The PRECISE working of sleep and sleeping pills – *version 1.0 draft 21 sep 2013 for peer review – final article will follow – JP Blankert M.Sc. M.A. Academia.edu*

1. Introduction

Insomnia has been a problem for centuries; there are many novels telling about it, from such superb authors as Shakespeare and Goethe so no one doubts its truthfullness. There is a huge difference between temporary insomnia – familiar to most people – that is due to preoccupation with a feeling or certain problem – and chronic insomnia, that may persevere in times the individual's life is happy and problemless. Appr. 3% of humanity has chronic insomnia; think of at least 3 nights of zero hours of sleep, whereafter many muscles ache, coordination is weak, suffering is high. Natural sleep does not return; the sleep remains as little as 2-3 hours per night. The person remains on a 'borderline vegetative life' not being able to work, hold a job or keep healthy relationships.

With chronic insomnia there are at least 3 problems with the surrounding:

1) everybody sleeps, so everybody has an opinion, thinks sleep is subject to will, and tells the insomniac 'do as I do' and if the 101 tips do not help, the insomniac is blamed (also by physicians)

2) 99% of humanity phantasises and flees into unfounded psychological explanations. Strangely enough, when an individual has a broken leg, or cancer, almost no one comes up with a psychological theory. Up to now, 2013, no psychological explanation proved better than $p>0.05$ and 'explained variation of 20%'- so: very inprecise and very inconclusive

3) the very few who know the secret of sleep, keep quiet about it. The secret of sleep is big money (sleeping pills) , up to the know how to produce poison gas (the working of poison guess requires more or less the same knowledge).

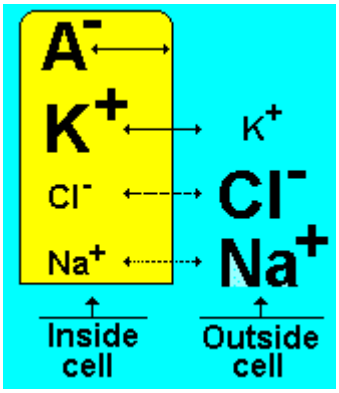
As Insomnia Clients Foundation, it took us over one year of desk research (from foundation in July 2012 to September 2013) to find the 'holy grail'- how sleep precisely works. Other sleepfoundations in the world keep quiet about the secret, so they can earn money with it. We also would like to earn money to keep our research going, but not earning money by withholding the truth. Therefore we are proud to present you the PRECISE/EXACT working of sleep and sleeping pills. The explanation is not part of a medical practice, but of neuroscience, and especially electrophsyiology and molecular chemistry and molecular biology.

2. The main electronic mechanism of the neuron

A neuron consists of biomass, but the biomass serves to pass on, or otherwise generate, store or inhibit electric signals. The whole of the brain works – electronically – through either a) straight conduction of electricity (electric current) or b) locally decreased permeability of ions in order to generate an electric potential.

In underneath picture, the neuron is represented by yellow. You see A- ions, of protein, that

can never leave the neuron. K+, positive Potassium ions, that can easily go through the membrane and Cl- chloride ions, that can only pass the membrane through 'GABA receptors' that have to open a 'ion channel' in order for the Cl- to pass. Na+ hardly passes the membrane at all.



Conclusion: 'who wins?'

- the A- protein ions. BUT: because the A- proteins cannot cross the membrane, the electric potential they cause is zero.
- the K+ potassium ions, because of the positive load of Potassium ions, and the fact potassium can EASILY pass the membrane, the free electrons around the K+ ions are numerous, and make the inside of het neuron significantly negative in charge
- the CL- ions within the neuron are quite seldom. Permeability of the membrane for Cl- ions is appr. 1/100 of that for potassium.

