

depolarizations, decreased  $K^+$  conductance and enhancement of excitatory signals such as Glutamate [12]. Serotonin plays a dual (may be synergistic effect) role in increasing susceptibility to seizures. Firstly through 5-HT<sub>2A</sub> receptors (as mentioned above) and secondly through its effects on sleep; on the one hand, it promotes NREM sleep (NREM increases susceptibility to seizures), while on the other hand it exerts inhibitory role in actual REM initiation and PGO wave generation, the latter two supposed to be potent anti-epileptic.

Thus, the evidences put forward do support the possibility of risk of epileptogenesis during meditation as hypothesized in my article at the same time refuting the objections and controversies raised in above comment-letters.

Finally, funded by the Indian government, a ten-year study by Desiraju [13] could yield no beneficial positive effects of meditation as claimed by its proponents. Lazarus [14] and Otis [15] have also on the contrary reported adverse outcomes and effects of meditation.

## References

- [1] Anand BK, Chhina GS, Singh B. Some aspect of electroencephalographic studies in yogis. *Electroen Clin Neurophysiol* 1961;13:452–6.
- [2] Banquet JP. Spectral analysis of EEG in meditation. *Electroen Clin Neurophysiol* 1973;35:143–51.
- [3] Khare KC, Nigam SK. A study of electroencephalogram in meditators. *Indian J Physiol Pharmacol* 2000;44(2): 173–8.
- [4] Pagano RR, Milrose R, Stivers RM, Warrenburg S. *Science* 1976;191:308.
- [5] Herman ST, Walczak TS, Bazil CW. Distribution of partial seizures during the sleep-wake cycle: Differences by seizure onset site. *Neurology* 2001;56:1453–9.
- [6] Gastaut H, Tassinari CA, editors. *Handbook of Electroencephalography and Clinical Neurophysiology*, part A, vol. 13. Amsterdam: Elsevier Scientific Publishing Company; 1975. p. 31–8.
- [7] Shouse MN, Staba R, Farber PR. Physiological basis: how NREM sleep components can promote and REM sleep components can suppress seizure discharge propagation. *Clin Neurophysiol* 2000;111(Suppl. 2):S9–S18.
- [8] Murphy M, Donovan S. *The Physical and Psychological Effects of Meditation*. Big Sur, CA: Esalen Institute; 1989.
- [9] Pacia SV, Ebersole JS. Intracranial substrates of scalp ictal patterns from temporal lobe foci. *Epilepsia* 1997;38(6): 642–54.
- [10] Gastaut H, Tassinari CA, editors. *Handbook of Electroencephalography and clinical neurophysiology*, part A, vol. 13. Amsterdam: Elsevier Scientific Publishing Company; 1975. p. 12.
- [11] Persinger MA. Transcendental meditation (TM) and general meditation are associated with enhanced complex partial epileptic like signs: evidence for "cognitive" kindling? *Percept Motor Skill* 1993;76:80–2.
- [12] Sanders-Bush Elaine, Mayer Steven E. Goodman and Gilman's *The pharmacological basis of therapeutics*. 10th ed. International Ed.; 2001. p. 276.
- [13] Desiraju T. The Yoga and Consciousness Project. National Institute of Mental Health and Neuroscience. Bangalore, India: Omni Magazine; 1990. pp. 84–8.
- [14] Lazarus AA. Psychiatric problems precipitated by transcendental meditation. *Psychol Rep* 1976;39:601–2.
- [15] Otis LS. Adverse effects of transcendental meditation. In: Shapiro D, Walsh R, editors. *Meditation: Classic and contemporaneous perspectives*. New York: Alden; 1984.

Harinder Jaseja\*  
*Physiology Department,  
 G.R. Medical College,  
 Gwalior 474001 MP,  
 India*  
 E-mail address: dr\_jaseja@yahoo.com

\* Address: "8, 10" C-Block, Near Paliwal Health Club, Harishanker-puram, Lashkar, Gwalior 474009, MP, India. Tel.: +91 751 2631147.

