Traditional Chinese Medicine and Western Psychopharmacology: Building Bridges

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Abstract

This paper demonstrates that in the treatment of psychiatric disorders, there are striking similarities between the mechanisms of psychoactive agents used in Traditional Chinese Medicine (TCM) and those of western psychopharmacology. While western researchers search for new treatments and novel mechanisms of action, investigators in Asia are analyzing traditional remedies in order to understand the mechanisms responsible for their effectiveness. A review of contemporary pharmacologic studies of agents used in TCM for psychiatric indications reveals that virtually all of the active principles of drug action established in 20th century psychopharmacology were encountered empirically in Chinese herbal medicine over the past 2000 years. Building bridges between these two traditions may thus be of benefit to both cultures. In addition to providing western patients with a wider selection of treatment options, the effort may help Asian clinicians and researchers avoid some of the errors that have troubled their western counterparts.

Keywords

Traditional Chinese Medicine; psychiatry; psychopharmacology; psychiatric disorders; pharmacological mechanisms; neurotransmitters

INTRODUCTION

In Asia's encounter with western-style medicine, there is often an uneasy rapport between western and traditional therapies. Yet, in some medical disciplines, the two schools may have more in common than it initially appears.

This paper demonstrates that in the treatment of psychiatric disorders, there are striking similarities between the mechanisms of psychoactive agents used in Traditional Chinese Medicine (TCM) and those of western psychopharmacology.

In the West, clinicians and psychopharmacologists are now in search of new therapeutic agents and novel mechanisms of action. At the same time, a growing number of Asian

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Conflict of Interest

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investigators are subjecting traditional remedies to pharmacologic analysis in order to establish the mechanisms responsible for their effectiveness.

Both schools may learn from each other. This paper demonstrates that virtually all of the important principles of drug action established in western psychopharmacology in the 20th century were discovered empirically in TCM in a 2000-year-old process of evolution. Despite cultural differences in diagnostic indications, such as ‘major depression’ vs disturbances of ‘qi,’ or ‘Dian Kuang’ (dullness and mania), whose symptoms ‘closely resemble those of bipolar disorder,’ yet may also ‘correspond to some cases of schizophrenia’ (Maciocia, 2009), the underlying drug mechanisms used in treating psychiatric disorders are essentially the same.

The following review examines current pharmacological investigations of individual herbs as well as herbal decoctions in terms of their apparent neurotransmitter profiles and other mechanisms of action. It must be emphasized that the mechanisms cited here include only those that have been studied and do not represent a complete list of the neurochemical mechanisms involved in a given herbal compound.

EPHEDRINE: A CHINESE HERB AT THE DAWN OF WESTERN PSYCHOPHARMACOLOGY

In 1887, Lazar Edeleano in Berlin synthesized the first phenyl-ethyl-amine compound (PEA), marking the discovery of the stimulant medications (Edeleano, 1887). The same year, Nagayoshi Nagai in Tokyo isolated the pure form of the alkaloid ephedrine (adrenaline) from the ephedra plant, an important constituent in TCM. Ephedrine, of course, also has a PEA structure (Miura, 1887). Yet the importance of Nagai’s discovery was not immediately perceived in the West, and, in 1923, Ku Kuei Chen, a Chinese scholar trained at the University of Wisconsin who had returned to lecture at Peking Union Medical College, and Carl Schmidt, an American pharmacologist visiting Peking Union, jointly established that ephedrine’s effects were similar to those of the hormone epinephrine. The Eli Lilly Company marketed ephedrine in 1926 for nasal congestion and bronchial spasm. (Chen and Schmidt, 1926). Chinese herbal medicine had thus borne its first commercial fruit in Western pharmacology.

Meanwhile, in 1910 George Barger and Henry Dale at the Wellcome Physiological Research Laboratories in London had described epinephrine pharmacologically as a ‘sympathomimetic amine’ (Barger and Dale, 1910). Their findings marked the beginning of the scientific understanding of the sympathetic nervous system, its receptors, and, ultimately of western psychoactive drugs. (The amphetamines are descended in a direct line from ephedrine). It is interesting that this breakthrough was accomplished with the aid of a Chinese medicinal herb.