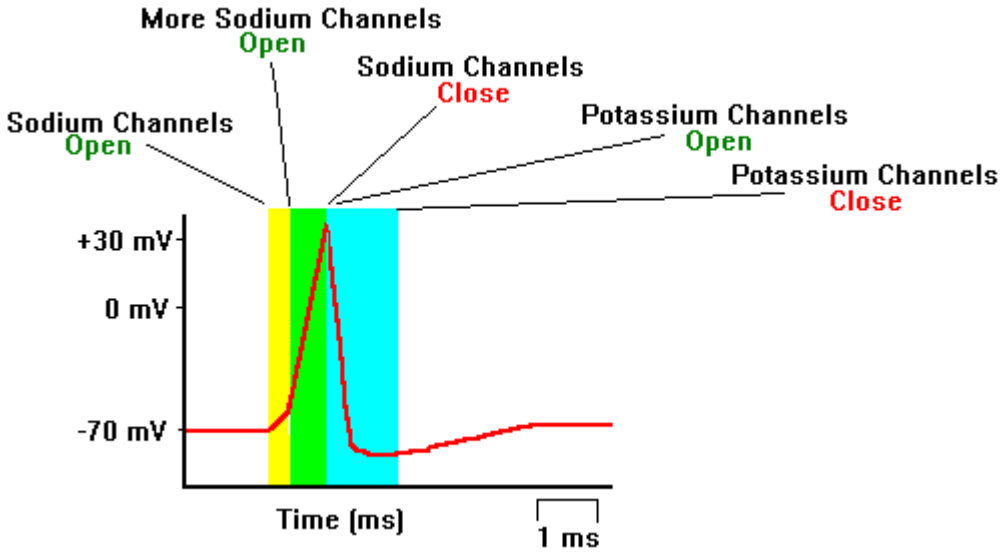
  This makes that the overall 'resting potential' (resting meaning a) no permability change in the membrane b) no current going over the neuron c) all inflows and outflows have stabilized to this status quo equilibrum) is appr. -70 m Volt. This can be calculated with the GHK (goldman-Hodgkin-Katz) equation that is mentioned in appendix 1 (for structural reasons of understanding, it is very important going though the formula).

  The concept and measurement of 'resting potential' are coined by Nobel prize winners Hodgkin and Huxley, 1956 who measured a neuron from a giant squid (neruon being appr. 1 mm).

  The word 'resting' is in this way misleading, in that a neuron in above state is EASY to excite.

  An electric current can be as well positive as negative.

  Image now a POSITIVE electric current comes to the neuron (this is not researched by named Nobel prize winners).



The positive voltage:

a) decreases the negative load, so from – 70 milli Volt to less...this is called 'hypopolarising' (note that hypo means 'less')
b) immediately opens the ion channels, GABA receptors. Through the ion channels CL- ions flow in – they are attracted by the positive electric current that came upon the neuron. The positive current and inflowing Cl- ions 'neutralise' eachother. The GABA receptors react very quickly. This essence is almost always overlooked. The Cl- ions in a word 'cushion' the hypopolarisation started by the external postivie current.

At this early stage, the two other ions in the neuron do NOT participate:

- the negative ions of the protein cannot pass the membrane. If they COULD, it would be ideal, because the negative ions would cross membrane, and electrons would come back as current to neutralise the incoming positive current
- the K+, potassium ions, react very slowly. If they could immediately be pushed trough the membrane, the free electons circuling around K+ would be 'free' to neutralise the positive current. But as long as the K+ is inside the cell, the electons are not free to neutralize the positive current.

So the 'quick reaction job' in order to inhibit to positive income current, comes all down the
a) the fastness of opening ion-channels (Cl- channels) in the GABA receptor
b) the largeness of INFLUX of Cl-

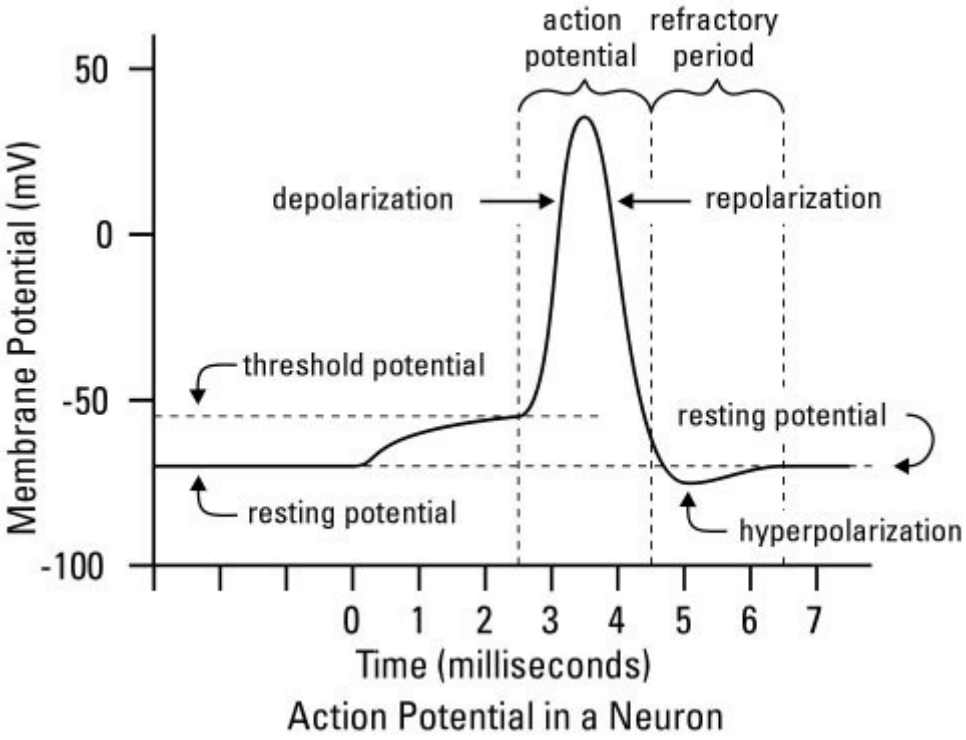
Above is the reason GABA is the only 'inhibitionary neurotransmitter' and only 'negative feedbackloop' in the electrophysiology. All other neurotransmitters 'de-escalate'.

