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ORIGINAL INVESTIGATION

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Clozapine and olanzapine, but not haloperidol, reverse cold-induced and lipopolysaccharide-induced cutaneous vasoconstriction

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Abstract *Rationale:* Reduction of body temperature is used as predictor of psychotropic drug action. The cutaneous circulation functions as a heat-loss component of temperature regulation. Clozapine and olanzapine reverse hyperthermia and sympathetically-mediated cutaneous vasoconstriction induced by MDMA (3,4-methylenedioxymethamphetamine, ecstasy), suggesting that these drugs might reverse other forms of sympathetically mediated cutaneous vasoconstriction. *Objectives:* Clozapine and olanzapine were compared with haloperidol with respect to their ability to reverse cold-induced and LPS (lipopolysaccharide)-induced cutaneous vasoconstriction in rabbits. *Methods:* Cutaneous blood flow was measured in conscious rabbits by Doppler ultrasonic flow probe implanted around the central ear artery, and body temperature was measured telemetrically. After control observations, animals were transferred from 26 to 10°C, or LPS (0.5 μg/kg IV) was administered. After 30 min, clozapine, olanzapine or haloperidol was administered and ear pinna blood flow and body temperature were measured for another 30 min. *Results:* Clozapine, in a dose responsive manner (1, 2.5 and 5 mg/kg IV), substantially reversed cold-induced ear pinna vasoconstriction and reduced body temperature. Clozapine (1 mg/kg IV) reversed LPS-induced cutaneous vasoconstriction and reduced the LPS-induced rise in body temperature. Olanzapine had generally similar effects. Haloperidol (1 mg/kg IV in cold experiments and 0.2 mg/kg IV in LPS experiments) did not reverse ear pinna vasoconstriction, or affect body temperature. *Conclusions:* Both clozapine and olanzapine, but not haloperidol, reverse physiologically induced cutaneous sympathetic vasomotor discharge. Because of the close link between psychological function and sympathetic regulation of cutaneous blood flow, similar neuropharmacological mechanisms might underly the cutaneous vasodilating action and the psychotropic actions of atypical antipsychotic drugs.

Keywords Schizophrenia · Cutaneous sympathetic nerve activity · Atypical antipyschotic agents

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Introduction

The ability of a drug to lower body temperature is a physiological property already in use as a predictor of psychotropic drug action (Millan et al. 1993, 1995; Salmi et al. 1994; Salmi and Ahlenius 1996, 1998). Clozapine and olanzapine, atypical antipsychotic agents, reduce body temperature in humans and experimental animals, but there is no consensus concerning mechanisms underlying this effect (Heh et al. 1988; Nash et al. 1988; Menon et al. 1990; Salmi et al. 1994; Millan et al. 1995; Salmi and Ahlenius 1996; Goudie et al. 1999; Oerther and Ahlenius 2000). This may be at least partially because body temperature is a complex variable, encompassing processes affecting heat production and heat exchange with the external environment. Heat exchange depends on the amount of blood circulating through the cutaneous vascular bed, and on the temperature difference between the blood and the environment.

The atypical antipsychotic agents clozapine and olanzapine powerfully inhibit cutaneous sympathetic vasomotor discharge, thereby reversing intense sympathetically-mediated cutaneous vasoconstriction elicited by administration of MDMA (3,4-methylenedioxymethamphetamine, ecstasy) (Pedersen and Blessing 2001; Blessing et al. 2003). The resulting cutaneous vasodilatation contributes to reversal of MDMA-elicited hyperthermia, because dissipation of heat to the environment cools the animal. Pharmacological mechanisms whereby clozapine and

olanzapine act include 5-HT_{1A} (5-hydroxytryptamine$_{1A}$) agonism and 5-HT_{2A} antagonism (Bymaster et al. 1996; Arnt and Skarsfeldt 1998; Meltzer 1999), actions which inhibit sympathetic cutaneous vasomotor discharge so that cutaneous blood flow increases and the body temperature is reduced (Blessing and Seaman 2003; Ootsuka and Blessing 2003; Blessing 2004a).