Thereafter, western psychopharmacology diverged radically from TCM. Yet interesting parallels remained. Let us compare some important western psychotropics with Chinese herbal products for which pharmacological mechanisms are being identified.

ANXIETY DISORDERS AND GABA

Historically, the first important class of synthetic psychopharmaceuticals was the barbiturate sedatives, introduced at the start of the 20th century (Fischer and von Mering, 1903). The psychiatric treatment of anxiety began with agents such as Veronal (barbital) and Luminal (phenobarbital). In the central nervous system, barbiturates act on GABA-A receptors (Saunders and Ho, 1990). It is of interest that in TCM, several herbs have a selective effect on the GABA-ergic system. One of the active principles in the decoction Yueju-Wan, a combination of five herbal drugs, is ligustilide, a component that affects GABA-A neurotransmission (Wei *et al.*, 2008). The popular herb Ginkgo biloba (gink go, ya chio) increases GABA levels in the mouse hippocampus as well as the activity of glutamic acid decarboxylase, the rate-limiting enzyme of GABA synthesis (Sasaki *et al.*, 1999). Ginkgo has served for a thousand years in TCM, the barbiturates in western psychopharmacology for a hundred. Yet both seem to share a mechanism.

Some herbal agents, such as the EGb 761 fraction of Ginkgo biloba (Ahlemeyer and Krieglstein, 2003), have such a wide ranging effect upon the biogenic amines that the following analysis of individual neurotransmitters will not list all actions in their entirety.

During the 1960s, the barbiturates were largely supplanted by the benzodiazepines (BZD), which entered psychiatric history in 1955 when Hoffmann La Roche chemist Leo Sternbach synthesized chlordiazepoxide, launched five years later under the trade name Librium (Sternbach, 1978). The world-beating agent Valium (diazepam) followed in 1963. The BZD were an extraordinarily successful drug class, though they somewhat unfairly acquired a reputation as highly addictive. Yet at least one ‘benzo’ has always existed, an herbal compound active at the BZD receptor: the herb Salvia miltiorrhiza Bunge (dan shen). Its diterpene quinone miltirone is said to be a ‘partial agonist’ at the BZD receptor to enhance the inhibitory effect of GABA. In Chinese traditional medicine it is considered a treatment for neurasthenia (Lee *et al.*, 1991).

MOOD DISORDERS

Monoamine oxidase inhibitors

With the exception of lithium (1949), the first important modern drug class in the treatment of mood disorders was the inhibitors of monoamine oxidase (MAO). The Hoffmann La Roche company launched iproniazid (Marsilid) in 1951 for the treatment of tuberculosis. After Swiss chemist E. Albert Zeller discovered that iproniazid inhibited the enzyme MAO, trials for the drug in psychiatric illness began in 1953 (Shorter, 2009). It is fascinating to discover that by this time several remedies for mood disorders involving MAO inhibition had been used in TCM for two millenia. On the basis of such standard pharmacological tests as forced swim and tail suspension, berberine, an alkaloid found in a number of traditional Chinese remedies, inhibits MAO (Kulkarni and Dhir, 2010a). Several investigators have reported that extracts of Curcuma longa (yu jih, turmeric in English), from which curcumin is extracted, inhibit MAO in one or both of its two forms (Yu *et al.*, 2002; Bhutani *et al.*, 2009).

Tricyclic antidepressants

Imipramine, the first of the tricyclic antidepressants (TCAs), was introduced in 1957 (Kuhn, 1957), and in the United States two years later, for the treatment of what was then described as ‘vital depression,’ and what some authorities considered ‘endogenous depression.’ Under either name, this was a serious condition, including much melancholic illness, and the TCAs represented a major improvement over the addictive opiates in its treatment. It was believed initially that imipramine acted mainly to inhibit the reuptake of norepinephrine, but in fact, among several actions, it also inhibits serotonin reuptake (Barker and Blakely, 1995).

A number of agents in TCM have likewise been found to inhibit the reuptake of norepinephrine (see Table 1).