If the GABA do their and organise inflow fo CL- at maximum speed, the incurrent positive current is decreased, and at a certain moment 'stopped' at a threashold point as -50 m V. BUT:

if at that moment No MORE Cl- flows in to stop the electric current from further hyperpolarising the neuron, the positive current passes a point of 'no return': it is unstoppable, the Cl- have worked out, and the potassium +ion have not ben quick enough to be pushed through the membrane to outside.

The the voltage goes to zero, and then PEAKS across zero voltage to a high peak. The neuron fires, with this action potential.

After the peak of (positive) firing, the charge of the original electric current has largely been used up, and finally potassium ion K+ are pushed to outside, which causes an electron inflow into the neuron that further cushions and neutralises the (past) positive electric current until order is restored:



Action Potential in a Neuron

3. Increasing 'REST' or SLEEP

In ordinary language, we say things as 'my nerves are tense' and 'relax'. We will see how truthful this is in an electronic way.

In order to keep the neurons quiet, it is preferable to have:
a) less stimulus, in this case: less positive currents that 'surprise' a neuron
b) increased working of the 'negative feedback loop' – consisting of QUICK and LARGE inflow of positive ions (as Cl-) and LARGE outflow of negative ions (as K+).
c) maximum membrane permeability, as this would 'earth' the whole neuron and make it less excitable
d) lowering the theshold (for example from -50 mV to -30 m V, or even 0 m V!) so there is far more time to neutralize an incoming positive current before 'threshold value' is reached during hyperpolaristion and the 'point no return' (th threshol) is reached, after which a firing/Action Potential is 'unstoppable'.

These four points are exactly the secret of sleep as well as sleeping pills! The solution is thus in ELECTROPHSYSIOLGY, not in chemicals (chemicals only aid to achieve certain electronic behavior). This is 'the world upside down' for many phsyicians. We will work out abouve points throughout the 1) supposed working of 'natural GABA ' and 2) the working of BZD (Benzodiazenpines) when 1) natural GABA fails.

Sleeping occurs when the 'wake state' (with activating neurotransmitters as Glutamate) 'loses' from the 'sleep state' (with GABA). This overall mechanism that involves almost all parts of the brain, is described by Saper in 2010, under the name 'sleep wake switching' (Saper, 2010).

Towards 'bed time', due to a carcadian circle (light-dark, biological clock) as well as homeostasis ('done enough for today'), the VLPO emits more GABA. This GABA is supposed to reach many neurons of the inner brain.

The aim of this is:
a) – as prevention – to already open the Cl- ion channels of the GABA receptors, to maximalise the quietening inflow of Cl- in case a positive current 'strikes' the neuron
b) – as prevention as well – to LOWER the threshold potential. This means that not – 50 m Volt anymore is the threshold potential (after which there is 'no point of return' and an action potential is released) – but: maybe – 30 m Volt

The larger inflow per time unit of quietening Cl- ions during 'supposed sleep time' is the CRUX of maintaining sleep.

After use of GABA neurotransmitters, they are metabolised, or 'taken up' so disappear of the 'electric circuit'. During the night, towards morning, the VLPO also diminishes the production and diffusion of GABA neurotransmittors.

