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(54) Title: USE OF INDOLONE DERIVATIVES FOR THE TREATMENT OF MEMORY DISORDERS, SEXUAL DYSFUNCTION AND PARKINSON'S DISEASE

(57) Abstract

Selective dopamine D_3 receptor agonists and their use in therapy, inter alia, in the treatment of memory disorders.

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USE OF INDOLONE DERIVATIVES FOR THE TREATMENT OF MEMORY DISORDERS, SEXUAL DYSFUNCTION AND PARKINSON'S DISEASE

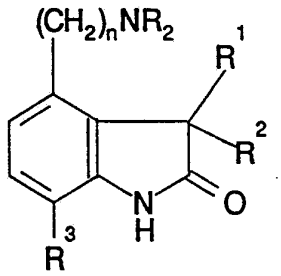
The present invention relates to the use of selective dopamine D_3 receptor agonists in therapy, for example in the treatment of memory disorders.

Compounds capable of binding selectively to dopamine D_3 receptors are known in the art (see, for example, Nature, 1990, **347**, 146). To date, however, no specific therapeutic utility has been identified for compounds having such properties.

The present invention resides in the identification of such a utility and, in a first aspect, provides selective dopamine D_3 receptor agonists for use in therapy.

More specifically, the present invention relates to selective dopamine D_3 receptor agonists for use in the treatment or prophylaxis of diseases in which agonism of the D_3 receptors will prove advantageous, for example, in the treatment of memory disorders, sexual dysfunction and Parkinson's disease.

Particular selective dopamine D_3 receptor agonists include, for example, compounds of the structure (I):



(I)

in which,
each group R is the same or different and is hydrogen or C_{1-4}alkyl;

R^1 and R^2 are the same or different and are each hydrogen or C_{1-4}alkyl; and
n is 1 to 3,
or a pharmaceutically acceptable salt thereof.

Within the scope of the structure (I) and the most preferred selective dopamine D_3 receptor agonist of the present invention is the compound 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone hydrochloride having the INN: ropinirole. The compound ropinirole and other compounds of structure (I) are known in the art, for example as having utility in the treatment of Parkinson's disease (EP 0299602-A).

The compounds of structure (I) and, in particular, ropinirole, can be prepared according to the procedures described in EP 113964-B.

Selective dopamine D_3 receptor agonists are of use in therapy, in particular in the treatment of memory disorders, for example, in the treatment of impaired cerebral functionality, as well as dementia, amnesia and decreased cognitive capacity; in the treatment of sexual dysfunction in both males and females, in particular in the treatment of male and female impotence; and in the treatment of Parkinson's disease.

When used in therapy, the compounds of structure (I), in particular ropinirole, are formulated into a standard pharmaceutical composition, for example as described in EP 113964-B and EP 0299602-A.

Preferably the composition is administered in unit dose form. Each dosage unit for oral administration contains preferably from 1 to 50 mg (and for parenteral administration contains preferably from 0.1 to 15 mg) of a compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base.

The daily dosage regimen for an adult patient may be, for example, an oral dose of between 1 mg and 100 mg, preferably between 1 mg and 50 mg, or an intravenous, subcutaneous, or intramuscular dose of between 0.1 mg and 50 mg, preferably between 0.1 mg and 15 mg, of the compound of the formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base, the compound being administered 1 to 4 times per day. Suitably the compounds will be administered for a period of continuous therapy.

DATA

The ability of the compounds to bind selectively to human D_3 dopamine receptors can be demonstrated by measuring their binding to cloned receptors. The inhibition constants (K_i) for ropinirole displacement of [^{125}I] iodosulpride binding to human D_2 and D_3 dopamine receptors expressed in CHO cells have been determined. Human D_2 receptors were obtained from Garvan Institute of Medical Research, St. Vincent's Hospital, Darlinghurst, New South Wales 2010, Australia. Human D_3 receptors originated from Unite de Neurobiologie et Pharmacologie (U.109) de l'INSERM, Centre Paul Broca, 2ter rue d'Alesia, 75014 Paris France (B. Giros (1991) Path. Biol. **39**, 252-254). Crude cell membranes were prepared by homogenisation followed by high-speed centrifugation, and characterisation of cloned receptors achieved by radioligand binding.

