explains the synergy between NREM (non REM: Light Sleep + SWS) and REM sleep, acting together to guarantee that when the subject awakes, his inhibitory synaptic efficiency is restored and his (excitatory) long distance associations are still there.

A number of findings should be made clear, in the context of the ToS-HRIS:

- 1- REM is only required because of SWS. If there is no SWS, then no REM is required.
- 2- SWS is only required because of the LTD of the inhibitory synapses (I-LTD) during wakefulness.
- 3- If inhibitory synapses' LTD (I-LTD) is reduced or impeded, then SWS is not required anymore (our hypothesis).

Total insomnia: hypothesis

Could it be that I-LTD is reduced or impeded in such a way that SWS is not required anymore (*i.e.*, total insomnia)? The observation that Morvan's syndrome may induce severe (even total) insomnia without any negative impacts on cognitive functions is intriguing.

Morvan's syndrome

The insomnia of Morvan's syndrome is similar to that described in delirium tremens and fatal familial insomnia. It is characterized by reduced or absent sleep spindles and K complexes. It is also characterized by REM sleep without atonia and absent or severely reduced SWS [39]. As opposed to fatal familial insomnia in which degeneration of the thalamus is progressive, the dysfunction in Morvan's syndrome is thought to be reversible. Hallucinations and delusions are commonly associated positive symptoms related to the encephalopathy. Seizures are uncommon in Morvan's syndrome. They can appear during the acute phase of the disease, or a few months earlier.

Less than 30 cases of Morvan's syndrome were documented in the literature between 1986 and 2009 [39]. Current evidence supports the concept of Morvan's syndrome as an autoimmune synaptic disorder. Voltage-gated potassium channel (VGKC) antibodies have been found in several patients with this syndrome [40,41] and symptoms may improve with immuno-modulating therapy (*e.g.*, steroids, azathioprine, plasmapheresis). The natural history of Morvan's syndrome is highly variable, including spontaneous remission, and has a fatal issue in 10% of cases [42].

Typical presentation of Morvan's syndrome includes muscle twitching (thus the name “shaker”), hyperhidrosis, insomnia, fluctuating cognition, and limb paresthesia. The precise pathophysiology of Morvan's syndrome has not yet been established [43], and is highly variable [39].

Voltage-gated potassium channels and Morvan's syndrome

K⁺ channels play a crucial role in returning the depolarized neuron to its resting state. If missing, then the return to the resting state takes much longer, which affects synaptic plasticity. There is a high degree of diversity in the neuronal K⁺ channel population, probably serving specific

physiological requirements of different locations. VGKC are the most ubiquitous and diverse group of voltage-dependent ion channels found in the body. VGKC are expressed widely in the central nervous system, but the cerebellum and hippocampus have received the most attention due to the genetic disorders associated with the dysfunction of VGKC (especially epilepsy and episodic ataxia) [44].

VGKC play a major role in regulating the excitability of hippocampal pyramidal neurons by modulating neurotransmitter release, post-synaptic responses to excitatory inputs, neuronal spike properties, and firing frequency. How auto-antibodies impair VGKC function remains unclear. They appear to be heterogeneous and may bind to multiple Kv subunits [44]. Kv1.1-1.6 are highly expressed in different combinations in the cerebellar molecular and granule cell layers as well as at the basket cell terminal, and in specific layers of the hippocampus containing excitatory axon terminals, most prominently in the molecular layer of the dentate gyrus, in the CA3 mossy fiber zone and in the stratum radiatum of CA1-3.

Antibodies to *Shaker*-type (KvI) K⁺ channels are known to be associated to neuromyotonia, limbic encephalitis and Morvan's syndrome. In the central nervous system, each disease correlates positively with at least one Kv1.1, Kv1.2 or Kv1.6 antibodies. However, compared to the two others, Morvan's syndrome is the most variable and less prominent [45].

K⁺ channels and LTD/ LTP

Active conductances located and operating on neuronal dendrites are expected to regulate synaptic integration and plasticity. Studies support the notion that Kv4.2 subunits are required to form A-type K1 channels in dendrites of CA1 pyramidal neurons [46]. Pharmacological block and genetic elimination of the Kv4.2-mediated IA currents facilitates the induction of long-term potentiation of excitatory inputs [46,47].

Using Kv4.22/2 mice, Zhao *et al.* investigate how Kv4.2-mediated A-type K1 channels (and Ca21-activated K1 channels) are involved in the induction process of Hebbian type plasticity that requires correlated pre- and post-synaptic activities [48]. They demonstrate using CA1 pyramidal neurons that elimination of dendritic A-type K1 currents resulted in an expanded time window, making LTP less dependent on the temporal relation of pre- and post-synaptic activity. For LTD, the threshold was significantly increased. This shift in the depression threshold was restored to normal when the appropriate amount of internal free calcium was chelated during induction.

