SDZ PSD 958, a novel D₁ receptor antagonist with potential limbic selectivity

R. Markstein¹, P. Gull¹, C. Rüdeberg², S. Urwyler², A. L. Jaton¹, K. McAllister², A. K. Dixon², and D. Hoyer¹

¹Preclinical Research, Sandoz Pharma Ltd., Basle, and ²Sandoz Research Institute Berne Ltd., Berne, Switzerland

Accepted September 10, 1995

Summary. SDZ PSD 958, a novel benzo[g]quinoxaline derivative exhibits the properties of a potent orally active selective D₁ receptor antagonist. It has high affinity for D₁-like receptors (D₁, D₅; pKi = 9.7–9.8) labelled by [³H]SCH23390 and is at least 400 fold less active at D₂-like receptors (i.e. D₂, D₄) labelled by [³H]spiperone. Effects in functional tests are consistent with D₁ receptor antagonist properties. SDZ PSD 958 inhibited apomorphine-induced rearing in mice and prevented prolongation of novelty-induced locomotion in rats elicited by the selective D₁ receptor agonist CY 208-243. By contrast, SDZ PSD 958 did not induce catalepsy and only weakly inhibited apomorphine-induced stereotyped gnawing in rats. This suggests that SDZ PSD 958 preferentially inhibits responses mediated by dopamine systems innervating the limbic system.

Keywords: SDZ PSD 958, D₁ receptor antagonist, catalepsy, rearing, stereotypy, locomotion.

Introduction

Originally, based on biochemical criteria central dopamine receptors were divided into two types termed D₁ and D₂ (Kebabian and Calne, 1979). More recently, molecular cloning revealed the existence of further dopamine receptors increasing their number from two to five subtypes. Based on structural and functional similarities the five dopamine receptors have been classified into two families of D₁-like and D₂-like receptors (Sibley and Monsma, 1992). The D₁-family contains D₁ and D₅ receptors and the D₂ family includes the D₂, D₃ and D₄ receptors. Until recently, the majority of the central effects of dopamine were thought to be mediated by D₂ receptors. Only after the discovery of drugs acting selectively on D₁ receptors was it possible to investigate their role in physiological and pathological conditions. More recently, interest has focused on the D₁ receptor as a potential new target for atypical
neuroleptics since SCH23390, the prototype of a selective D₁ receptor antagon-
ist, produces behavioral effects typical of antipsychotic agents (Iorio et al.,
1983). For instance, it blocks apomorphine-induced behavior in rodents
(Christensen et al., 1984; Gerhardt et al., 1985), inhibits conditioned avoid-
ance responding in rats and monkeys and shares a binding site with atypical
neuroleptics (Andersen et al., 1986). Moreover, clozapine, the prototypical
"atypical" antipsychotic agent, produces in vivo effects consistent with cetral
D₁ receptor blockade (Ellenbroek et al., 1991; Murray and Waddington,
1989; Imperato and Angelucci, 1989). In the mean time besides SCH23390
other selective D₁ receptor antagonists have been described such as the
benzazepine congeners SCH39166 (Chipkin et al., 1988); NNC-112, NNC-687,
NNC-756 (Andersen et al., 1992) or the isoquinoline derivative A 69024
(Kerkman et al., 1989) and some of them were tested in patients with schizo-
phrenia. While SCH23390 and SCH39166 failed to improve psychotic symp-
toms (Gessa et al., 1991; Karlsson et al., 1994) NNC-687 has been reported to
exhibit some mild antipsychotic activity (Gerlach et al., 1994; Lublin, 1994).
Since SCH23390 and other benzazepine D₁ receptor antagonists including the
isoquinoline derivative A 69024 produce catalepsy in rats which is considered
to predict extrapyramidal side effects in man the usefulness of D₁ receptor
antagonists as novel antipsychotics has been questioned (Hietala et al., 1990).
Besides the question whether D₁ receptor blockade is sufficient for
antipsychotic activity the question as to whether D₁ receptor blockade and
extrapyramidal side effects are inevitably linked is not yet answered. The
present study describes a novel D₁ receptor antagonist, SDZ PSD 958, which
belongs to a new chemical class of compounds and which may be a tool to
investigate the relationship between D₁ receptor blockade and extrapyrami-
dal side effects.

**Materials and methods**

SDZ PSD 958 ((−)-[4αR, 10αR]-1,2,3,4,4α,5,10,10α-octahydro-4-(4-chloro-2-methyl-
phenyl)-1-methyl-benzo[g]quinoxaline-6-ol) (Fig. 1), clozapine, bromocriptine and
CY 208-243 ((−)-4,6,6a,7,8,12b-hexahydro-7-methyl-indolo[4,3-ab]phenanthridine) were
synthesized at Sandoz Pharma, Basle, Switzerland. SCH23390, haloperidol and spiperone