Dopamine Receptors on Prefrontal Neurons

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Received for publication on October 16, 1989

Key words: dopamine receptors — dopaminergic neurons — dopamine-recipient neurons — prefrontal cortex — nucleus accumbens

Abnormalities in the cerebral dopaminergic activity are involved in the etiology of schizophrenia (cf. Carlsson, 1988). Recent studies on rodent brain slices revealed that the neurons in the nucleus accumbens which is one of the major structures receiving the mesolimbic dopaminergic fibers are endowed with dopamine D₁ and D₂ (Kebabian and Calne, 1979) receptors (Uchimura et al. 1986; Higashi et al. 1989), whereas that the substantia nigra neurons which synthesize and release dopamine are endowed with dopamine D₂ receptors (Lacey et al. 1988). These studies also demonstrated that activation of the D₁ and D₂ receptors on accumbens neurons produces hyperpolarization and depolarization, respectively (Uchimura et al. 1986; Higashi et al. 1989), while that activation of the D₂ receptors on nigral neurons generates hyperpolarization.

The present study was undertaken to clarify what subtypes of dopamine receptor exist on the prefrontal neurons which receive, similarly to the accumbens neurons, the dopaminergic inputs from the A-10 area. It was also intended to study what kind of responses the prefrontal dopamine receptors produce.

The forebrain of male Wistar rats weighing 150-180g was quickly removed under a light ether anesthesia, and sliced frontally by a vibratome (Oxford) at about

400 μ m intervals. A fresh slice of the prefrontal region was transferred to a recording chamber and completely submerged in a continuously flowing Krebs solution (37°C) gassed with 95% O₂-5% CO₂ (Uchimura et al. 1986). Intracellular recordings were obtained from neurons in and near the Vth layer of the medial prefrontal cortex. Recording electrodes were 3M K-acetate-filled glass micro-pipettes with tip resistances of 40 to 80 M Ω , and connected to a high-input-impedance pre-amplifier (WPI M701). All drugs were applied to the tissue by superfusion. The neurons had resting membrane potentials of -70 to -80 mV and input resistances of 40 to 60 M Ω .

Dopamine actions were studied on 32 neurons. In 21 of these neurons, dopamine (3-10 μ M) reduced or stopped action potential firing and hyperpolarized the membrane by up to 8 mV (Fig. 1). The dopamine-induced hyperpolarization was accompanied by a fall in input resistance. Responses to dopamine took 1-2 min to reach a steady state and following wash-out of dopamine with drug-free solution, at least a further 2-5 min for membrane potential or firing to recover its control level. Hyperpolarizations produced by dopamine were blocked by haloperidol (1 μ M), a well known blocker of D₁ and D₂ receptors, and by R (+)-SCH-23390 (1 μ M;

Fig. 1 Reduction of action potential firing and hyperpolarization of a rat prefrontal neuron caused by dopamine ($3\mu\text{M}$, trace *A*; $10\mu\text{M}$, trace *B*) applied by superfusion (horizontal bar above each trace). Hyperpolarizing electrotonic potential induced by inward current pulses of 0.7 nA , 200 msec at every 3 sec were superimposed. Notice the reduction of tonic pulses during the dopamine-produced hyperpolarization. Both *A* and *B* traces were recorded from the same neuron. Full heights of action potentials were cut off by pen recorder response.

Fig. 2), an antagonist of dopamine D_1 receptors (Itoh et al. 1984).

When the concentration of dopamine added to the superfusing solution was raised to $30\text{--}100\mu\text{M}$, 14 of the 21 neurons showed a biphasic response; a slow depolarization appeared after the initial hyperpolarization. The initial hyperpolarization was slightly larger than those produced by $3\text{--}10\mu\text{M}$ of dopamine. The succeeding depolarization was $2\text{ to }6\text{ mV}$ in amplitude, associated with an increased input resist-

ance, and often accompanied by action potential firing (Fig. 3*A*). The biphasic response was suppressed or eliminated by haloperidol ($1\mu\text{M}$), the initial hyperpolarization by $\text{R}(+)\text{-SCH-23390}$ ($1\mu\text{M}$), and the succeeding depolarization by $(-)\text{-sulpiride}$ ($1\mu\text{M}$) or piquindone ($1\mu\text{M}$), as seen in Fig. 3*B*. Piquindone is a dopamine D_2 antagonist (Olson et al. 1981; Nakajima and Iwata, 1984; Nock et al. 1986) as $(-)\text{-sulpiride}$.

The result suggests that many prefron-

Fig. 2 Elimination of the dopamine-induced hyperpolarization by SCH-23390. Records *A* and *B* were obtained before and 20 min after application of 1 μ M SCH-23390. Record *C* was taken 30 min after washing out the SCH-23390 with a drug-free solution. Horizontal bar above each record indicates superfusion of 10 μ M dopamine. Notice the disappearance of dopamine-hyperpolarization after the SCH-23390 application (*B*) and also the reappearance of dopamine-hyperpolarization after wash out (*C*). Electrotonic potentials induced by inward current pulses of 0.5 nA, 200 msec at every 3 sec were superimposed on each trace. All records were obtained from the same prefrontal neuron.

tal neurons are endowed with both dopamine D₁ and D₂ receptors, activation of which produces hyperpolarization and depolarization, respectively. This is characteristically similar to the accumbens neurons (Uchimura et al. 1986; Higashi et al. 1989), but different from the nigral neurons which are endowed with D₂ receptors only and activation of which generates hyperpolarization instead of depolarization

(Lacey et al. 1988). Since the facts that both the prefrontal and accumbens neurons are dopamine-recipient neurons and that the nigral neurons are dopaminergic ones, the pattern of distribution of dopamine receptors and the polarity of their responses might be dependent on the dopamine producing or recipient nature of the neurons in question.

Fig. 3. Suppression of the dopamine-induced depolarization by piquindone. Records *A* and *B* were obtained before and 20 min after application of piquindone (1 μ M), a dopamine D₂ antagonist. Note the marked reduction of dopamine-induced depolarization and action potential firing 10 min after the piquindone application (*B*). Electrotonic potentials induced by inward current pulses of 0.5 nA, 200 msec at every 3 sec were superimposed on each trace. *A* and *B* records were obtained from the same prefrontal neuron. Dotted lines indicate the control level of membrane potential. Full heights of action potentials were cut off by pen recorder response.

Acknowledgment: This study was supported by a grant from Japan Private School Promotion Foundation.

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