In summary, actions on the K⁺ channels of the post-synaptic neuron (of glutamate excitatory synapse) modify the LTP and LTD. If the action removes the K⁺ currents (with an antagonist of the Kv) then LTP is facilitated (expanded time window) and LTD is made more difficult (a shift of threshold allows an easier potentiation).

The previous research focused on excitatory synapses, but inhibitory (GABA) synapses target the same post-synaptic neurons and exhibit similar LTP/LTD variations [49,50].

Conclusion

When VGKC action is impeded (by a disease such as Morvan's syndrome), then LTP and LTD are modified in such a way as to render inhibitory synapse LTD (I-LTD) very difficult. Since ToS-HRIS asks for SWS as long as I-LTD occurs (SWS is supposed to replenish the inhibitory synapse efficiency through I-LTP), if there is no I-LTD, then there is no requirement for SWS (*i.e.*, for sleep – since REM is only required because of SWS's negative impact on the excitatory long distance connections). This agrees with the “local” aspect of sleep: the local duration of sleep depends on the use of a given cortical region in the wakefulness state [27].

ToS-HRIS is the only sleep theory able to account for prolonged wakefulness without negative impact on cognitive performances.

Total insomnia without any adverse effect?

In addition to severe (even total) insomnia, Morvan's syndrome patients may be affected by many problems such as daytime drowsiness, intermingled with confusional oneiric status, and the

emergence of atypical REM sleep from wakefulness. The symptoms picture is highly variable, certainly associated with the fact that the distribution of the various (about 50) Kv channels is highly variable between individuals. Could it be that there exist individuals who show no other symptoms than total insomnia?

For example, Al Herpin (1862–1947) was an American known as the "Man Who Never Slept". In 1904, journalists reported that he had not slept during the last 10 years (which starts his total insomnia at the age of 32). His claim was investigated by medical professionals who could not demonstrate the opposite. He was in good health, and lived until his 85th year without sleeping. He had a constant level of high awareness.

Another case is reported (2006) in Vietnam: Hai Ngoc (1942-) says that he could not sleep at night after getting a fever in 1973 (which starts his total insomnia at the age of 31). He has already spent three decades without sleep, and is considered healthy by local medical doctors.

Interestingly, in both cases the total insomnia started after 30 years old, in one case after a "fever". Following our hypothesis, there is a high probability that these people were affected by an autoimmune disease inducing the "just right" combination of K⁺ channels inactivation to end up with only one symptom: total insomnia.

Future directions

Why did evolution not find and retain this solution, if not for humans, then for another species? Maybe the necessary conditions to reunite are extremely rare. Humans amount to several billions and only two cases were reported in the twentieth century.

Should humans consider developing a total insomnia without side effect technology in order to increase their life time (within the same lifespan), then a logical direction of research would be to seek a better understanding of the various K⁺ channelopathies.

References

1. Roth, T. C., Lesku, J. A., Amlaner, C. J., & Lima, S. L. (2006). A phylogenetic analysis of the correlates of sleep in birds. *Journal of sleep research*, **15**(4), 395-402.
2. Seymour, J. E., Carrette, T. & Sutherland, P. (2004). Do Box Jellyfish Sleep at Night? *Med J Aust.*, **118**:707.
3. Hobson, J. A., Goin, O. B. & Goin, C. J. (1968). Electrographic Correlates of Behaviour in Tree Frogs, *Nature* **220**, 386-387. doi:10.1038/220386a0
4. Ayala-Guerrero, F. & Huitrón-Reséndiz, S. (1991). Sleep patterns in the lizard *Ctenosaura pectinata*, *Physiology & Behavior*, **49**:6, 1305-1307.
5. Nitz, D.A., van Swinderen, B., Tononi, G. & Greenspan, R. J. (2002). Electrophysiological Correlates of Rest and Activity in *Drosophila melanogaster*, *Current Biology*, **12**, 1934–1940.
6. Gilestro, G. F., Tononi, G. & Cirelli, C. (2009) Widespread Changes in Synaptic Markers as a Function of Sleep and Wakefulness in *Drosophila*, *Science*, **324**, 109-112.
7. Yokogawa, T., Marin, W., Faraco, J., Pézeron, G., Appelbaum, L., Zhang, J., Rosa, F., Mourrain, P. & Mignio, E. (2007) Characterization of Sleep in Zebrafish and Insomnia in Hypocretin Receptor Mutants, *PLoS Biology* **5**:10.
8. Amlaner, C. J. & Ball, N. J. (1994). Avian sleep. In Kriger, M.H., Roth, T. & Dement, W.C. (eds) *Principles and Practice of Sleep Medicine*, 81–94. W.B. Saunders, Philadelphia.
9. Rattenborg, N.C. (2006). Do birds sleep in flight?, *Naturwissenschaften*. **93**(9): 413-25.
10. Siegel, J. M. (2008). Do all animals sleep? *Trends in Neuroscience* **31**: 208-213.
11. Siegel, J. M., Manger, P. R., Nienhuis, R., Fahringer, H. M. & Pettigrew, J. D. (1999). Sleep in the platypus. *Neuroscience* **91**(1): 391–400.
12. Mukhametov, L. M., Supin, A. Y. & Polyakova, I. G. (1977). Interhemispheric asymmetry of the electroencephalographic sleep patterns in dolphins, *Brain Research* **134**(3), 581-584.
13. Rattenborg, Neils C.; Amlaner, C.J.; Lima, S.L. (2000). Behavioral, neurophysiological and evolutionary perspectives on unihemispheric sleep. *Neuroscience and Biobehavioral Reviews* **24** (8): 817–842