Such a robust sympathoinhibitory effect suggests that clozapine and olanzapine might also reverse more physiologically induced increases in cutaneous sympathetic vasomotor discharge. Exposing the individual to a cold environment, or administering a pyrogen such as lipopolysaccharide (LPS) increases cutaneous sympathetic vasomotor discharge. The resulting vasoconstriction reduces heat loss, contributing to maintenance of body temperature during cold exposure, and to rise of body temperature in response to pyrogen. These effects are well developed, robust, and readily measurable in the rabbit ear pinna (Grant et al. 1932; Riedel et al. 1972; Stitt 1979; Saigusa 1990; Ootsuka and Blessing 2003; Blessing 2004a).

The present experiments were conducted to determine whether clozapine and olanzapine reverse cutaneous vasoconstriction induced by exposure to cold or by administration of LPS in conscious unrestrained rabbits. Actions of these atypical antipsychotics were compared with those of the conventional antipsychotic haloperidol. Control data, with Ringer treatment following exposure of the rabbit to cold or LPS, were obtained from recent publications from my laboratory (Ootsuka and Blessing 2003; Blessing 2004a).

Materials and methods

Experiments were performed on New Zealand White rabbits (2.5–4 kg), instrumented with a chronically implanted ear pinna Doppler ultrasonic flow probe around the central artery at the base of the ear pinna, and a telemetered temperature probe in the peritoneal cavity (Blessing et al. 2003). Principles of laboratory animal care (http://www.nap.edu/readingroom/books/labrats/) were followed, and all experiments were approved by and conformed with the guidelines issued by the Flinders University Animal Welfare Committee on the ethical use of animals. Ear pinna blood flow and body temperature were measured in conscious unrestrained animals in a cage maintained at 26°C. In some rabbits, superior mesenteric blood flow was also measured (Doppler flow probe). Control measurements of ear pinna blood flow and body temperature were made for 20 min and then the animal was transferred to a cage maintained at 10°C (cold exposure experiments), or the animal was kept in the 26°C cage and LPS (0.5 μg/kg IV) was administered (pyrogen experiments). Either clozapine or olanzapine was administered after the experimental treatment had increased cutaneous sympathetic nerve activity and lowered ear pinna blood flow.

All drugs were administered intravenously into the marginal ear vein contralateral to the implanted ear pinna Doppler probe. Lipopolysaccharide (LPS) was purchased from Sigma Chemical Company (Castle Hill, Australia). Clozapine (ampoules of 50 mg/2 ml) was kindly supplied by Novartis Pharmaceuticals (Sydney, Australia). Olanzapine (kindly supplied by Eli Lilly and Co., Indianapolis, Ind., USA) was dissolved in acidified Ringer and dimethyl sulfoxide. Haloperidol solution (5 mg/ml) was purchased from Sigma Pharmaceuticals (Clayton, Australia).

Data were analysed with Chart software, IgorPro (WaveMetrics, Lake Oswega, Ore., USA) and Statview (SAS Institute, Cary, N.C., USA) software. Conscious unrestrained rabbits have variable "baseline" pulsatile ear pinna blood flow signals, with episodic sudden falls from high levels to near zero levels, and gradual return to the previous high level within approximately 1 min (Yu and Blessing 1997). For each animal in a particular condition, we used Chart software to measure mean ear pinna blood flow and body temperature averaged over a 2-min period when the baseline flow was not affected by these alerting responses (Ootsuka and Blessing 2003). Temperature and Doppler signals were processed and digitised (2 and 40 Hz, respectively) using PowerLab and Chart software (ADInstruments, Sydney, Australia) and a Macintosh computer. Group data were analysed by repeated measures analysis of variance, with comparison of particular post-injection values with each other and with the corresponding control values. Factorial analysis of variance was used to compare values from corresponding time points in vehicle and drug-treated animals. Fisher's protected *t*-test was used to determine significant differences, with the significance threshold set at the 0.05 level.