doi:10.1016/j.mehy.2005.12.012

## Salmeterol and paroxetine: More evidence for paradoxical medicine

Lurie and Wolfe of Public Citizen recently suggested in the *Lancet* that Glaxo SmithKline (GSK) bundled post-trial data with trial data that effectively downplayed the risk of death with use of salmeterol [1]. Similar claims were recently levied against GSK only last year with respect to studies of paroxetine in children and adolescents in which data on suicide was not initially fully disclosed [2,3]. While these

discussions have focused on incomplete disclosure, we remain intrigued by the possibility that chronic use of these drugs can produce an exacerbation of the underlying condition. In the case of paroxetine, the phenomenon of serotonin withdrawal syndrome has become increasingly recognized, and, as such may have contributed to an increased risk of morbidity and mortality. In the case of salmeterol, although

the beta-agonist may have directly produced some of the witnessed sequelae, this putative risk may actually be less than what has been traditionally presumed [4]. However, an additional explanation may merit consideration—the idea that paradoxical effects caused from interval withdrawal between times of administration may have caused autonomic remodeling and patient deaths. If so, beta-agonists may potentially represent the fourth class of drugs to show paradoxical responses that did not emerge initially with shorter term trials and that only became revealed with chronic use. Each of these drug categories has an entirely independent mechanism of action—we have previously discussed cyclooxygenase-2 inhibitors [5] and more recently the PPAR agonist muraglitazar [6]. Given such a consistent pattern of behavior for different types of medications, we believe that this phenomenon warrants a more fundamental explanation—namely that we are witnessing paradoxical medicine in action [7], but as a detriment rather than as a benefit.

## References

- [1] Lurie P, Wolfe SM. Misleading data analyses in salmeterol (SMART) study. *Lancet* 2005;366(9493):1261–2. discussion 1262.
- [2] Is GSK guilty of fraud? *Lancet* 2004;363(9425):1919.
- [3] Hay A. Questions about SSRI antidepressant drug regulation. *Lancet* 2004;364(9434):577.
- [4] Murray JJ. Cardiovascular risks associated with beta-agonist therapy. *Chest* 2005;127(6):2283–5.
- [5] Doux JD, Bazar KA, Lee PY, Yun AJ. Can chronic use of anti-inflammatory agents paradoxically promote chronic inflammation through compensatory host response. *Med Hypotheses* 2005;65(2):389–91.
- [6] Yun AJ, Lee PY, Doux JD. Paradoxical inflammation revisited: muraglitazar and cardiovascular risk. *Med Hypotheses* 2006;66(4):855.
- [7] Yun AJ, Lee PY, Bazar KA. Paradoxical strategy for treating chronic diseases where the therapeutic effect is derived from compensatory response rather than drug effect. *Med Hypotheses* 2005;64(5):1050–9.

Anthony J. Yun  
Patrick Y. Lee

Radiology, Stanford University  
470 University Avenue  
Palo Alto, CA 94301  
United States

Tel.: +1 650 387 6667;

fax: +1 650 325 5028. (A.J. Yun)

E-mail address: ayun@stanford.edu (A.J. Yun)

John D. Doux  
Palo Alto Institute  
Palo Alto, CA 94301  
United States

doi:10.1016/j.mehy.2005.11.006

# Tumor-causing plant bacteria may infect animals

*Agrobacterium tumefaciens* is a well known phytopathogen; it is a soil bacterium that causes plant's tumors disease called Crown Galls [1]. The microbe contains a DNA plasmid called DNA Ti (tumor inducing) [7]. The bacterium is introduced in a wounded plant and the plasmid is then integrated in to the cell plant genome and overproduces growth regulators (auxins and cytokines) that can initiate the Crown Gall [6] disease. The growth regulators are also present in mammal's metabolism. Discovered by Erwin Smith (1854–1927) [2–5], we know now that the soil bacterium may jump Kingdoms [8]. In 2001, Vitaly Citovsky from the State University of New York and colleagues found that the plant bacterium was able to attach human cells in vitro and insert its DNA as it does with plant cells [9]. Recently, the soil microbe has been isolated from blood samples of cancer patients [10–12]. We are studying the

potential infectivity and oncogenetic flow between *Agrobacterium* and animals in vivo [13].

After 120 days of wild *Agrobacterium* injection on wounded *Chrisantemum maximum*, galls are evident and pathologically confirmed. Then, we treated 40 SWISS mice, 8 mice each group, with *A. tumefaciens* cultured: Orally, SC and intraperitoneal injections weekly shaved skin and topicated with crown galls bacteria and only shaved as control. After 11 weeks, skin lesions and regionally nodes are evident in 6–8 mice in shaved and topicated group. At optical microscope, H–E  $\times$  450, lymphoid hyperplasia, neoangiogenesis and neofibrinogenesis are confirmed. After 18 weeks, multiple tumors and distant metastasis are seen, due to hyperplasia and mesenchymal metaplasia.

Our observations confirmed in vivo the pathogenicity of *A. tumefaciens* on mammals and we think