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LETTER TO THE EDITOR

Inhibition of haloperidol-induced catalepsy in rats by root extracts from *Piper methysticum F.*

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Kava beverages prepared from the roots of *Piper methysticum* F. are widely used for their calming and tranquilizing properties by the native population of the South Pacific (Singh, 1992). During the past few decades several pharmaceuticals containing Kava extracts as their active ingredients are marketed in various European countries as mild and safer anxiolytics. Although several controlled clinical trials and other reports do add evidences for such therapeutic uses, a recent communication point out to the potential of extrapyramidal side effects (EPS) of Kava preparations and caution their uses, particularly in elderly patients (Schelosky et al., 1995). This warning was based on the observations made with four patients who developed clinical signs suggestive of central dopaminergic antagonism after exposure to two different Kava preparations. One of these two preparations (Laitan®) contained a standardized Kava extract (WS-1490) enriched in Kava pyrones (~60%) as the only active ingredient. The authors report that a single 100 mg dose of this extract caused involuntary dyskinesia and other clinical EPS symptoms in two patients within four hours after the administration.

Since catalepsy is a well validated rodent model for detecting compounds with EPS liability in humans (Hoffman and Donovan, 1995), it was of interest to test the effects of WS-1490 in such a rat model. The experiments were conducted using the so called bar test in male Sprague-Dawley rats (200–250 g) with minor modifications according the procedure described by Hoffman and Donovan. The extract or the pure known components of Kava extracts available to us were administered orally one hour before the observations and the duration of catalepsy during a 3 minutes test period was quantified. In the first series of experiments no cataleptogenic effect of the extract or its components could be detected after the doses mentioned in the accompanying table. Under similar conditions, however, 0,2 mg/kg (s.c.) dose of haloperidol always induced catalepsy in all the animals. Thus the total mean (± SD) amount of time (seconds) spent immobile by the animals in the control groups and with the test agents treated groups (n = 8/group) were always between 3 ± 1 to 7 ± 4, whereas those in the various haloperidol treated groups were between 114 ± 42 and 168 ± 17. These observations clearly demonstrate that possible EPS of the extract and the tested components of the extract are not detected in the rat catalepsy model.

Attempts to clarify whether the extract could potentiate the EPS of neuroleptics or dopamin antagonists led us conduct experiments in which its effects on animals treated with marginally cataleptogenic or non-cataleptogenic doses of haloperidol was studied. Surprisingly, however, the results of one of these experiments revealed that the extract actually inhibit the cataleptogenic effects of the dopamin antagonist.

To examine these possible anticataleptogenic effect of the extract we conducted further experiments using 0,2 mg/kg (s.c.) dose of the dopamin antagonist (see table). The results summarized in the table demonstrate that co-administration or pretreatment of the animals with the extract can completely abolish the EPS of haloperidol as judged the bar test and indicated that this effect of the agent is dependent on the dose and preadministration period. None of the known constituents of the extract tested, except dihydrokavain, antagonized the effects of haloperidol. It must be mentioned, though, that the concentration of dihydrokavain in the extract used is only 17%. Since the observed effects of this constituent of the extract (after 100 mg/kg) was much lower than that of 100 mg/kg of WS-1490 it is difficult to interpret the effects of the extract in terms of its dihydrokavain content. We speculate, therefore, that either the effects of dihydrokavain are potentiated by other component(s) of the extract or that the extract contains some other till now undefined but potent anti-cataleptogenic agent(s). Efforts to clarify the situation are now, therefore, being made in our laboratories.

The experimental observations reported here allow us to conclude that the Kava extract WS-1490 is devoid of haloperidol like cataleptogenic properties and sug-

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Table 1. Effects of a Kava-Extract and some of its constituents on haloperidol-induced catalepsy in the rat bar test. The reported data represent (mean ± s.d.) immobility time (seconds) of the group (n = 8) recorded during 3 minutes observation period. All animals were treated with haloperidol (0.2 mg/kg s.c.) and additional with test substance or vehicle. * = $p < 0.01$ Student's T-test.

Substance	Dose (mg/kg)	Pretreatment time (hours)	Vehicle treatment	Substance treatment
Extract	100	1	119 ± 54	10 ± 9*
Extract	100	4	114 ± 42	20 ± 10*
Extract	100	24	165 ± 43	140 ± 21
Extract	100	48	165 ± 22	104 ± 64
Extract	200	1	119 ± 54	9 ± 8*
Extract	200	4	114 ± 42	10 ± 3*
Extract	200	24	165 ± 43	63 ± 59*
Extract	200	48	165 ± 22	95 ± 44*
Kavain	100	1	143 ± 43	157 ± 43
Dihydrokavain	100	1	150 ± 45	77 ± 49*
Methysticin	100	1	148 ± 49	108 ± 73
Dihydromethysticin	100	1	162 ± 35	174 ± 12
Flavokavin A	100	1	129 ± 47	142 ± 55
Flavokavin B	100	1	128 ± 58	158 ± 36

gest that co-administration of this extract with conventional antipsychotics could as well be an effective means of combating their extrapyramidal side effects. The question regarding the observed four cases of extrapyramidal side effects (Schelosky et al., 1995) in a given neurological clinic remains, however, to be a puzzle, which we do not think is easily clarifiable on the basis of our current understanding of the pharmacology of Kava extracts and their constituents or on that of the description of the clinical symptoms and diagnosis of the patients who unfortunately developed clinical signs after exposure to Kava preparations. In any case, central dopaminergic antagonism seems unlikely to be involved in these reported cases.

From the pharmacological point of view it was interesting to note that in two of the reported four cases of dyskinesia, the symptoms observed after Kava exposure could be ameliorated after biperiden administration. The symptoms in the other two cases disappeared either after Kava withdrawl or spontaneously 40 minutes after the appearance of the clinical symptoms. Since the anti-Parkinson agent biperiden is a potent anticholinergic agent, it can be argued that cholinergic hyperactivity in the patients caused by Kava could as well be involved in the symptoms observed. Results of some ongoing studies based on this speculation could clarify the situation and will be reported in due course.

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