Preparation of CHO cell membranes

Cell pellets were gently thawed at room temperature, and resuspended in about 20 volumes of ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), 20mM EDTA, 0.2 M sucrose. The suspension was homogenised using an Ultra-Turrax at full speed for 15 sec. The homogenate was centrifuged at 18,000 r.p.m for 20 min at 4°C in a Sorvall RC5C centrifuge. The membrane pellet was resuspended in ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), using an Ultra-Turrax, and recentrifuged at 18,000

r.p.m for 15 min at 4°C in a Sorvall RC5C. The membranes were washed two more times with ice-cold 50 mM Tris salts (pH 7.4 @ 37°C). The final pellet was resuspended in 50 mM Tris salts (pH 7.4 @ 37°C), and the protein content determined using bovine serum albumin as a standard (Bradford, M. M. (1976) Anal. Biochem. **72**, 248-254).

Binding experiments on cloned dopamine receptors

Crude cell membranes were incubated with 0.1 nM [^{125}I] iodosulpride (~2000 Ci/mmol; Amersham, U. K.), 50 mM Tris salts (pH 7.4 @ 37°C), 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$, 0.1% (w/v) bovine serum albumin, in a total volume of 1 ml for 30 min at 37°C. Following incubation, samples were filtered using a Brandel Cell Harvester, and washed three times with ice-cold 50 mM Tris salts (pH 7.4 @ 37°C), 120 mM NaCl, 5 mM KCl, 2 mM $CaCl_2$, 1 mM $MgCl_2$. The radioactivity on the filters was measured using a Cobra gamma counter (Canberra Packard). Non-specific binding was defined as the radioligand binding remaining after incubation in the presence of 100 µM iodosulpride. For competition curves, 14 concentrations (half-log dilutions) of competing cold drug were used.

Competition curves were analysed simultaneously whenever possible using non-linear least-squares fitting procedures, capable of fitting one, two or three site models.

RESULTS

The binding data revealed the existence of two binding sites in both human D_2 and D_3 receptors. The inhibition constant (K_i) for ropinirole at the high affinity site was found to be 1380 nM (n=5) at D_2 and 69.1 nM (n=6) at D_3 receptors. These results indicate that ropinirole binds selectively (20 fold) to human D_3 dopamine receptors.

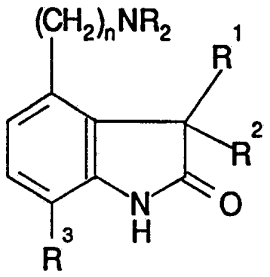
Claims:

1. A selective dopamine D_3 receptor agonist for use in therapy.

2. A selective dopamine D_3 receptor agonist for use in the manufacture of a medicament for use in the treatment of memory disorders.

3. A selective dopamine D_3 receptor agonist for use in the manufacture of a medicament for use in the treatment of sexual dysfunction.

4. The use according to claim 2 or claim 3 in which the selective dopamine D_3 receptor agonist is a compound of the structure (I):



(I)

in which,
each group R is the same or different and is hydrogen or C_{1-4}alkyl;
R^1 and R^2 are the same or different and are each hydrogen or C_{1-4}alkyl; and
n is 1 to 3,
or a pharmaceutically acceptable salt thereof.

5. The compound 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone hydrochloride (INN: ropinirole) for use in the manufacture of a medicament for use in the treatment of memory disorders.

6. The compound 4-(2-di-n-propylaminoethyl)-2-(3H)-indolone hydrochloride (INN: ropinirole) for use in the manufacture of a medicament for use in the treatment of sexual dysfunction.

7. The use of a selective dopamine D_3 receptor agonist other than a compound of structure (I) or a pharmaceutically acceptable salt thereof as described in claim 4, in the manufacture of a medicament for use in the treatment of Parkinson's disease.