Results

Changes in ear pinna blood flow and body temperature induced by transferring the rabbit from the cage maintained at 26°C to a cage maintained at 10°C, or by administration of LPS (0.5 μg/kg IV) were similar to those previously documented (Ootsuka and Blessing 2003; Blessing 2004a). Ear pinna blood flow fell to near zero levels within 15 min of transfer to the 10°C cage, and within 15 min of administration of LPS. Body temperature remained constant or increased slightly after exposure to cold, and increased after administration of LPS. Without active pharmacological treatment, ear pinna blood flow remained at a very low level for the duration of the observation period used in the present experiments.

Cold-induced cutaneous vasoconstriction

Clozapine

The ear pinna blood flow Doppler signal fell to near zero levels within 15 min of transfer from the cage maintained at 26°C to the cage maintained at 10°C (Fig. 1); 30 min

after transfer flow was 3±1 cm/s, significantly less (P<0.01, n=6) than the pre-transfer control value of 55 ±8 cm/s. Administration of 0.1 mg/kg clozapine did not significantly change mean ear pinna blood flow. Administration of 5 mg/kg of clozapine increased ear pinna blood flow to 56±6 cm/s (P<0.01, n=7) within 5–10 min, with the increase lasting for the duration of the 30-min observation period (Fig. 1 top two panels). In additional experiments using 1.0 and 2.5 mg/kg doses of clozapine in separate groups of rabbits transferred to a 10°C cage the cutaneous vasodilatation induced by clozapine was shown to be dose dependent (linear regression for log dose P<0.0001, r=0.80, see Fig. 1 inset for mean values).

During the 30 min after administration of clozapine 5 mg/kg, body temperature decreased by 0.9±0.2°C (P<0.01, n=6), with the hypothermic effect being dose dependent (linear regression for log dose P<0.01, r=0.46).

Clozapine did not increase mesenteric blood flow when administered 30 min after transfer of the rabbit to the 10°C cage (23±3 cm/s at 26°C, 29±4 cm/s 30 min after transfer to 10°C and 18±4 cm/s after clozapine 5 mg/kg, P>0.05, n=4).

Olanzapine

Exposure to cold caused ear pinna blood flow to fall to near zero levels within 15 min. Administration of olanzapine (0.1 mg/kg) did not change the ear pinna blood flow signal (3±1 before olanzapine and 4±1 cm/s 5 min after olanzapine, P>0.05, n=7). Administration of 0.5 mg/kg olanzapine 30 min after exposure to the 10°C environment slightly increased the ear pinna Doppler signal from 2±1 to 7±2 cm/s (P<0.05, n=6). In other rabbits exposed to a 10°C environment for 30 min, administration of 2.5 mg/kg olanzapine increased the ear pinna Doppler signal from 1±1 to 52±10 cm/s (P<0.01, n=6) within 5–10 min, a value equivalent to 44±12% of the signal level recorded before cold exposure. The increase lasted for approximately 20 min, after which time ear pinna blood flow again fell to near zero levels. The effect of olanzapine in reversing the cold-induced fall in ear pinna blood flow was dose dependent (linear regression for log dose P<0.01, r=0.79).

Administration of olanzapine 30 min after transfer to the 10°C cage caused body temperature to fall, so that 30 min after the 2.5 mg/kg dose the temperature fell by 2.0±0.2°C