14. Cirelli, C. & Tononi, G. (2008). Is sleep essential? *PLoS Biol* **6**(8): e216. doi:10.1371/journal.Pbio.0060216
15. Hirshkowitz M., Whiton K. *et al.* (2015) National Sleep Foundation's sleep time duration recommendations: methodology and results summary. *Sleep Health: Journal of the National Sleep Foundation*. doi:10.1016/j.sleh.2014.12.010.
16. Kang, J. E., Lim, M. M., Bateman, R. J., Lee, J. J., Smyth, L. P., Cirrito, J. R., Fujiki, N., Nishino, S. & Holtzman, D. M. (2009). Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. *Science* **326** (5955):1005-7. doi: 10.1126/science.1180962.
17. Youngstedt, S. D. & Kripke, D. F. (2004). Long sleep and mortality: rationale for sleep restriction. *Sleep Med Rev.* **8**(3):159-74.
18. Bernert, R. A., & Joiner, T. E. (2007). Sleep disturbances and suicide risk: A review of the literature. *Neuropsychiatric Disease and Treatment*, *3*(6), 735–743.
19. Taheri S, Lin L, Austin D, Young T, Mignot E; Lin; Austin; Young; Mignot (2004). Short Sleep Duration Is Associated with Reduced Leptin, Elevated Ghrelin, and Increased Body Mass Index. *PLoS Med.* **1** (3): e62. doi:10.1371/journal.pmed.0010062.
20. Van Dongen, H. P. A., Maislin, G., Mullington, J. M. & Dinges, D.F. (2003). The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* **2**:117-126.
21. Van Dongen, H., Rogers, N. L., & Dinges, D. F. (2003). Sleep debt: theoretical and empirical issues. *Sleep and Biological Rhythms*, *1*(1), 5-13.
22. Everson, C. A., Bergmann, B. M., & Rechtschaffen, A. (1989). Sleep deprivation in the rat: III. Total sleep deprivation. *Sleep*, *12*(1), 13-21.
23. Fischer-Perroudon C., Mouret J. et Jouvét M. (1974). Sur un cas d'agrypnie (4 mois sans sommeil) au cours d'une maladie de Morvan. Effet favorable du 5-hydroxytryptophane *Electroencephalography and Clinical Neurophysiology*, 1974, 36: 1-18.
24. Diekelmann, S. & Born, J. (2010). The memory function of sleep. *Nature Rev. Neurosci.* **11**, 114–126.
25. Walker, M. P. & Stickgold, R. (2010). Overnight alchemy: sleep-dependent memory evolution. *Nature Rev. Neurosci.* 19 Feb 2010 (doi:10.1038/nrn2762-c1).
26. Rasch, B. & Born, J. (2007). Maintaining memories by reactivation. *Curr Opin Neurobiol.* **17**(6):698-703. doi: 10.1016/j.conb.2007.11.007. Epub 2008 Jan 28.
27. Huber, R., Ghilardi, M. F., Massimini, M. & Tononi, G. (2004). Local sleep and learning. *Nature* **430**(6995):78–81.
28. Sejnowski, T. & Destexhe, A. (2000). Why do we sleep? *Brain Research* **886**, 208–223.
29. Tononi, G. & Cirelli C. (2006). Sleep function and synaptic homeostasis. *Sleep Med Rev.* **10**(1):49-62.
30. Touzet, C. (2015). Sleep: the hebbian reinforcement of the local inhibitory synapses, *Med. Hypotheses* **85**, 359-364.
31. Maffei, A. (2011). The many forms and functions of long term plasticity at GABAergic synapses. *Neural plasticity*, 2011.
32. Lamsa, K., Heeroma, J., H. & Kullmann, D., M. (2005). Hebbian LTP in feed-forward inhibitory interneurons and the temporal fidelity of input discrimination. *Nat Neurosci.* **8**(7): 916-24.
33. Turrigiano, G. G. (2011). Too many cooks? Intrinsic and synaptic homeostatic mechanisms in cortical circuit refinement. *Ann. Rev. Neurosci.*, vol. **34**, pp. 89–103.
34. Scelfo, B., Sacchetti, B. & Strata, P. (2008). Learning-related long-term potentiation of inhibitory synapses in the cerebellar cortex, *PNAS*, **105**(2):769-774. DOI:10.1073/pnas.0706342105
35. Kullmann, D. M., Moreau, A. W., Bakiri, Y. & Nicholson, E. (2012). Plasticity of Inhibition. *Neuron* **75**(6), 951-962. doi:10.1016/j.neuron.2012.07.030.

