Non-Amphetaminic Central Stimulation by Alkaloids from the Ibogane and Vobasine Series

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Abstract: Ibogane alkaloids were shown to have a very high arousal activity. Similarly, a stimulating CNS activity was demonstrated for vobasine alkaloids. The influence of certain substituents was evidenced: a methoxy substituent increases the activity, while it is lowered by a methoxycarbonyl substituent.

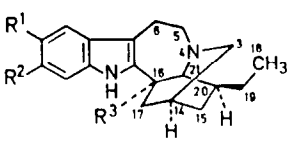
Introduction

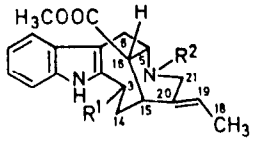
The roots of *Tabernanthe iboga* H. Bn (Apocynaceae) are known for their central stimulating activity, from empirical observations as well as from some experimental data (1, 2, 3, 4). However, due to the toxicity of ibogane alkaloids, these data are equivocal as they consist only of induction of tremor and increase of locomotor activity at high dosages.

We were therefore looking for a psychopharmacological test which would afford sufficient sensitivity and more specificity. As the SCR-habituation test (5) detects and quantifies (from already very low dosages) a drug's ability to maintain arousal at a certain level during monotonous solicitations, it was selected to assess and quantify the central stimulating activity of a series of ibogane alkaloids.

In the course of our study, some "dimeric" alkaloids resulting from the association of an ibogane unit with a vobasine unit such as voacamine (**3**) showed a significant activity. We therefore decided to study also the activity of various vobasine derivatives towards the SCR-habituation test.

Most of the alkaloids studied, ibogaine (**1**), voacangine (**6**), coronaridine (**8**), voacamine (**3**), tabernamine (**9**), vobasine (**11**), perivine (**12**), and pagisulfine (**13**) were obtained from *Pagiantha cerifera* (Panch. et Seb.) Mrgf (Apocynaceae); tabernanthine (**5**) was isolated from *Tabernanthe iboga* H. Bn.; and conopharyngine (**7**) from *Conopharyngia durissima* Stapf (Apocynaceae). Some products such as voacanginol (**4**), *O*-acetylvoacanginol (**2**) and vobasinol (**10**) resulted from simple chemical modifications of natural alkaloids.





	R^1	R^2	R^3
1	OCH_3	H	H
2	OCH_3	H	$-CH_2-O-\overset{O}{\overset{\|}{C}}-CH_3$
3	OCH_3	H	vobasinyl
4	OCH_3	H	$-CH_2-OH$
5	H	OCH_3	H
6	OCH_3	H	$-COOCH_3$
7	OCH_3	OCH_3	$-COOCH_3$
8	H	H	$-COOCH_3$
9	H	H	vobasinyl

	R^1	R^2
10	OH	CH_3
11	O	CH_3
12	O	H
13	$-S-(CH_2)_2-NH_2$	CH_3
vobasinyl	H	CH_3

Materials and Methods

Subjects: Male Swiss or mice purchased from a local breeder.

Apparatus: The apparatus used was a palmar skin conductance meter specially designed and built for use with mice (6). This apparatus has already been described (6, 7, 8).

Methods: A mouse is placed so it grips each of the two electrodes with one of its front paws and thus completes the circuit. The strength of the current changes with the conductivity of the circuit which itself varies following the intensity of the palmar sweating of the mouse: this is known as the electrical palmar conductivity (EPC) (6). A 100 W lamp is switched on above the mouse's head for 7 to 12 s. The EPC increases; this phenomenon is termed the psychogalvanic reaction (PGR) (7). The habituation test (5) uses iterative photostimuli until a decrease and eventual extinction of the PGR is achieved. This phenomenon is called habituation (5).

At first, the EPC is recorded (6) before the treatment. After administration of the drug, (*i.p.* injection of alkaloid tartrate) the PRG is recorded every 10 min until its extinction.

