and this review shows that the major aim of this synthetic process is the deactivation of the drug. This means that the inhibition of any of the enzymes necessary for this process may cause the drug to reach a toxic blood level. Also, it has been shown that some drugs are more active than the parent compounds, for example, morphine-6-glucuronide is more active than the parent drug. Inhibition of glucuronide formation therefore reduces the potency of the drug. The probable increase of β-glucuronidase in the bladder may cause the breakdown of glucuronide to an active unchanged compound which may cause the drug to attain a toxic level in this organ.

In conclusion, the results obtained suggest that during malarial infection the ability of the liver to deactivate xenobiotics is reduced, tending towards overdosing of the animal. Further investigation is needed to clear up some unanswered questions.

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Benzamide potentiation of behavioral apomorphine-induced effects; mechanism involved

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Summary. A new N-pyridinyl benzamide was found to potentiate strongly the effects of apomorphine on the motility of reserpinized mice and on circling behavior. Since dopaminergic agonist activity could not account for this potentiation, involvement of α_2-adrenergic agonist activity provided the only consistent explanation.
Key words. Apomorphine-induced behavior; N-pyridinyl benzamide; α_2-adrenergic agonists.

Because of its direct dopaminergic agonist effect, apomorphine elicits characteristic behavioral modifications in rodents[2,3]. Administration of reserpine or 6-OH dopamine leads to development of hypersensitivity to dopaminergic agonists and allows more specific investigations about related central phenomena. For instance, the reversal of reserpine-induced akinesia indicates activation of postsynaptic dopamine receptors[4], and a distinction between a direct or indirect mechanism can be determined by observing the circling behavior elicited in unilaterally striatal 6-OH dopamine-lesioned mice[5]. In addition, the circling behavior and/or hypermotility induced by apomorphine can be increased by drugs such as caffeine, central anticholinergics, parachlorophenylalanine and clonidine[6-9].

The N-(4,6-dimethyl 2-pyridinyl) 3-chloro benzamide (N-PCB; fig. 1) like other pyridinyl benzamide derivatives[10] exhibits some antiinflammatory properties. However, its structural features led us to investigate its possible effects on dopaminergic transmission. In our work, potentiation of the above-mentioned apomorphine effects was observed with N-PCB, and the mechanism involved was studied.

Materials and methods. Male Swiss C.F. mice weighing 25 ± 5 g, kept in a quiet room at 21 ± 1 °C with artificial lighting (lights on between 07.00 and 19.00 h), were used for motility and circling behavior experiments. Food and water were given ad libitum. All drugs were injected i.p., except N-PCB which was administered orally in a 10% acacia gum aqueous suspension as it is insoluble in water. All controls also received this vehicle (10 ml/kg). Results were compared using Student's t-test.

Motility experiments on reserpinized mice were performed between 09.00 and 13.00 h in a Boissier photoactimeter (Apelex, France). Each individual activity cage (L = 25.5 cm, W = 20 cm, H = 9 cm) was fitted with two photoelectric units with IR lights located 1 cm above the floor of the cage in the middle of each side. These cages were placed in a closed compartment and connected to a counter. Motility was expressed as the number of interruptions of photocell beams. Mice received apomorphine hydrochloride (2 mg/kg) 20 h after reserpine (10 mg/kg) and were placed one per cage. The motility recording started immediately after apomorphine injection and lasted 60 min. N-PCB

Table 1. Effects of N-PCB, yohimbine and clonidine on apomorphine-induced motility and circling behavior

	Motility of reserpinized animals (counts per 60 min)	Circling behavior (turns per 2 min)
Apomorphine	435 ± 44 (40)	14.5 ± 1.1 (23)
Apomorphine and N-PCB[d]	721 ± 139[c] (27)	19.0 ± 1.9[a] (16)
Apomorphine and yohimbine[d]	424 ± 53 (19)	16.0 ± 2.7 (8)
Apomorphine and clonidine[d]	704 ± 106[b] (12)	26.3 ± 2.1[c] (7)
Apomorphine, clonidine and yohimbine	436 ± 87[e] (13)	14.6 ± 4.4[f] (5)

Values are means ± SEM, with number of animals in parentheses. [a]$p < 0.05$, [b]$p < 0.01$, [c]$p < 0.005$, compared to apomorphine-treated mice, [d]N-PCB, clonidine or yohimbine given alone, without apomorphine, had no significant effect either on motility or on circling behavior at the doses used; these results are in agreement with previous works[5,6,9,16]. [e]$p < 0.10$, [f]$p < 0.01$, compared to mice treated with both apomorphine and clonidine.

Table 2. Effects of N-PCB and N-PCB with yohimbine on pupil diameter and nociception

	Pupil diameter (μm)	Antinociceptive effect (tail-flick latency in s) t:30 min	t:60 min
Controls	684 ± 33 (9)	3.6 ± 0.3 (11)	3.4 ± 0.3 (11)
Yohimbine	709 ± 25 (10)	3.7 ± 0.4 (10)	3.8 ± 0.3 (10)
N-PCB	796 ± 29[b] (14)	4.9 ± 0.5[a] (11)	5.2 ± 0.4[c] (11)
N-PCB and yohimbine	644 ± 36 (10)	3.8 ± 0.2 (11)	4.1 ± 0.3 (11)

Values are means ± SEM, with number of animals in parentheses. [a]$p < 0.05$, [b]$p < 0.02$, [c]$p < 0.005$ compared to control rats.