36. Woodin, M. A., Ganguly, K., Poo, M. M. (2003). Coincident pre- and postsynaptic activity modifies GABAergic synapses by postsynaptic changes in Cl⁻ transporter activity. *Neuron*. **39**(5): 807-20.
37. Massimini, M., Huber, R., Ferrarelli, F., Hill, S. & Tononi, G. The Sleep Slow Oscillation as a Traveling Wave, *The Journal of Neuroscience* **24**: 6862-6870 (2004).
38. Euston, D., Tatsuno, M. & McNaughton, B. Fast-Forward Playback of Recent Memory Sequences in Prefrontal Cortex During Sleep, *Science* **318**, 1147 (2007).
39. Abou-Zeid, E., Boursouliau, L. J., Metzger, W. S., Gundogdu, B. Morvan syndrome: a case report and review of the literature. *J Clin Neuromuscul Dis* 2012 Jun; **13**(4):214-27
40. Liguori R, Vincent A, Clover L, Avoni P, Plazzi G, Cortelli P et al . Morvan's syndrome: Peripheral and central nervous system and cardiac involvement with antibodies to voltage-gated potassium channels. *Brain* 2001; **124**:2417-26.
41. Cornelius JR, Pittock SJ, McKeon A, et al. Sleep Manifestations of Voltage-Gated Potassium Channel Complex Autoimmunity. *Arch Neurol*. 2011; **68**(6):733-738. doi:10.1001/archneurol.2011.106.
42. Cottrell DA, Blackmore KJ, Fawcett PR, Birchall D, Vincent A, Barnard S, et al . Sub-acute presentation of Morvan's syndrome after thymectomy. *J Neurol Neurosurg Psychiatry* 2004; **75**:1504-5.
43. Josephs KA, Silber MH, Fealey RD, Nippoldt TB, Auger RG, Vernino S. Neurophysiologic studies in Morvan syndrome. *J Clin Neurophysiol* 2004; **21**:440-5.
44. Kleopa KA. (2011). Autoimmune Channelopathies of the Nervous System. *Current Neuroparmacology*. **9**(3):458-467. doi:10.2174/157015911796557966.
45. Kleopa KA, Elman LB, LangB, Vincent A, Scherer SS (2006). Neuromyotonia and limbic encephalitis sera target mature Shaker-type K⁺ channels: subunit specificity correlates with clinical manifestations, *Brain* **129** (6), 1570-1584. R
46. Chen X., Yuan L-L., Zhao C., et al. (2006). Deletion of Kv4.2 Gene Eliminates Dendritic A-Type K⁺ Current and Enhances Induction of Long-Term Potentiation in Hippocampal CA1 Pyramidal Neurons *The Journal of Neuroscience*, 22 November 2006, **26**(47): 12143-12151; doi: 10.1523/JNEUROSCI.2667-06.2006
47. Ramakers, G. M., & Storm, J. F. (2002). A postsynaptic transient K⁺ current modulated by arachidonic acid regulates synaptic integration and threshold for LTP induction in hippocampal pyramidal cells. *Proceedings of the National Academy of Sciences*, **99**(15), 10144-10149.
48. Zhao, C., Wang, L., Netoff, T., & Yuan, L. L. (2011). Dendritic mechanisms controlling the threshold and timing requirement of synaptic plasticity. *Hippocampus*, **21**(3), 288-297.
49. Luscher B., Fuchs T. & Kilpatrick C. (2011). GABAA Receptor Trafficking-Mediated Plasticity of Inhibitory Synapses, *Neuron* **70**(3): 385 – 409.
50. Castillo, P. E., Chiu, C. Q., & Carroll, R. C. (2011). Long-term plasticity at inhibitory synapses. *Current opinion in neurobiology*, **21**(2), 328-338.