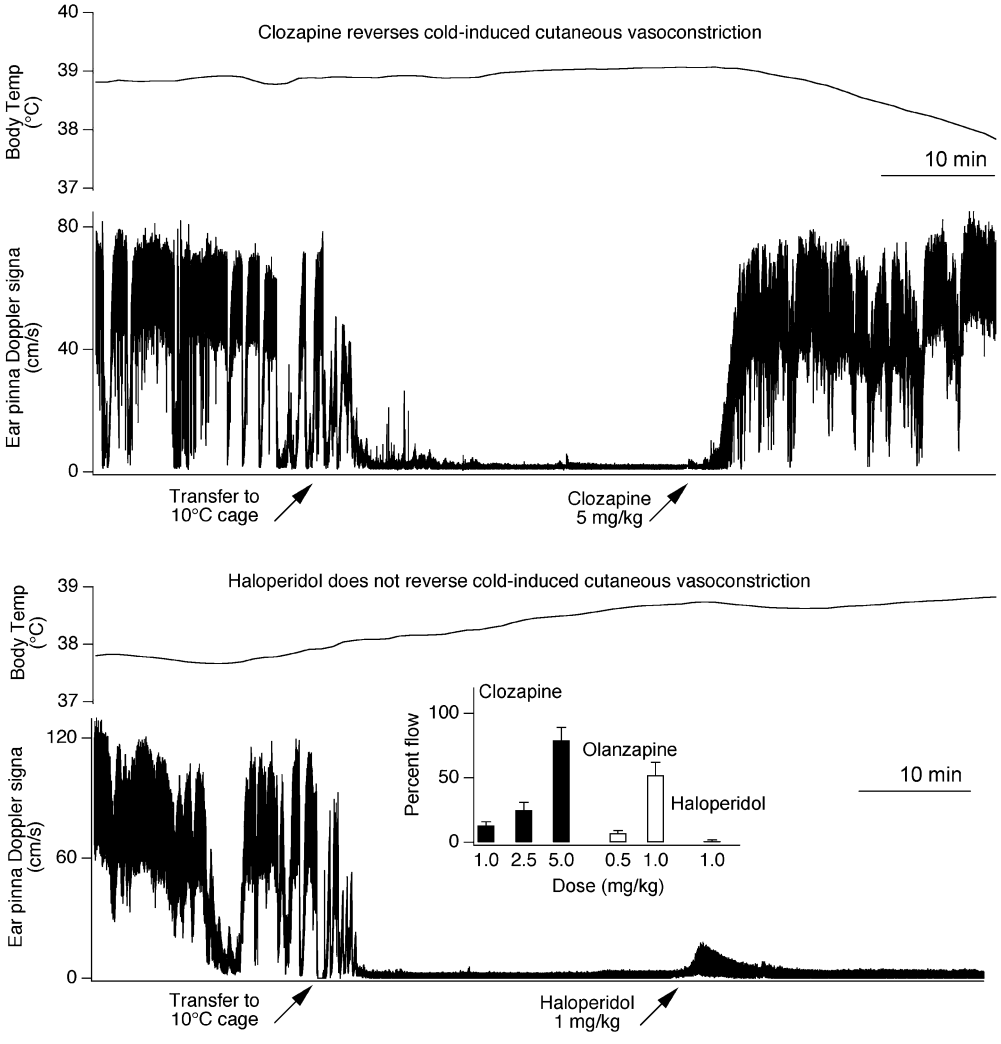

Fig. 1 Experimental records of body temperature and ear pinna blood flow (Doppler signal) obtained from two separate rabbits. Rabbits were initially maintained in cage at 26°C and then transferred to a 10°C cage (*first arrow*). After approximately 30 min, when ear pinna blood flow was at near zero levels, either 5 mg/kg clozapine (*top two panels*) or 1 mg/kg haloperidol (*bottom two panels*) was administered intravenously. *Inset* shows means and standard errors for dose–response experiments and for the effect of haloperidol 1 mg/kg. In the *inset*, the *vertical axis* (percent flow) refers to the percentage ratio of the Doppler signal recorded 5–10 min after administration of drug compared with the control value recorded in the 26°C cage

(P<0.01, n=6). The effect of olanzapine in reversing the cold-induced fall in ear pinna blood flow was dose dependent (linear regression for log dose P<0.001, r=0.87).