Simultanously, the senses are more stimulated through more light (sunrise), more noise, more smell....the PFC (Pre Frontal Cortex) starts to work again and the 'wake state' 'wins' from the 'sleep state'. Day starts.

With a chronic insomniac, the binding of GABA to the ligand-gated ion channels that should let CL- flow in, FAILS. There is no evidence whatsoever that a psychological state is responsible for the failure of GABA binding.

A psychological state (as panic) can be responsible for an overdose of Glutamate (activity) so that the sleep wake has a 'difficut job' to win. But in case nothing excitatory happens in the live of an insomniac, the fault must rather be with the GABA binding.

In the recent years, from many perspectives, it became clear that many problems exist with ion channelling in the brains. The book 'Physiology and Pathology of Chloroide Transporters in the Nervous System' (Academic Press, 2009) is very important. A whole range of diseases is due the malfunctioning of chloride transporters and channels. This is an extreme difficult area of research: molecular biology, molecular pharmacology, gen technology and modern molecular electronics all play a role.

4. Natural GABA binding replaced by BZD binding

Now we know the very well kept secret of sleep, consisting of the 'organisation' of an extremely fast and in electronic terms powerful Cl- influx, looking for a sleeping pill solution is not difficult. BZD, Benzodiazepine, proves to be a far more 'failsafe' solution to open the ion channels than the natural GABA-ligands.

Time will learn 'why' chloride transport and chloride channelling so often fail – not only in case of insomnia. It also counts for example, for inflammations and epilepsy.

Anno 2013 we do not exactly how GABA ligands are, by nature, supposed to bind to GABA receptors.

But better than GABA ligands, we know how BZD binds.

Realising above, it is clear that questions like 'why are you insomniac?' are totally out of order. It is not even totally understood how nature is supposed to work, other solutions than BZD are not available for chronic inomniacs that have no co-morbidity with illnesses as depression, panics, worries or mood disturbances. The 'why' question is for the 22th century.

5. Checking truth

Invisable illnesses are a very popular area for people (and often physicians as well) to hold on to Medieval prejudices, denying feelings, denying what is happening in the dark, denying what they never experienced themselves etc.

Also, a very large part of so called 'research' is futile. Still, much research is conducted pretending brains would be a 'black box'. As in all in-exact sciences, hypotheses are invented, correlations are checked, if the zero hypothesis can be rejected with p = 0.05, or explained variation is 20%, researchers claim to have 'proven' something which is totally untrue because

a) it holds only for a tiny minority of cases b) the mechanism is unknown.

This is the reason that ICF, Insomnia Clients Foundation, rejects in-exact sciences and sticks to exact sciences – the exact sciences within neuroscience, as amongst others electrophysiology. The vast majority of people love biology, beauty and all they can see, but stay far away from mathematics, electronics, complex systems and anything that is 'unromantic'.

Finally, we give you some help to check our truthfulness in this article:

- the basic of electrophysiology is laid by Weidmann 1955, and Nobel prize winners Hodgkin – Huxley in 1956. Their work is widely available for free
- what is overlooked by almost all physicians is the electrophysiological side of sleep and insomnia – that is the reason it has, to our knowledge, never been typed out that sleep would be improved by quietening neurons and facilitating in all ways the influx of Cl- ions to inhibit positive currents coming to the neuron. Familiarize yourself totally with the GHK formula of appendix 1, otherwise you are not able to 'reason effects'.
- very often, currents, positive and negative ions, electrons are mixed up. That is why we explain in detail what each ion does, and where electrons come from; and we add appendix 1 within the corresponding mathematics.
- all writers talk about 'electronic signals' coming to a neuron, not reflecting whether it would be a positive or negative current. This is a sign of 'evading' precision. A negative current would generate a bit of hyperpolarisation (a bit more negative voltage than – 70 m V), but no action potential. Only a positive current can decrease the negative voltage. And almost nobody mentions the logic that a positive current attracts negative loaded Cl- ions.
- To realise the enormous complexity of 'sleep wake', reading the 'sleep wake switchting' by dr. Saper (2010) is crucial. The man must be praised for his yearlong attempt to refine the model, and to have – as physician! – the courage to coin the term 'switch' – a term very popular in exact sciences, but quite a taboo amongst physicians. But, nevertheless, reading his work you realise he NEVER mentions any electrophysiology. Electrophysiology is the large value added to all existing neuropyshiology.
- Use scirus.com and scholar.google.com and to distill electophsyical articles, inlude as 'electrophsyiology' as search word, exclude 'clinics' and 'physians' by applying boolean search adding '-clinical -physicians' at the end of your search string. Note that top research is not done in clinics and done by physicians (or very seldomly) , but in quiet research centers with biologists, chemists, phsycians and electronic engineers. Avoid the 'obligatory publication stream' of PhD thesis' of physcians or other clinical 'researchers'. 'Physician' and 'clincs' are practising professions without the required exact background, and represent 'exercising a practice'- not 'research'. Look for example at the famous article of Dr. Saper of 2010 : it is in a way excellent, but in an other way totally illustrates the absolute lack of electrophysiological knowledge of the neurologists involved. If dr. Saper would have cooperated with exact scientists, his model may have grown out to Nobel prize status. Now it cannot because all phsyics fail and no attempts are made to modelling or measurement.

