Physiology & Behavior xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Physiology & Behavior

journal homepage: www.elsevier.com/locate/phb

Review

Randall Sakai, chronic social stress, and the research tradition of Curt Richter

Gerard P. Smith [a,*], Gary J. Schwartz [b,c]

[a] Department of Psychiatry, Weill Cornell Medical College, New York, NY, United States
[b] Department of Medicine, Albert Einstein College of Medicine, Bronx, NY, United States
[c] Department of Neuroscience, Albert Einstein College of Medicine, Bronx, NY, United States

ARTICLE INFO

Article history:
Received 27 January 2017
Accepted 23 February 2017
Available online xxxx

Keywords:
Chronic social stress
Subordinate stress
Fat distribution
Metabolic stress
Curt Richter
Research tradition
Mentoring

ABSTRACT

This paper describes Randall Sakai's professional career from graduate school at the University of Pennsylvania, through postdoctoral work at Rockefeller University, and to being an independent investigator at the University of Cincinnati. He was fortunate in having Alan Epstein, Bruce McEwen, and Eliot Stellar as mentors. Early in Sakai's graduate work, Epstein and Stellar introduced him to Curt Richter, the legendary investigator at Johns Hopkins. This early introduction to Richter and his tradition of research was crucial for Sakai's scientific development. We review Sakai's research with the Visible Burrowing System (VBS) at Cincinnati. This was the most original of Sakai's research interests. His experimental proficiency in the investigation of salt appetite, food intake, and obesity led him to focus on the effect of chronic social stress on food intake, body composition, metabolism, and the distribution of fat. He and his colleagues, many of them his students, were able to demonstrate that chronic social stress produced changes in metabolism and fat distribution that were characteristic of an incipient metabolic syndrome that could lead to obesity. This did not solve the problem, but showed the way to further investigation. This opening up of problems to experimental investigation was a hallmark of Richter's research. Thus, Sakai worked in the mainstream of the research tradition of Richter. He did what he revered.

Contents

During his undergraduate experience at the University of Washington, Randall Sakai developed a strong interest in the relationships between brain and behavior. His first mentor was John Simpson, a young faculty member of the Psychology department and already a leader in the investigation of the site and function of angiotensin in the central control of salt and water intake. Simpson encouraged Sakai to do graduate work with Alan Epstein in the Department of Biology at the University of Pennsylvania. This advice reflected Simpson's productive postdoctoral experience there. It was good advice and Sakai took it.

What did Sakai find on arrival in Epstein's laboratory? A laboratory consisting of a couple of experimental rooms and Epstein's office. The most important component of the laboratory was Epstein himself. He had an international reputation for research on the controls of food intake and sodium appetite. He was also known for superb mentoring of

* Corresponding author.
E-mail address: gpsmith@med.cornell.edu (G.P. Smith).

http://dx.doi.org/10.1016/j.physbeh.2017.02.033
0031-9384/

graduate and postgraduate students. His mentoring extended from attention to experimental details to the style of oral presentations and written publications. Epstein had high standards for being a scientist and he enforced them. A master of the encouraging critique, Epstein insisted that science was about designing penetrating experiments and interpreting the results critically and heuristically. This program of experimental thinking suited Sakai perfectly.

Epstein did more than shape Sakai scientifically. Sensing the potential loneliness of a young man removed from family and friends and too poor to go back to Hawaii often, Epstein opened his home to Sakai, and made him family. Epstein also introduced him to many of his friends at the University, and took him out for dinners and baseball games. Sakai was very grateful–he often referred to Epstein as his second father.

Early in his graduate work, Sakai learned about the research tradition of Curt Richter through visits to Richter's laboratory at Johns Hopkins. These visits were arranged by Epstein and his mentor, Eliot Stellar.

Sakai noted all of this in the Acknowledgments of his thesis: "It has been a wonderful experience to learn from and to work under the supervision of Dr. Alan N. Epstein. His support and encouragement as a mentor and colleague over the course of my training has been invaluable. His friendship and enthusiasm for science will never be forgotten as he has made my tenure at the University of Pennsylvania a most memorable and enjoyable experience. Thank you Alan… Special recognition must go to Dr. Eliot Stellar whose colleagueship, advice and ever present enthusiasm and concern for my work has been invaluable".

On April 6, 1988, Sakai presented his thesis entitled "The Hormonal Basis of Salt Appetite in the Rat." Shortly afterward he was on his way to New York to Bruce McEwen's laboratory at Rockefeller University.

McEwen knew Sakai well. He had been a member of the Examining Committee for Sakai's preliminary examination on June 18, 1985 and, as Stellar noted in his letter to the Biology Graduate Group, "We are particularly pleased that he (Sakai) will be strengthening and extending his experience in cell and molecular biology in the laboratory of Bruce McEwen at Rockefeller".

