Evidence for antidopaminergic properties of some alpha antagonists

Modulation of dopaminergic transmission by alpha-noradrenergic agonists and antagonists: Evidence for antidopaminergic properties of some alpha antagonists

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Summary. The effects on dopamine (DA) metabolism, on [3H]spiperone binding and on amphetamine-induced stereotypes of a variety of drugs on actions on alpha₁ and alpha₃-noradrenergic (NA) receptors have been investigated.

The preferential alpha₂-antagonists yohimbine, rauwolscine, piperoxane and esproquin as well as the preferential alpha₁-antagonists corynanthine and WB4101 increased homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) in the rat striatum, mesolimbic area, and cortex. Prazosine and clonidine tended to
reduce HVA and DOPAC. The preferential alpha<sub>2</sub>-antagonists, tolazoline and RX-781094 A, had no measurable effects on DA metabolism even at high doses.

Those compounds which in comparable doses increased DA metabolism inhibited <sup>3</sup>H-spiperone binding in the hippocampus. The effects in the striatum and cortex were smaller and did not show a relation to those in hippocampus or on DA metabolism. Only the yohimbine alkaloids antagonized amphetamine-induced stereotypies.

The results suggest that the effects on DA metabolism at least of yohimbine, rauwolscine, and corynanthine are related to their intrinsic antidopaminergic properties. The same might be true, although with a lesser degree of certainty, for piperoxane, esproquin, and WB 4101.

Since many of the tested compounds possessing alpha-antagonistic properties interacted with the DA system, a close molecular relationship between alpha-noradrenergic and DA receptors might be anticipated. The preference of these compounds for the hippocampal subtype of DA receptors might indicate a particular role of the latter in the regulation of DA metabolism. On the other hand, the antagonism against haloperidol's enhancing effect on DA metabolism by clonidine suggests a modulatory NA influence on DA transmission. The observation that clonidine reduced the effects of yohimbine and piperoxane to a lesser degree than that of haloperidol, is in agreement with this notion.

**Introduction**

A considerable amount of evidence from pharmacological and biochemical investigations suggests the existence of interactions between noradrenergic and dopaminergic systems in the brain (for a detailed discussion, see Antelman and Caggiula, 1977). The principal facts can be summarized as follows. The preferential alpha<sub>2</sub>-antagonist yohimbine increases dopamine (DA) turnover (Papeschi and Theiss, 1975; Anden et al., 1976; Anden and Grabowska, 1976), whereas clonidine in doses preferentially acting on alpha<sub>2</sub>-receptors (Rochette and Bralet, 1975; Anden et al., 1976; Anden and Grabowska, 1976), whereas clonidine in doses preferentially acting on alpha<sub>2</sub>-receptors (Rochette and Bralet, 1975; Anden et al., 1976; Anden and Grabowska, 1976) reduce DA turnover in DA-rich areas of the rat brain. Moreover, the effects of yohimbine on DA turnover is antagonized by a combination of clonidine and phenoxybenzamine (Anden and Grabowska, 1976).

Lesions of the noradrenergic ventral bundle reduces DA concentrations in the caudate nucleus and in other areas containing DA terminals, but increases it in the cell body regions (O'Donohue et al., 1979). Alpha<sub>2</sub>-agonists and alpha<sub>2</sub>-antagonists were found to potentiate haloperidol catalepsy, whereas an antagonism was described for drugs with alpha<sub>1</sub>-lytic or alpha<sub>2</sub>-agonistic properties (Brown and Handley, 1979). This is controversial, however, since Al-Shabibi and Doggett (1978) reported an attenuation of haloperidol-induced catalepsy by both clonidine and yohimbine in similar doses.

Ipsiversive circling was induced in rats after unilateral locus coeruleus lesions; injection of phenoxybenzamine into the substantia nigra showed a similar effect, whereas noradrenaline (NA) injections caused contraversive rotation (Donaldson et al., 1979).

Scatton et al. (1980) have recently suggested that the effects of yohimbine on DA metabolism are due to intrinsic antidopaminergic properties of this compound rather than to its alpha-adrenoceptor blocking effects. The question, whether dopaminergic transmission is altered by drugs primarily affecting NA transmission, and if so, in which way, is of considerable importance with respect to the development of new drugs for the treatment of mental diseases. Therefore, we have studied the effects on DA metabolism of a number of compounds with different effects on alpha receptors, in order to examine whether they exhibit a consistent pattern of effects. Moreover, the effects on in vivo <sup>3</sup>H-spiperone binding and on amphetamine-induced stereotypies were assessed in an attempt to characterize possible direct antidopaminergic effects.

**Materials and methods**

Clonidine-HCl and 2-[2-(1,4-benzodioxanyl)]-2-imidazoline HCl (RX 781094A) were kindly donated by Boehringer Sohn, Ingelheim, FRG, and Reckitt & Colman Ltd, Hull, England. Haloperidol was purchased from Cilag AG, Schaffhausen, Switzerland, and rauwolscine-HCl and corynanthine-HCl from Carl Roth, Karlsruhe, FRG. Esproquin-HCl, prazosine-HCl, tolazoline HC1 (RX781094A) were kindly donated by Boehringer Sohn, Ingelheim, FRG, and Reckitt & Colman Ltd, Hull, England. Haloperidol was purchased from Cilag AG, Schaffhausen, Switzerland, and rauwolscine-HCl and corynanthine-HCl from Carl Roth, Karlsruhe, FRG. Esproquin-HCl, prazosine-HCl - H<sub>2</sub>O and WB 4101-HCl were synthesized in our Chemistry Department by Dres H. Schroeter, A. Storni, Th. Leutert and F. Ostermayer, respectively. Tolazoline-HCl is a product marketed by Ciba-Geigy (Priscol®).

For biochemical experiments, female Tif:RAIF(SPF) rats (Tierfarm Sisseln, Switzerland) weighing 160-200 g were used. For the spiperone binding experiments and amphetamine antagonism, male animals of the same strain and weight range were used. Homovanillic acid (HVA) and 3,4-dihydroxyphenylacetic acid (DOPAC) were isolated from the corpus striatum, the mesolimbic area (containing the nucleus accumbens and the tuberculum olfactorium as the major components; for the dissection procedure see Waldmeier and Maitre, 1976) and the neocortex on Sedaphex G10 columns (Westerink and Korf, 1976) and quantified by HPLC with electrochemical detection (Waldmeier, 1980). A BAS system (Bioanalytical