6. Final note – the future

To our relief, we see that brilliant minds pick up the subject defectie chloride transport and channelling. Researchers of pharmacology, molecular biology, gen technology and molecular electronics/organic electronics work together. This field is all together probably more difficult than rocket science.

We hope that physicians will read this article, and other electrophysiological literature and abandon medieval by-beliefs and amateur psychology. Chronic insomniacs do deserve the sleeping pills allowed to the max. as prescribed by the FDA. Prescribing only half or a third of the required dose ruins many lives and causes many suicides.

Once the exact mechanisms are known, the time returns to link the mechanism to psychology. Although we repeatedly 'condemn' psychology, we must say that the professional psychologists do an excellent in embracing neuroscience to make their profession more exact. The huge danger of psychology comes from non-professional psychologists, as laymen, press, regular people and physicians. Chronic insomnia is an unbearable illness if one cannot obtain enough sleeping pills. In the mechanisms, the evidence at all can be found of 'dependency' or 'desensitivation'. But as 'science', sleep-wake switching is one of the most beautiful areas imaginable. Humankind broke records by conducting electricity, electrons, in a digital manner over metal – but in the brains it becomes clear why conducting analogue electricity over biomass may be superior.

21 September 2013, Philippe Blankert M.Sc. M.A., chairman Insomnia Clients Foundation, version 1.0 = draft for peer review – internetavenue@outlook.com

APPENDIX 1: Mathematics of currents a) due to ions b) interaction incoming incoming currints and possible ion currents

Phsyicians, neurophysiologistst and biologists still have to get used that including of 'mathematical modelling' electronic engineers and physicists (of university level) is crucial, in order to be to able to find the right equations, apply them correctly, and peform an overall mathematical modelling.

The membrane potential Em is given by the GHK-equation (Goldman Hodgkin Katz):

$$E_m = \frac{RT}{F} \ln \left(\frac{\sum_i^N P_{M_i^+} [M_i^+]_{\text{out}} + \sum_j^M P_{A_j^-} [A_j^-]_{\text{in}}}{\sum_i^N P_{M_i^+} [M_i^+]_{\text{in}} + \sum_j^M P_{A_j^-} [A_j^-]_{\text{out}}} \right)$$

This formula is a further working out of the Hodgkin-Huxley Nobel work of 1956

This is the reasons physians and engineers have to be involved.

E_m = The membrane potential (in volts, equivalent to joules per coulomb)
•P_{ion} = the permeability for that ion (in meters per second)
•$[ion]_{\text{out}}$ = the extracellular concentration of that ion (in moles per cubic meter, to match the other SI units)
•$[ion]_{\text{in}}$ = the intracellular concentration of that ion (in moles per cubic meter)
•R = The ideal gas constant (joules per kelvin per mole)
•T = The temperature in kelvins
•F = Faraday's constant (coulombs per mole)

This is where many textbooks for non-exact studies err. In an attempt simplify, some ions are forgotten, the role of electronics is not explained, and the student remains with a lifelong wrong interpretation.

See how well the formula is made. The A- ion protein, that is supposed not to pass a membrane, is neverthelesss mentioned on the right. This is very important for circumstances where it CAN penetrate, and to think over the role of the electrons around th ion- Aj ion. If the Aj ion can really not permeate the membrane, permeability Paj is set to zero. For the rest, one is reminded to take in accoun all ions and all permeabilities. Many textbooks simplity wrongly by sometimes taking Na+, sometimes Ca+ and not Cl- – etc.