Haloperidol

Exposure to cold caused ear pinna blood flow to fall to near zero levels within 15 min. Administration of haloperidol (1 mg/kg) 30 min after transfer of the rabbit to the 10°C cage occasionally led to a transient (1–2 min) small increase in the ear pinna Doppler flow signal (Fig. 1, bottom panel), but the signal was unchanged 5 min after administration of the haloperidol signal (1±1 before and 2 ±1 cm/s 5 min after haloperidol, P>0.05, n=6). Administration of haloperidol 30 min after transfer to the 10°C cage did not affect body temperature (Fig. 1), so that 30 min after administration of the drug the difference in body temperature between the pre-injection value and the 30-min post-injection value was +0.02±0.10°C (P>0.05, n=6).

LPS-induced cutaneous vasoconstriction

Clozapine

Ear pinna blood flow fell to near zero levels within 15 min of administration of LPS (0.5 μg/kg). Administration of 0.1 mg/kg clozapine 20 min after LPS did not change ear pinna blood flow. Administration of 1.0 mg/kg clozapine 30 min after LPS caused the ear pinna blood flow signal to increase from 3±1 to 38±8 cm/s (P<0.01, n=6), with the increase being maintained for the duration of the 60 min post-LPS observation period. In animals treated with clozapine (0.1 then 1.0 mg/kg) the rise in body temperature 60 min after administration of LPS (0.7±0.5°C, n=5) was less (P<0.05) than the corresponding rise in animals given LPS and then treated with vehicle (+1.8±0.2°C, n=7).

Olanzapine

Ear pinna blood flow again fell to near zero levels within 15 min of administration of LPS (0.5 μg/kg). Administration of 0.1 mg/kg olanzapine 20 min after LPS did not significantly change ear pinna blood flow. Administration of 1.0 mg/kg olanzapine 30 min after LPS caused the ear pinna blood flow signal to increase from 2±1 to 43±7 cm/s (P<0.01, n=6), with the increase being maintained for the duration of the 60-min post-LPS observation period (Fig. 2). Olanzapine (0.1 then 1.0 mg/kg) prevented the rise in body temperature occurring in vehicle-treated animals 60 min after administration of LPS (−0.1±0.2°C after olanzapine, n=6, and +1.8±0.2°C after vehicle, n=7, P<0.01).

Haloperidol

Administration of LPS (0.5 μg/kg) caused ear pinna blood flow to fall to near zero levels within 15 min as previously observed. Administration of haloperidol (0.2 mg/kg) 30 min after LPS did not change the ear pinna Doppler signal when measured 5 min after injection of haloperidol (2±1 cm/s before haloperidol and 3±1 cm/s 5 min after haloperidol, P>0.05, n=6), or at any time during the 30-min post-haloperidol observation period. Similarly, ad-