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

Inhibiting the reuptake of serotonin became a popular approach to psychopharmacology in the late 1980s and gave this biogenic amine center stage in neurotransmitter research. The story of blocking the reuptake of serotonin to combat depression began in 1969 with Swedish pharmacologist (and later Nobel Laureate) Arvid Carlsson’s discovery that the secondary amines better inhibited serotonin reuptake, while tertiary amines such as the TCAs, were superior in inhibiting the reuptake of norepinephrine (Carlsson *et al.*, 1969). Meanwhile, in TCM, it turns out that for the previous 2000 years a large number of compounds had effects on the serotonin system. A number of these are listed in Table 2.

PSYCHOTIC DISORDERS AND DOPAMINE

The study of dopamine entered western psychiatry in a serious way in 1976, when, in separate studies, teams led by Solomon Snyder at Johns Hopkins University, and Philip Seeman at the University of Toronto, discovered that antipsychotic medications owed their efficacy to blocking the D₂ receptor (Creese *et al.*, 1976, Seeman *et al.*, 1976). TCM made the same discovery empirically 2000 years previously. Table 3 shows the preparations in TCM that affect the dopamine system. (Given that the activation of dopamine usually entails other neurotransmitters as well, the list probably overemphasizes the effect of dopamine as such).

ENDOCRINE APPROACHES

Treating psychological illness through the endocrine system is one of the oldest treatments in modern psychiatry and goes back to the era of grinding up the endocrine organs of animals and marketing the product as a dried powder capable of various kinds of ‘stimulation’. Endocrine-based diagnoses have also proven important in modern psychiatry as serum cortisol levels and a positive response to the dexamethasone suppression test (DST) in the study of melancholic depression are among the few biological markers we possess. A positive DST test (dexamethasone nonsuppression) reliably confirms the diagnosis of melancholia, ‘much as the EEG verifies a seizure disorder, or the ECG a cardiac event.’ Yet following a brief surge of research and clinical interest in the 1970s, the test was virtually abandoned with the reclassification of a variety of mood disorders into the disease category

of ‘major depression’ in 1980. Its disappearance has had tragic consequences in that the DST reliably predicts suicide in severe depressive illness (Shorter and Fink, 2010). Australian psychiatrist Bernard Carroll discovered in 1968 the DST as a biomarker of melancholia (Carroll *et al.*, 1968).

However, TCM had beaten us to the punch! Several traditional herbs rely upon endocrine mechanisms for their principles of action. Total glycosides of peony (*Paeonia lactiflora* Pall., bai shao) have an antidepressant effect in some mouse models of ‘behavioral despair,’ or chronic unpredictable mild stress, driving up serum cortisol. This treatment effect is apparently mediated ‘by modulating the function of the hypothalamic-pituitary-adrenal axis,’ one group of researchers concludes (Mao *et al.*, 2009). Sini Tang, a traditional decoction of three herbs, reverses the increases in corticosterone in plasma and the mRNA expression corticotropin-releasing hormone in the hypothalamus, both caused by chronic unpredictable stress (Guo *et al.*, 2009).

Research from the State Key Laboratory of Pharmaceutical Biotechnology of the School of Life Sciences, Nanjing University, studied the interaction among the HPA axis, the serotonin system, and transmembrane proteins such as adenylyl cyclase (as measured in platelets), finding that *Magnolia officinalis* has substantial effects on all of these systems (Xu *et al.*, 2008).

These results – albeit in rodents – are superior to most western clinical efforts to apply endocrine treatments to psychiatric illness, where the most solid finding to date has been potentiating the action of TCAs with a thyroid hormone (Posternak *et al.*, 2008). The study of the endocrine system, which has largely vanished from western psychiatry, belongs to the most promising areas of future TCM research on the pathophysiology of psychiatric illness.

BRAIN-DERIVED NEUROTROPHIC FACTOR

In 1982 Yves-Alain Barde and co-workers at the Max-Planck Institute for Psychiatry in Munich purified a substance that first became known as ‘brain-derived nerve growth factor’ (Barde *et al.*, 1982). This development was exciting because it opened up the study of possible new mechanisms of drug action. Chinese investigators have not been slow to examine brain-derived neurotrophic factor (BDNF) in the mechanism of herbal medications. Table 4 shows some of the herbal preparations in TCM that increase BDNF.