(130 mg/kg), clonidine hydrochloride (3 mg/kg) and yohimbine hydrochloride (0.25 mg/kg) were administered 60, 15 and 5 min before apomorphine, respectively.

Circling behavior was studied in unilaterally striatal 6-OH dopamine-lesioned mice[11]. Apomorphine hydrochloride (2 mg/kg) was given 15 min before recording the number of contraversive turns performed during 2 min. N-PCB (130 mg/kg), yohimbine hydrochloride (0.07–0.25 mg/kg) and clonidine hydrochloride (1.5 mg/kg) were administered 45, 20 and 10 min before turning behavior evaluations respectively. The animals were tested with apomorphine 36 h before the experiments.

Male Wistar C.F. rats weighing 225 ± 20 g, housed under the conditions previously described for mice, were used for evaluation of mydriatic and antinociceptive effects. All drugs, including N-PCB solubilized in a 60% (v/v) propylene glycol aqueous solution, were injected i.p. Control animals received only the vehicle.

Pupil diameter was measured[12] under constant illumination at × 30 magnification 25 min after N-PCB administration.

The antinociceptive effect was assessed by the radiant-heat tail-flick procedure[13] (Socrel tail-flick unit, Apelex, France) 30 and 60 min after N-PCB injection. Yohimbine hydrochloride (0.25 mg/kg) was administered 10 min before the drug.

Results and discussion. The administration (p.o.) of 2600 mg/kg of N-PCB did not induce mortality in mice after 48 h. The 130 mg/kg dose actually used in our motility and circling behavior experiments was only $\frac{1}{20}$th of this quantity; it was, however, sufficient to increase apomorphine motility in reserpinized mice by 66% (table 1). Nevertheless, in experiments performed with the benzamide alone, without apomorphine, it was noted that a dose of 260 mg/kg was required to increase significantly the motility of reserpinized animals.

The benzamide studied potentiated apomorphine-induced circling: it increased the number of contraversive turns performed in 2 min by 31% (table 1), though it did not induce such behavior when given alone at the same dose (130 mg/kg) during the same period. However, when mice were observed for 30 min, it elicited slight but significant contraversive turning (7.3 ± 1.8 turns instead of 2.3 ± 0.4 turns for controls, $p < 0.10$). The potentiation could not have been due to central anticholinergic activity, amphetamine-like activity or phosphodiesterase inhibitory effect of N-PCB, because these pharmacological or biochemical effects are known to induce ipsiversive circling[5,7,8]. Furthermore, if (like parachlorophenylalanine) the drug had caused central serotonin depletion, the potentiation of apomorphine effects should not have persisted in reserpinized mice. Moreover, the synergistic effect observed in reserpinized animals was not affected by an additional pretreatment with α-methylparatyrosine methylester (250 mg/kg), a tyrosine-hydroxylase inhibitor[14], 17 h after reserpine injection; this result excludes involvement of an indirect mechanism such as MAO inhibition or catecholamine release. The potentiation observed in both tests was gradually diminished by increasing doses of yohimbine (fig. 2) and even disappeared with 0.25 mg/kg, a dose reported to block α_2-adrenergic receptors selectively[15]. This dose did not modify the effects of apomorphine in reserpinized mice or in 6-OH dopamine-lesioned mice, but it totally inhibited the potentiation of apomorphine-induced effects by clonidine (table 1).

Additional experiments were in agreement with the presence of α_2-agonist activity for N-PCB which induced significant mydriasis and analgesia in the rat. These effects were also antagonized by low doses of yohimbine (table 2). Thus, involvement of central α_2-adrenergic receptor activation provides the only consistent explanation for N-PCB potentiation of the behavioral apomorphine-induced effects studied.

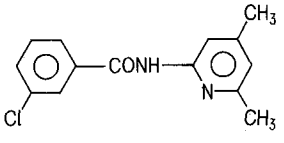

Figure 1. Chemical formula of N-PCB.

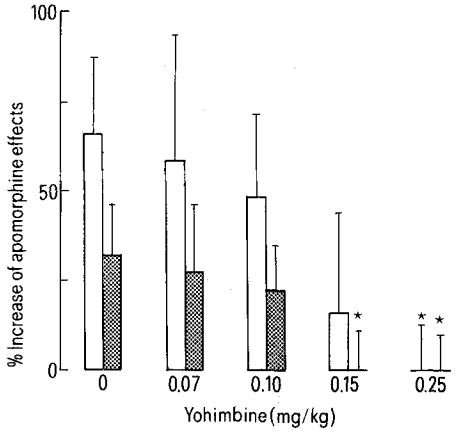

Figure 2. Influence of yohimbine on N-PCB induced potentiation of apomorphine effects (motility and circling behavior). □ motility of reserpinized mice; ■ circling behavior. The values correspond to mean ± SEM (7–27 animals per group); *$p < 0.02$ compared to groups not treated with yohimbine.

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