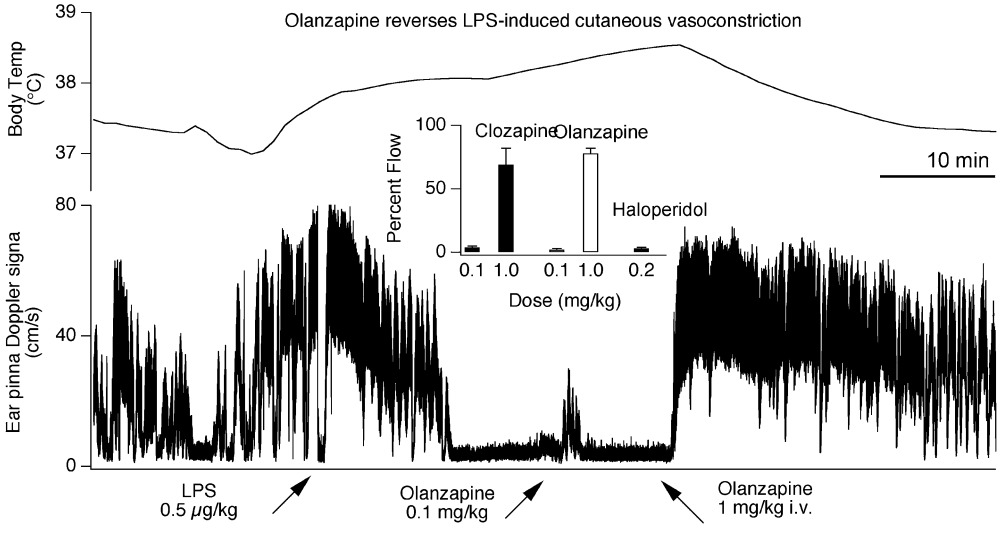

Fig. 2 Experimental records of body temperature and ear pinna blood flow (Doppler signal) obtained from one rabbit maintained in cage at 26°C. After a control period, 5 μg/kg lipopolysaccharde (LPS) was administered intravenously (*first arrow*). After approximately 20 and 30 min, when ear pinna blood flow was at near zero levels, 0.1 and then 1 mg/kg olanzapine (*second and third arrows*) was administered intravenously. *Inset* shows means and standard errors for dose–response experiments and for the effect of haloperidol 0.2 mg/kg. In the inset, the *vertical axis* (percent flow) refers to the percentage ratio of the Doppler signal recorded 5–10 min after administration of drug compared with the control value recorded in the 26°C cage

ministration of haloperidol (0.2 mg/kg) 30 min after LPS did not decrease the LPS-induced rise in body temperature (+1.5±0.3°C after haloperidol, n=6, and +1.8±0.2°C after vehicle, n=7, P>0.05) measured 60 min after LPS.

Discussion

Clozapine and olanzapine reversed cutaneous vasoconstriction induced either by exposing the rabbit to a cold environment or by administering the pyrogen LPS. Haloperidol did not reverse the vasoconstriction. Clozapine and olanzapine also lowered body temperature when administered in the cold environment, and reduced or abolished the rise in body temperature normally observed after administration of LPS. Given that clozapine substantially reduces cutaneous sympathetic vasomotor nerve discharge (Blessing et al. 2003), it is reasonable to assume that the cutaneous vasodilatation elicited in the present experiments reflects drug-induced inhibition of sympathetic cutaneous vasomotor nerve discharge, an effect mediated centrally rather than via effects on the vasculature.

Restoration of cutaneous blood flow was substantial, toward pre-stimulus values. Such a dynamic flow range in the cutaneous bed is unlikely to be associated with similar dilatation of multiple vascular beds, and indeed clozapine was shown not to change mesenteric blood flow when administered at 10°C in the present study. In conscious rats, clozapine does acutely lower arterial pressure when administered as in the present experiments, but the effect is modest even at a dose of 5 mg/kg (van den Buuse 2003).

Neural and pharmacological mechanisms underlying cutaneous sympathoinhibitory actions of clozapine and olanzapine; comparison with haloperidol

Clozapine and olanzapine have complex receptor interactions that include effects on dopamine and 5-HT receptors (Bymaster et al. 1996; Hartman et al. 1996; Arnt and Skarsfeldt 1998; Meltzer 1999).

Dopamine receptors have been implicated in body temperature regulation, without a consensus regarding the specific contributions of the individual receptors (Millan et al. 1993, 1995, 2000; Salmi et al. 1994; Salmi and Ahlenius 1996, 1998; Oerther and Ahlenius 2000; Eltayb et al. 2001; Chaperon et al. 2003). In the present study, haloperidol was used at doses of 1 mg/kg in the cold exposure experiments and at 0.2 mg/kg in the LPS experiments. At higher doses (2.5 mg/kg), haloperidol reduces body temperature in rabbits (Vybiral and Jansky 1989). However, this dose is associated with extrapyramidal rigidity and it is higher than maximal doses of haloperidol (approximately 0.2 mg/kg) recommended for antipsychotic effects in humans (Geddes et al. 2000), and for behavioural effects in experimental animals (Barrett 1982; Snow and Horita 1982; Christensen et al. 1984; van den Buuse 2003). Given that the affinity of haloperidol for dopamine D_2 receptors is approximately 50–200 times that of clozapine (Meltzer et al. 1989; Bymaster et al. 1996; Kulagowski et al. 1996; Arnt and Skarsfeldt 1998; Weiner et al. 2001), it is unlikely that D_2 receptor antagonism is responsible for the cutaneous vasodilatation and reduction of body temperature observed in the present study. Haloperidol also has a reasonably high affinity for dopamine D_3 receptors (Hartman et al. 1996; Kulagowski et al. 1996), and it is therefore important to note that activation of D_3 receptors (Millan et al. 1995; Audinot et al. 1998; Eltayb et al. 2001; Chaperon et al. 2003) lowers body temperature, suggesting the possibility that these receptors may also be involved in the CNS regulation of the cutaneous circulation.