This will surely be only a partial list as many investigations are still underway or have not yet been fully reported. Professor Peter Houghton has unpublished data ‘showing that some Chinese herbs stimulate outgrowths of neuritis in cultural neural stem cells’ (Houghton, P., personal communication, 2 March 2011).

Other traditional Chinese compounds utilize different nerve growth factors, such as the original nerve growth factor, or neurotrophin-3 (Zhu *et al.*, 2006; Mao *et al.*, 2010b). There are other mechanisms, too: Xiaobuxin-Tang increases neurogenesis in the hippocampus (An *et al.*, 2008b). The offering of pharmacological principles in TCM does indeed reach across the board.

LESSONS

Are there lessons from the historic experience of western psychopharmacology that may be applicable to efforts today to give TCM a solid scientific basis in pharmacology and to encourage the adoption of Chinese herbal remedies in western psychiatry? Merely posing the question in this manner suggests hubris, an implied superiority of western over TCM models. Our own thoughts are more modest: We have made a number of mistakes in the West, and this article invites our Asian colleagues not to repeat them.

What are these caveats?

(1) Diagnostic classifications

The first concerns the indications used in western psychopharmacology for therapeutic interventions: It is not clear that these represent genuine scientific constructs. Rather, there is concern that some of the indications in the DSM classification, the influential manual of psychiatric disorders issued by the American Psychiatric Association, may lack a scientific basis. From one viewpoint, the DSM is a political document, assembled on a consensus basis (Horwitz and Wakefield, 2007), and consensus diagnoses do not necessarily correspond to underlying natural illness entities. There has been widespread uneasiness about such diagnoses as ‘major depression’ and ‘schizophrenia’ (Swartz and Shorter, 2007).

It is therefore uncertain whether the western diagnostic system is superior to many of the diagnoses in TCM, with the gravity of their 200 year tradition. A systematic review of controlled trials involving Chinese herbal remedies in the treatment of schizophrenia, for instance, concluded that their effectiveness was compromised by following the Western diagnostic model rather than tailoring treatment to the various syndromes that fall within the disease category of ‘dian kuang.’ (Rathbone *et al.*, 2007).

Similarly, it is quite possible that ‘qi stagnation,’ defined by one authority as ‘an insidious, long-standing, serious discomfort that is projected into the body and is manifested by ... insomnia, fatigue, panic and dyspnea’ represents a real illness entity in scientific terms (Wei *et al.*, 2008, p.343), and that ‘major depression’ is an artificial one. In the United States, drugs are marketed for indications approved by the Food and Drug Administration, rather than for reasons of their intrinsic effectiveness. If marketed ‘over-the-counter,’ meaning without a prescription, western drugs would probably target such non-official indications as ‘stress’ and ‘burnout,’ rather than ‘depression.’ These terms are probably closer to TCM indications such as ‘qi’ than those of DSM (Healy, D., personal communication, 22 Feb. 2011).

There may thus be much wisdom embodied in the age-old diagnostic schema of TCM, and some momentary faddism in the DSM system. Let us therefore be cautious in shifting from the old system to the new.

(2) Neurotransmitter hypotheses

A second caveat concerns the western overemphasis on neurotransmitters, to the neglect of other mechanisms of drug action in the central nervous system, such as second messengers

within the neuron, or to the neglect of the endocrine system. Within western neuroscience, there has been a recent a shift away from the tight focus on monoamine neurotransmitters such as serotonin, norepinephrine, and dopamine that characterized the 1970s and '80s (Ban and Ucha Udabe, 2006). Within Asian psychopharmacology today, there is still a heavy emphasis on identifying the biogenic amines involved in the action of herbal agents, and this could prove shortsighted.

(3) Animal models

A third caveat sounds an alarm about overreliance on animal models of 'depression.' Of the various models in the recent literature – the tail suspension test, the swimming test, and the chronic mild stress (CMS) test – the CMS model seems closest to replicating the human biological experience of depression (Willner, 2005). The CMS test has received validation from the DST in the functioning of the hypothalamic-pituitary-adrenal axis (Greenberg *et al.*, 1989; Zhukov, 1990; Rittenhouse *et al.*, 2002; Ushijima *et al.*, 2006), and we may be dealing here with a genuine physiological replication in other species of the biophysical experience of depression.