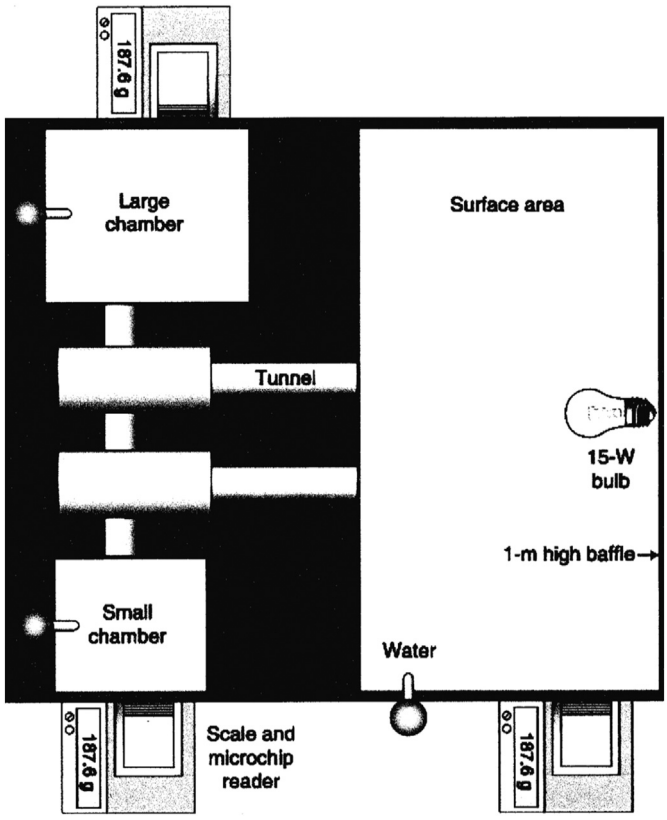

Fig. 1. This is a diagram of a Visual Burrowing System that has been revised by Sakai to measure food intake and meal patterns of individual rats (see scale and monitors; from [9], p. 537).

1. Sakai and Blanchard

When Sakai arrived in McEwen's laboratory in 1988, chronic stress was being modeled by repetitive restraint tests. On one of his trips back to Honolulu, Sakai visited Robert and Caroline Blanchard's laboratory at the University of Hawaii and saw the Visual Burrow System (VBS) they had developed. The VBS was a system of connected plastic burrows with roofs that permitted visualization and videotaping of the rats living in the burrows (Fig. 1). Some of the burrows in the VBS were connected to a large open space where food and water were available (see McEwen in this issue for details).

If a group of male and female rats, usually 3–4 males and 2–3 females, were put into the VBS, the male rats formed a social hierarchy spontaneously within 2–7 days. The hierarchy consisted of one dominant male rat, and subordinate male and female rats. This formation of a social hierarchy mimics the behavior of wild rats living in dirt burrows.

Dominance is achieved and maintained by aggressive behaviors, such as wounding and biting. Subordinate male rats display defensive behaviors very similar to the defenses elicited by predatory exposure. They also have reduced longevity due to unexplained sudden deaths that are not caused by attacks of the dominant male [1].

Male rats do not form a social hierarchy in the laboratory if female rats are not present. Female rats never form a hierarchy. Thus, formation of a dominance hierarchy appears to be an innate, unlearned action by male rats in the presence of female rats in the VBS. The possible contribution of learning to dominance hierarchy formation, particularly in repetitive VBS tests, has not been investigated.

The experimental advantages of the VBS test are: (1) it has biological validity because it produced an environment in the laboratory that was sufficient for the formation of a dominance hierarchy, and (2) it has experimental usefulness because the formation of a dominance hierarchy did not habituate within a test or across two tests separated by three weeks of recovery in individual home cages.

The correlates of male subordination in the VSB were interpreted as isomorphic with behavioral symptoms of human depression and this suggested male subordination in the VSB as a new animal model of depression. "If this model proves to be useful it will enjoy the considerable benefit of a ready-made relationship to an extensively characterized set of neurobehavioral systems, those involved in defensive behavior" ([2], p. 461). McEwen agreed with Sakai about the advantages of the VBS as a test of chronic social stress. Thus, Sakai and McEwen began to collaborate with the Blanchards.

On 9 January 1992, tragedy struck—Alan Epstein was killed in an automobile accident in Mexico. Sakai, like many of Epstein's friends, was shattered. Many of us thought that Sakai never recovered from this loss of his "second father".

Despite his personal loss, Sakai agreed with Stellar and McEwen to return to Penn to maintain Epstein's research, personnel, and funding. He did this very difficult task extremely well for seven years and managed to pursue the VBS research with McEwen at Rockefeller simultaneously.

The first review of the collaborative work with the VBS by the Blanchards, Sakai, and McEwen was published in 1993 [3]. It focused on the video recorded behavioral correlates of subordinate male rats in the VBS. These included increased movement inhibition, reduced social and sexual behavior, decreased number of episodes of eating and drinking, a general inhibition of ongoing, nondefensive activities, a profound slowing down of activities from initiation to completion, impaired risk assessment, significant loss of body weight, and earlier deaths than normal. This subordinate male syndrome was maintained in the VBS by the social relationship of subordination to the dominant male, not by frequent aggressive fighting, because the time spent in

Please cite this article as: G.P. Smith, G.J. Schwartz, Randall Sakai, chronic social stress, and the research tradition of Curt Richter, Physiol Behav (2017), http://dx.doi.org/10.1016/j.physbeh.2017.02.033