The resting potential of -70 m V inside the neuron as only possible because there is CONTACT between inside of the neuron and the outside – through the voltage gates. So the electrons from the inside could – reasoned on their own – flow to outside the neuron, and thereby, buiding off the voltage to NIL. But: the free electrons IN the neuron, are also attracted by the Potassium K+ ions on the inside of the neuron. And as the K+ ions are 'forbidden' to outflow the membrane (the potassum gates/channels are closed, in steady state rest potential, as are the CL- GABA receptor channels), the electons cannot freely flow out.

However, if a positive current from outside comes, the a) CL- gates open first: this LOWERS the Pcl- in above GHK euqation, and lowers Em (Cl- is flowing IN!). This cushions the current, until a 'threshold' of appr. -50 m V. Other ions, as K+ and A- are too slow to react, if the 'cushioning' of Cl- is worked out, the incoming current simply seeks its way through the VOLTAGE channels to outside the membrane. The rest of the current (that was not sufficiently 'cushioned' by Cl- inflow) reaches a positive peak; the neurons fires. When the current has reached its peak and decreases, 'finally' Potassium ions K+ are pushed from inside the neuron to outside – just because they are K+ and there is too much K+ potential within the neuron. As long as the neuron was in the negative, K+ ions would not be pushed through the membrane!

In the neuron the A- protein ions remain of the exact same quantity, the Cl- ions have increased in quantity, the K+ decreased in quantity and thus further make the voltage of the neuron NEGATIVE again – helped by the fading out of the incoming positive current. The potassium keep on working pushing K+ out even after the neuron has reached its resting potential. That is the reason the voltage of the neuron goes into a little 'hyperpolarisation', for some millicons reaching a more negative voltage than resting potential. But thereafter: potassum stop, and Cl- ion gates close.

The neuron has reached its resting potential again.

From a standpoint of 'cushioning' an incoming positive current:
1) it is good Cl- ions open so fast en let Cl- flow in
2) it is a pity so little Cl- flows in that threshold potential is -50 mV instead of -10 mV (latter would prevent many cases of firing)
3) it is a pity Potassium K= ions only start to be driven out the neuron when potential is positive; but is understandable, positive ions are only excluded when overall voltage is positive, within the neuron.

One can als look at it in another way.

The unit of a electric CURRENT is 'Ampere'. The unit of Em, electic potential, is 'Volts'. To understand the dynamics of an electric current flowing, it is important to realise that Current = I (ampere) = Voltage (V) / Resistance (Ohm). When the current comes in, membrane resistance is lowered by the opening of ion channels (GABA, Cl-) and later by opening of Potassium gates (K+ – but only after the action potential). The current, however, is much faster than conductance over biomass to in a way 'impatient'. As soon as the remaning current has found a voltage gate in the neural membrane, it has found a way to pass the membrane at almost zero resistance. With almost zero resistance, the Voltage in I = V/R 'peaks'.

With chronic insomniacs, much is wrong in the either a) timely opening of Cl- ion channels b) flow of Cl- ions or c) availability or transport of CL- to the ion channels.

In the (already mentioned) book 'The book 'Physiology and Pathology of Chloroide Transporters in the Nervous System' (Academic Press, 2009)' one can read there are many problems with ion chloride transporting and channelling anyway in the body. For insomniacs, the BZD proof to be

more 'fail safe' than a 'nature restore' solution of natural GABA binding. In modern molecular biology, no correlation at all has been found between malfunctioning of chloride, and mental states. The conclusion that still many people have Medieval prejudices regarding chronis insomnia – prejudices that have no base at all in exact neuroscience.

Understanding above model, one could also investigate OTHER sleeping solutions than larger influx of Cl-:

- 'nightly' increase of membrane gates /increase membrane permeability ; however, during daytime the old (higer) premability should restored, so neurons are more excitable again than at night
- larger availability of CL- around the GABA receptors outside the gate
- 'nightly' larger incapacitance of membranes and others cells, so signals to membranes are 'cushioned' by 'condensators'

This version is for peer review – a final version will follow mid October 2013.

Insomnia Clients Foundation seeks contact with research Centers and Pharm industry: all proposals are welcome. We are unsubsidized and have a gigantic large job te perform in updating physicians and clients on the real working of sleep and sleeping pills. Knowledge of the real meachism frees millions of clients of 'being blamed by physicians' or 'doubting about themselves' or 'receiving a far too low dosage of sleeping pills' so they end up with a life full of suffering, not being able to hold a job and dying significanlty more early.