Interaction with particular subtypes of 5-hydroxytryptamine (5-HT) receptors in the central nervous system may well be important for the cutaneous vasodilatory effects of clozapine and olanzapine. It is well established that drugs acting at these receptors markedly alter body temperature, and the hypothermic property of 5-HT_{1A} agonists has been even proposed as a model for predicting the likely clinical effectiveness of proposed psychotropic agents (Hjorth 1985; Gudelsky et al. 1986; Martin et al. 1992; Millan et al. 1993; Salmi and Ahlenius 1998; Cryan et al. 1999). Buspirone, a 5-HT_{1A} partial agonist has anxiolytic properties (Peroutka et al. 1989), and both 5-HT_{1A} agonism and 5-HT_{2A} antagonism are considered important pharmacological mechanisms in the ability of clozapine and olanzapine to alleviate psychiatric symptoms (Meltzer 1999; Millan 2000).

Drugs interacting with 5-HT_{1A} and 5-HT_{2A} receptors also affect sympathetic cutaneous vasomotor outflow. Activation of CNS 5-HT_{1A} receptors inhibits cutaneous sympathetic vasomotor nerve activity, reversing and preventing cutaneous vasoconstriction initiated by exposure to cold (Ootsuka and Blessing 2003) or to the pyrogenic action of lipopolysaccharide (Blessing 2004a). Activation of CNS 5-HT_{2A} receptors is associated with selective excitation of cutaneous sympathetic vasomotor nerve activity, with consequent intense vasoconstriction in the cutaneous vascular bed (Blessing and Seaman 2003). Clozapine and olanzapine are well-documented 5-HT_{1A} receptor agonists and 5-HT_{2A} receptor antagonists (Meltzer 1999; Millan 2000). Clozapine has previously been shown to reduce hyperthermia induced by 5-HT_{2A} agonists (Nash et al. 1988). Clearly, interactions with these 5-HT receptors could contribute to the cutaneous vasodilatation observed in the present experiments.

Link between cutaneous sympathetic discharge and psychological function

The cutaneous sympathoinhibitory vasomotor effects of clozapine and olanzapine could be linked with their effects on psychological function. We go pale with fright and clozapine substantially reduces this effect (Blessing 2004b). Alerting-related episodes of cutaneous vasoconstriction are closely integrated with alerting-related chang-

es in the EEG (Yu and Blessing 1997). Intact neuronal function within the amygdala is essential for the occurrence of alerting-related falls in cutaneous blood flow in rabbits (Yu and Blessing 1999, 2001), consistent with the known role of the amygdala in the expression of both the somatic and the autonomic components of emotional responses (LeDoux 1994). In humans, anticipation of external threat may also activate cutaneous sympathetic vasomotor activity (Delius et al. 1972) and patients judged to be clinically anxious have been shown to have vasoconstricted extremities (Ackner 1956). Inhibition of alerting-related cutaneous vasoconstriction by clozapine has been documented in schizophrenia (Zahn and Pickar 1993).

Conclusion

Clozapine and olanzapine both have a robust inhibitory action on cutaneous sympathetic vasomotor discharge, an action that contributes to the tendency of these agents to lower body temperature. Elucidating the CNS mechanisms underlying this physiological effect could illuminate the psychotherapeutic actions of these drugs. The robust cutaneous vasomotor sympathoinhibitory action described for clozapine and olanzapine might prove useful in screening new potential atypical antipsychotic agents.

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