Biographies
August 20, 2015

Events and Memories

6. Indole alkaloids

Samuel Gershon

Yohimbine, Harmine and Ibogaine

Yohimbine

While still in Australia, before going to the University of Michigan, we started to study this group of compounds. They drew our attention from reports claiming they produced psychological, especially hallucinogenic, effects in humans. We also thought, after our studies with Ditran, that we might be able to find other models of such states. So we began to evaluate YOHIMBINE (YOH) in animal preparations including anesthetized rats, guinea pigs and dogs to establish pharmacological baselines. In all these animal preparations, YOH produced a fall in blood pressure as reported in the literature. We also injected the same dose intramuscularly to conscious dogs. The effect was arousal, increased activity and some distress with increased panting. We also heard the heart pounding strongly. These simple superficial observations did not seem to make sense. So we decided to plan studies in conscious beagle dogs to observe behavior and physiological effects. We were fortunate that a group in the physiology department at the Florey Institute were working intensively with sheep. They had a technician, an immigrant physician, Ben, from Poland, who developed a preparation with an exteriorized carotid artery under a cover of skin to keep the animal viable after it had catheters inserted into the carotid artery. Ben also developed an exteriorized opening for the salivary gland and was assigned to help us get set up. This assistance and advice was given free with support from the Chairman. Ben became a friend to our group, ready to help at any time. I don't believe this sort of support, given to junior people, would be readily available today.
We could measure blood pressure from the carotid artery and inject the dose of YOH intravenously. The dog was either suspended in a leather harness with feet off the ground

or free for behavioral observations in a large open mesh cage. In the conscious dog, intravenous YOH produced elevation of blood pressure with heart rate; blood pressure did not go down as usual in anesthetized animal preparations. Accompanying this finding was behavioral activation which became a central part of our interest in YOH.

At the lowest dose, we saw restless behavior, rise in blood pressure and increase in salivation. As the dose was increased, cardio-vascular and behavioral responses increased from restlessness to general bodily movements in the cage into what we considered to be anxiety and panic.

While I was at the NIMH funded unit at the University of Michigan, I worked under the supervision of Professor RW Gerard. I studied YOH effects in man and published extensive and detailed observations (Holmberg and Gershon, 1961). The major finding was that the experiments presented us with a drug induced model of ‘anxiety’. Now that our subjects could talk we documented all the behavioral and psychological features obtained by observation, physical recording and interrogation. With increased dosing, symptoms reached a ‘panic’ state.

My colleague in these human experiments was Gunnar Holmberg from Sweden, a psychiatrist and physiologist. We became friends and maintained a relationship long after we returned to our home countries. These physiological, behavioral and psychological studies established early bench marks for developing drug induced models for psychological disorders.

The next question was to establish the etiology of the effects of YOH in animals and man. Patients with a baseline of clinical anxiety were sensitive to the YOH injection and developed high levels of anxiety with a smaller dose. Without detailing the effects at this time, by chance, we also came up with an observation that suggested a possible screen for antidepressant agents.

LATER DEVELOPMENTS

The key finding of the effect of YOH in producing a physiological and behavioral model of anxiety in humans was followed up intensively by the Yale group. Some years later, at NYU, I learned from Don Kline of the effects of intravenous lactate infusion as another agent for inducing anxiety in man. Don’s work attracted considerable attention but, unfortunately, neither of us did any direct comparison of the two models. More recently, neuroscientists have

reported the presence of a gene and its relationship to basal high and low levels of anxiety. Other compounds have a reverse effect to YOH; Anandamide has an anti-anxiety effect and low levels are present when the patient has high anxiety. It has also been postulated that cannabinoids have an anti-anxiety effect, as do benzodiazepines. In the light of these findings and lack of a synthesis, we suggested possible modes of action for YOH (Holmberg, Gershon and Beck, 1962,a). Later the Yale group reported that with varying basal levels of clinical anxiety, the dose of YOH could be graded, low basal levels of anxiety required larger doses of YOH.

To proceed with investigations of YOH and its interaction with other psychoactive drugs, our first test compound was imipramine (Gershon, Holmberg, Mattson E, Mattson N and Marshall, 1962). With this extensive collection of data in man we went back to more detailed studies in the conscious dog. These studies showed that the physiological and psychological effects of YOH were increased by the tricyclic antidepressants, the early SSRI's and 5 HTP (Lang and Gershon, 1963, a).