Results

The ibogane alkaloids tested showed a very high activity. Some vobasine alkaloids have been tested too because of the surprising high activity of the "dimeric" alkaloid voacamine (**3**). They gave the same range of activity. The activity is expressed in mol/kg $\times 10^{-6}$ (and proportional with l/dosage). The standard de-

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laying dose 125 (SDD 125) (expressed in 100ths of an h) is the dose which represents a 47% increase in the delay of the habituation in relation to controls. The calculation has been described by Marcy et al (5). The results are mentioned in Table I and the activity in Figure 1.

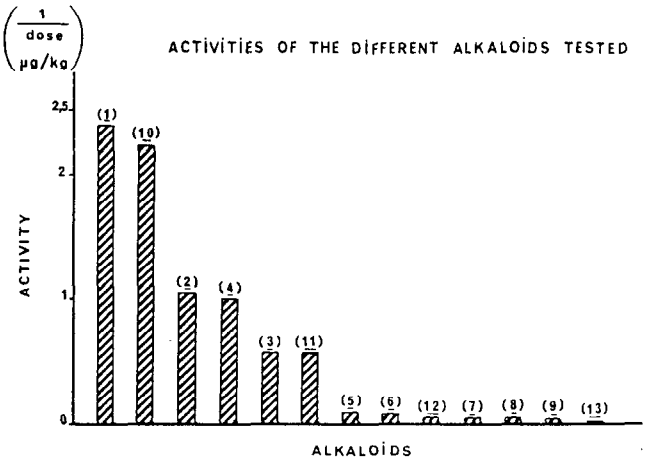

Fig. 1. Activities of the different alkaloids tested.

Table I. Results of the habituation test with alkaloids **1–13**.

Product	SDD 125 [mol/kg × 10^{-6}]
ibogane series	
ibogaïne (**1**)	0.00091
O-acetylvoacanginol (**2**)	0.0018
voacamine (**3**)	0.00198
voacanginol (**4**)	0.0021
tabernanthine (**5**)	0.0207
voacangine (**6**)	0.0212
conopharyngine (**7**)	0.0420
coronaridine (**8**)	0.0744
tabernamine (**9**)	0.0788
vobasine series	
vobasinol (**10**)	0.00092
vobasine (**11**)	0.00351
perivine (**12**)	0.0361
pagisulfine (**13**)	inactive

Discussion

The stimulating activity study on CNS for these different alkaloids shows favourable or unfavourable effects of the different structural parameters. In ibogane alkaloids, a methoxy substituent at C-10 seems very favourable (4) since ibogaine (**1**) is more active than tabernanthine (**5**). A methoxycarbonyl group at C-16 is highly unfavourable (4), voacangine (**6**) being 23 times less active than ibogaine (**1**). Replacement of the methoxycarbonyl group by a primary alcoholic group strongly increases the activity, since voacanginol (**4**) has a higher activity than voacangine (**6**). Nevertheless, ibogaine (**1**) is much more active than voacanginol (**4**). Consequently the presence of a substituent at C-16 position is responsible of a decrease of the activity.

Conopharyngine (**7**), which bears two methoxy groups at C-10 and C-11, is less active than voacangine (**6**). In contrast, voacamine (**3**) which also bears two substituents at C-10 and C-11 is more active than voacangine (**6**) itself. This phenomenon indicates that the vobasinyl unit may be responsible for a part of the activity. A study of the activity of vobasine-derived alkaloids revealed a very high stimulating activity similar to that observed for ibogaine itself. Some iboga alkaloids were proposed as treatment for asthenia (1) but their therapeutical use was impeded by their cardiac toxicity. This drawback was not of significance with the SCR-habituation test as the iboga alkaloids studied were highly active in this test at very low dosages and, thus, at non-toxic levels. As no locomotor hyperactivity nor stereotipy was observed, we can support the qualifications of "Nootrope" and "non-amphetaminic-like" central stimulant given to tabernanthine (**5**) respectively by Jacquot et al. (11) and Prioux et al. (12, 13). Tabernanthine and related compounds may act through a direct cortical effect (10), as was shown for piracetam, which is the leader of the Nootropic class (14).

In addition, our demonstration of a central stimulating activity of the vobasine class alkaloids at low doses level is the first step of a psychopharmacological study of these products since such an activity was not known previously.

Acknowledgements

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