Yet chronic stress and anxiety by themselves do not usually result in DST cortisol nonsuppression. Melancholic illness may strike out of the blue and is not necessarily associated with chronic mental stress (Carroll *et al.*, 1976). Animal models using CMS would therefore be inappropriate for assessing the efficacy of herbal medications in melancholia.

CONCLUSIONS

To sum up, there is some hope that the agents of TCM might confer a benefit in the treatment of psychiatric disorders in western patients, as they seem to have done over the centuries and millennia in the care of patients in Asia. There is, in other words, wisdom in the medicine of the people. Principles of drug action discovered scientifically in the West within the last century were discovered empirically in TCM over 2000 years. It remains to be seen what other principles of scientific value lie yet undiscovered in TCM.

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Table 1

TCM agents with an elective effect upon norepinephrine

Agent	Effect(s)	Source
Acanthopanax senticosus Harms (ci wu jia)	Single doses elevate levels of norepinephrine 'in a wide range of brain regions'	Fujikawa <i>et al.</i> , 2002:
Radix ginseng (ren shen)	Ginseng total saponins reverse the depletion of norepinephrine and dopamine caused by chronic mild stress	Dang <i>et al.</i> , 2009a
Glycyrrhiza glabra L. (gan cao)	'The antidepressant-like effect of liquorice extract seems to be mediated by increase of brain norepinephrine and dopamine, but not by increase of serotonin'	Dhingra and Sharma, 2006:
Kaixin-San, a traditional decoction of four herbs	Reverses the decrease of norepinephrine and dopamine caused by chronic mild stress. (Also increases serotonin)	Dang <i>et al.</i> , 2009b

Table 2

TCM agents with an elective effect upon serotonin (5-HT)

Agent	Effect(s)	Source
Albizia julibrissin (AEAJ; he huan pi)	Anxiolytic-like effects mediated by serotonergic system, especially 5-HT _{1A} receptors	Jung <i>et al.</i> , 2005
Cinnabaris (zhu sha)	Reduces serotonin levels	Wang, Q., <i>et al.</i> , 2007
Curcuma longa (yu jin)	Interaction with 5-HT _{1A/1B} and 5-HT _{2C} receptors	Wang <i>et al.</i> , 2008
Ginkgo biloba (yin hsing)	EGb 761 has a wide range of neurochemical effects, including the serotonergic system	Ahlemeyer and Kriegelstein, 2003
Xiaobuxin-Tang (XBXT) a traditional decoction of four herbs	'Serotonergic activation'	An <i>et al.</i> , 2008a
Banxia-Houpu, a traditional decoction of four herbs	Some fractions increase 5-HT and 5-HIAA levels	Wang <i>et al.</i> , 2005

Table 3

TCM agents with an elective effect upon dopamine (DA)

Agent	Effect(s)	Source
Berberine, an alkaloid in a number of plants in TCM.	Antagonizes D ₂ receptor and agonizes D ₁ receptor	Kulkarni and Dhir, 2010a
Apigenin, from <i>Perilla frutescens</i> (zu su ye)	'produced attenuation of forced swim test-induced decrease of DA turnover in the amygdala and increase of DA turnover in the hypothalamus'	Nakazawa <i>et al.</i> , 2003
Kai Xin San (KXS), a tradition decoction of several herbs	'remarkable dopaminergic activation'	Dang <i>et al.</i> , 2009b:

Table 4

TCM agents with an elective effect upon Brain-derived neurotrophic factor (BDNF)

Agent	Effect(s)	Source
Aconitum carmichaeli (fu zi)	Fuzi polysaccharide increases BDNF	Yan <i>et al.</i> , 2010
Curcuma longa (yu jin)	Enhances BDNF. See also serotonin table	Kulkarni and Dhir, 2010b
Radix Paeoniae Alba(bai shao)	Increases expression of BDNF	Mao <i>et al.</i> , 2009
Suyu-Jiaonang (SYJN) a decoction of four herbs	Acts on BDNF to normalize the changes introduced by chronic unpredictable stress	Mao <i>et al.</i> , 2010a
Xiaoyaosan (XYS) a decoction of eight herbs	'an antidepressant-like effect, which appears to involve BDNF in the brain.'	Chen <i>et al.</i> , 2008