We also conducted similar experiments with anti-anxiety agents and proposed a screening method for them (Lang and Gershon, 1963, b)

With these and other experiments, we concluded that part of the effects of YOH was mediated by serotonin, confirmed later in our synthesis inhibitor studies at NYU. Looking at all our data, we found all antidepressants we administered with YOH produced a picture of increased arousal and anxiety up to the occurrence of panic state with increased autonomic effects. We then did the opposite set of experiments with antianxiety agents such as Librium and Valium. In all of these trials, the compounds modulated and reduced the behavioural and physiological effects to baseline. We had now accumulated enough evidence to claim we had a model of anxiety and panic states in humans and dogs, confirmed by the actions of antidepressants and antianxiety drugs, consistent with the clinical effects in patients.

Harmine and Ibogaine

Our work in Australia and America also included two other indole alkaloids, harmine and ibogaine. Harmine was first reported to reverse catatonia in the 1920's and ibogaine was used as

a hallucinogen for therapeutic purposes by Shamans in South America to treat addictions and other problems.

My work on these compounds was collaborative in both countries. In Australia, I became Acting Chairman of Pharmacology and initiated a one year fellowship as an elective for talented third year medical students. Four fellows worked with me on the indoles and all later had significant academic careers. Included were Barney Carroll, who became Chair of Psychiatry at Duke University in America and Ian Gust, who became Director of the Virology Institute at the University of Melbourne.

I also collaborated with Bill Lang, first as a post-doc in Melbourne, and then as a visiting fellow at the Missouri Institute of Psychiatry. Shortly after he returned to Australia, he died of a blood cancer and I lost a friend and collaborator.

Our results with these other alkaloids, sometimes separately and sometimes with YOH, are referenced below. Both harmine and ibogaine produced similar effects to YOH with strong alerting and arousal effects against a large variety of compounds and depressed clinical states. Harmine has been reported by others to also have selegiline like effects inhibiting both forms of MAOI.

References:

Bell C, Gershon S, Carroll B, Hogan G. The analeptic activity and EEG effects of some indole alkaloids. Psychiat Neurol 1963; 146, 276-85

Bell C, Gershon S, Carroll B, Hogan G. Behavioral antagonists to a new psychotomimetic- JB 329. Arch Int Pharmacodyn 1964; 147: 3-25..

Garfield S, Sletten I, Sundland D,.Ballou SR, Gershon S.. Chemically induced anxiety. Int J Neuropsychiat. 1967; 5: 426-33.

Gershon S. Yohimbine analogues exhibiting differential pharmacological responses., Med. Pharmacol Exp 1966; 15(1): 24-34.

Gershon S, Bell C. A study of the antagonism of some Indole alkaloids to the behavioural effects of Ditran. Med Exp 1963; 8: 15-27.

Gershon S, Holmberg G, Mattson E, Mattson N, Marshall A. Imipramine Hydrochloride; its effects on clinical, autonomic and physiological functions. Arch Gen Psychiat 1962; 6: 96-101.

Ho A, Hoffman DB, Gershon S, Loh HH. Distribution and metabolism of tritiated Yohimbine in mice. Int Pharmacodyn Ther 1971; 194(2): 304-15.

Holmberg G, Gershon S., Autonomic and psychic effects of Yohimbine Hydrochloride. Psychopharmacology 1961; 2, 93-106.

Holmberg G, Gershon S, Beck L. Yohimbine as an autonomic test drug. Nature 1962; 193:1313-4.

Lambert GA, Lang WJ, Friedman E, Mellor E, Gershon S. Pharmacologic and biochemical properties of isomeric yohimbine alkaloids. Europe. J Pharmacol 1978; 49, 39-48..

Lang WJ, Gershon S. Effects of psychoactive drugs on yohimbine induced responses in conscious dogs; a study of antidepressant drugs. Med Exp 1963a; 7: 224-31..

Lang WJ, Gershon S, Effects of psychoactive drugs on yohimbine responses in conscious dogs. A proposed screening procedure for anti-anxiety agents. Arch Int Pharmacodyn 1963b; 142: 457-72.

Lang W Gershon S, Hogan G. Some antagonists of atropine-like psychotomimetics. J Pharm Pharmacol 1963; 15: 831-40.

Sanghyi I, Gershon S. Similarities between the behavioural and pharmacological actions of yohimbineand **5**-hydroxytryptophan in the conscious dog. Europ J Pharmacol 1970; 11: 125-9.

Samuel Gershon

August 20, 2015.

.