To: TFI, WHO, 20 Avenue Appia, 1211 Geneva 27, Switzerland

Re: Comment on Framework Convention on Tobacco Control

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I am a Director of Neurological Institute, Southern Tohoku General Hospital, Fukushima, Japan. On the occasion of preparing a proposed WHO framework convention on tobacco control, as a neurologist, I would like to propose WHO to consider the beneficial effects of nicotine on the brain, which is a point that is rarely discussed.

Five hundred years have elapsed since the habit of tobacco smoking began. Many people still maintain this habit despite many orders to ban smoking in the past and despite the constant antismoking campaign of the present day. The attraction of tobacco smoking has not been explained and the mechanism of action of tobacco smoking has not yet been revealed.

Everything has good and bad sides and tobacco is no exception. There is no doubt that tobacco smoking is a risk factor of cardiovascular disorder and brain vessel disorder or that tobacco has a carcinogenic action to organs such as the lung. However, the features of nicotine dependence are still being debated among scientists. Nicotine dependence is regarded as being similar to dependence on caffeine. It is very different from dependence on alcohol, psychostimulant drugs or narcotics.

Nicotinic cholinergic receptors (nAChRs) were discovered in the brain two decades ago. The existence of nAChRs inside the cerebral cortex, basal ganglia and the brainstem was revealed using methods such as immunofluorescent histochemistry and positron emission tomography (PET). The features of subtypes of nAChRs in different regions have been widely studied, with more than one thousand papers written on this topic in the last ten years. It is interesting to note that most of the research into physiological mechanisms involves the role of nAChRs in cognitive and memory function in the cerebrum, and that there is much less research into the dependence properties of nicotine.
There is clear evidence that nicotine is effective in the treatment of many ailments afflicting the central nervous system. Great importance is attached to molecular biological research into nAChRs, which is seen as being the first step towards solving the functional role of nicotine in the brain. Nicotine research in this field is now growing. For this reason, banning smoking only on the basis of epidemiological findings means ignoring people who enjoy the benefit of tobacco smoking.

Effect of nicotine on the cerebrum
Psychophysiological research has been performed into effects of nicotine on the cerebrum, from various aspects such as reaction times, attention, information processing, short-term memory and memory retrieval. The effectiveness of nicotine depends to a great extent on personality or mental state of smokers at the time of smoking. It has been shown that nicotine has a tranquilizing effect when a smoker is in a state of excitement and a stimulating effect when vigilance level is low.

It is generally believed that using subjects with mild cognitive impairment is more effective to detect subtle pharmacological action in studying the effects of tobacco smoking. We have administered nicotine patches to subjects with mild cases of Alzheimer’s disease continuously since 1994 and have examined the effects of nicotine on intellectual function.

Since the mechanism of cognitive impairments in Alzheimer’s disease was revealed based on cholinergic theory, Aricept, a choline esterase inhibitor, is now generally prescribed to treat this disease. There are two types of ACh receptor in the brain: the nicotinic receptor and the muscarinic receptor. The theory was formulated from the fact that Alzheimer’s patients have only half the normal quantity of nicotinic receptors in the hippocampus, although the quantity of muscarinic receptors is not greatly reduced. An animal study of the time required to learn how to avoid electric shocks revealed that rats fed a choline-free diet took longer to learn, but that the speed of learning improved after the rats were given nicotine. This study demonstrates that nicotine plays an important role in the intellectual functioning of the cerebrum.

Effect of nicotine on brain waves
Quantitative EEG analysis is generally performed to assess the drug effects on the brain. Some scientists have pointed out that smoking promotes arousal by increasing the alpha-wave component and the beta-wave amplitude and by decreasing the theta-wave component.
It is believed that the latency of P300, which is one of the event-related potentials, indicates cognitive function and that amplitude indicates information processing ability. Since dementia patients show abnormal P300 latency and amplitude, these parameters are used as indices to determine the effectiveness of anti-dementia drugs. Our research shows that the latency of P300 in Alzheimer patients is reduced after the patients were given nicotine patches.

Effect on cognitive function disorder
Some scientists believe that smoking improves test scores of learning, memory and cognition. It is thought that nicotine raises selective attention through synergistic action with the ascending meso-limbic dopaminergic pathway, and raises arousal through the ascending cholinergic pathway. Nicotine’s effect on cognitive function is suppressed by mecamylamine, which is a nAChR antagonist. This fact has been proved not only by tests using animals, but also on humans, and is evidence that nicotine is an effective medication.

Dr. Newhouse et al. proved a positive effect of administering nicotine on cognitive function in humans with Alzheimer’s disease. We also found that the nicotine patch reduces the latency of P300 and that the amplitude of the positive potential P1 in the middle-latency auditory response (MLR), which is believed to reflect the function of cholinergic neurons, tends to increase. Our research showed a significant increase in scores of the Uchida-Kraepelin test, which measures performance. The intellectual functions scale, such as minimental state examination (MMSE), tended to increase, although not significant. These results suggest that nicotine improves intellectual functions such as attention, cognition and learning. Therefore, I believe that research into nicotine’s pharmacological effectiveness on the brain would trigger the development of new drugs to treat degenerative diseases, including Alzheimer’s disease.

In addition to the above, animal and human studies have shown that nicotine has an anxiolytic action which is different from that of benzodiazepine, in that it does not have accompanying amnestic effects.

Effect on Parkinson’s disease
The reduction in the number, or complete disappearance, of nigro-striatal dopaminergic neurons in the substantia nigra of the midbrain is the cause of motor disturbances in patients with Parkinson’s disease. It has also been proved that not
only dopamine, but also the quantity of nAChR is also lower. Immunochemical research has shown that nAChR is distributed throughout the substantia nigra and the ventral tegmentum area and that dopaminergic neurons contain a subunit of the nicotinic receptor. There is a close relationship between nAChR and dopaminergic receptors.

We have proved by quantitative analysis that nicotine patches improve akinesia in Parkinson’s disease, when used as a supplementary drug in levedopa therapy. The effectiveness of nicotine in treating Toulette’s syndrome has also been proven.

Other effects
Recent research has shown that nicotine not only assists neuro-transmission by stipulating cholinergic neuron synapse receptors, but that nicotine also has a neuroprotective action. There is a report that nicotine suppresses production of beta-amyloid which is considered to be the cause of Alzheimer’s disease. It has also been revealed lately that one of the constituents of tobacco smoke is an MAO-B inhibitor which is involved in the production of superoxidants which are a major factor causing degenerative disease. A MAO-B inhibitor is already included in drugs used for the treatment of Parkinson’s disease. This coincides with the view that tobacco smoking is effective in the treatment of juvenile Parkinsonism.

It had been proved that nicotine affects dopaminergic neurons through cholinergic neurons in the brain and that it also promotes the release of various neurotransmitters such as catecholamine and serotonin. I believe that these facts prove that nicotine has a beneficial effect on the central nervous system in both physiological and pathological conditions. Nicotine improves learning, intellectual capacity, memory, actions, arousal level and motor function and it will be also effective in the treatment of Alzheimer and Parkinson’s disease.

Concluding remarks
The beneficial effects of nicotine on the central nervous system have been neglected, and overshadowed by the disadvantages of smoking.

There is unequivocal evidence of beneficial therapeutic effects of nicotine in a number of central nervous system disease states. With a thorough understanding of the pharmacological and functional characteristics of nAChR, some pharmaceutical companies are now trying to develop less toxic and more efficacious nAChR ligands, which may provide potential beneficial therapeutic agents for a variety of neurodegenerative diseases.
Recently, WHO issued new healthy life expectancy rankings where Japan is number one in the new ‘healthy life’ system. On the other hand, the smoking rate of Japanese male adults is the highest among developed countries. We must deeply consider the significance of this fact before accelerating smoking control.

For these reasons, I urge that discussions about the relationship between smoking and health should include not only the toxicity of nicotine on cancers and blood vessel disorders, but also the beneficial effects of nicotine on the brain.