Layer upon layer: thermoregulation in schizophrenia

Terence W.H. Chong, David J. Castle

Abstract

A review of the relevant published literature regarding disorders of thermoregulation in people with schizophrenia was undertaken. This entailed a search of the Medline and PsychINFO databases to 28th May 2003 using the search terms “schizophrenia and thermoregulation” and “schizophrenia and temperature”. The relevant articles as well as secondary references were reviewed. It has generally been shown that, when compared with controls, people with schizophrenia exhibit dysregulation of body temperature including different baseline temperatures; abnormal daily range of temperatures and diurnal variation showing an earlier peak; an impaired ability to compensate to heat stress; and compensating more effectively to cold stress. This may be intrinsic to the syndrome of schizophrenia but is potentially confounded by the administration of neuroleptic medication. The underlying cause is likely to be a combination of “peripheral” and “central” mechanisms of thermoregulation. Further study is required to delineate clearly the quality and magnitude of the temperature dysregulation as well as elucidating its mechanism(s). This could further our understanding of the mechanism underlying the syndrome of schizophrenia.

Keywords: schizophrenia; temperature; thermoregulation; neuroleptic medication

1. Introduction

Many clinicians have noticed a predilection of patients with schizophrenia to cover themselves in layer upon layer of clothing even in the height of summer. Even Shakespeare had noticed this phenomenon, describing Edgar, with many symptoms of schizophrenia, in King Lear, to be dressed in this manner (Altschuler, 1999). Furthermore, Arnold et al. (1993) described redundant clothing as a readily observable marker for schizophrenia.

Meanwhile, schizophrenia has been associated with conditions of dysregulation of temperature such as the neuroleptic malignant syndrome (NMS). NMS most commonly occurs with the use of antipsychotic agents, and has a clinical picture that may include diaphoresis, fever/hyperthermia, hypertension/auto-
nomic instability, tachycardia, incontinence/obstruction, muscular rigidity, confusion, agitation, altered consciousness, and raised creatinine kinase and leucocytosis (Taylor et al., 2001).

We reviewed the literature regarding disorders of thermoregulation in people with schizophrenia with the aim of furthering our understanding of the mechanisms underlying the syndrome of schizophrenia. Thus, this paper aims to review the relevant published literature, critically appraises it, and offers an interpretation of the pertinent findings.

2. Methods

We conducted a search of the Medline and PsychINFO databases to 28th May 2003, using the search terms, “schizophrenia and thermoregulation” and “schizophrenia and temperature”. Secondary references from these selected articles were also reviewed.

3. Results

The total number of studies identified was 19. Two very early articles were unable to be traced, and were omitted from further consideration. The remaining studies clustered into two main historical groups, viz. 1930–1950s (7 studies), and 1970s to current (10 studies). The early studies have a number of methodological shortcomings including lack of standardised and validated diagnostic criteria; selection bias (with most subjects being from institutions); usually small subject numbers; lack of blinding; lack of information regarding matching, or poorly undertaken matching of patients with controls; and the difficulty in standardising tests and conditions, such as ambient temperature, with the technology from the era. However, these studies do have the virtue of not having the potential confounding variable of neuroleptic administration. Consequently, we divided our report into two parts: Table 1 summarises studies from the pre-neuroleptic era, and Table 2 summarises the more recent studies. Neuroleptics were beginning to be used in the mid-1950s, therefore pre-1955s studies were considered as a group, whilst the more recent, more methodologically robust studies that may have the confounding variable of neuroleptic administration, were considered separately.

3.1. Pre-neuroleptic era

Studies from the pre-neuroleptic era are shown in Table 1. These studies investigated all or some of the following:

1. Baseline body temperature;
2. Range of temperature and diurnal variation. Range of temperature was typically measured by taking regular temperature readings during the day and subtracting the lowest from the highest reading, whilst diurnal variation was typically measured by calculating the difference between the morning and nighttime body temperatures;
3. Differential between core and peripheral temperature; this was measured as the difference between rectal and oral temperature (two studies) and between oral and axilla temperature (one study);
4. Heat stress; and
5. Cold stress.

Heat stress and cold stress were measured using three different methods. Gottlieb and Lindner (1935) and Freeman (1939) used heating and air conditioning to achieve hot or cold air temperatures to create heat and cold stress. In contrast, Cameron (1934) and Buck et al. (1950, 1951) achieved heat and cold stress by submerging subjects in baths in which the water temperature was maintained at pre-determined hot or cold temperatures for fixed periods of time. Finally, Freeman (1940) administered 300 mg of dinitrophenol to subjects to increase their metabolic rate and thus create a heat stress.

(1) Baseline temperature was compared in patients with schizophrenia and controls in the studies of Cameron (1934) and Buck et al. (1950). Both found that baseline temperature was lower in patients than controls. However, the chart in the paper by Cameron (1934) reveals that the greatest temperature difference between the groups was 0.2 °F, whilst Buck et al. (1950) did not quote the magnitude of the difference at all. Both studies were performed by multiple measurements during the day in an environment...
where variability in room temperature would inevitably have occurred. In contrast, Freeman (1940) found no difference in PR baseline temperature between patients and controls, but found that the control group’s skin temperature increased by more than the patient group’s in their “neutral environment” (30 °C and 20% humidity).

(2) Range of temperature and diurnal variation was investigated only by Buck et al. (1950). The study showed less diurnal variation in temperature in the patient group than in controls, with desynchrony in circadian peaks of temperature. Longer duration of illness correlated with less dysregulation of temperature (patients having been arbitrarily divided into psychosis of 4 years’ duration or less, and psychosis of more than 4 years’ duration).

(3) Differential between central and core temperature: Cameron (1934) and Buck et al. (1955) showed that patients had a wider temperature differential than controls, suggesting that patients have impaired ability to lose heat via the periphery through vasodilatation, as this would have altered the differential between core and peripheral temperatures. However, Gottlieb and Lindner (1935) found that the differential was narrower in the patient group than their control group.

(4) Heat stress was examined in five studies. Of these, only two studies reported a difference between patients and controls. Gottlieb and Lindner (1935) found that patients’ temperatures failed to accommodate to heat stress to the same extent as controls, whilst Freeman (1940) found no difference in PR temperature, but found that the control group had a

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### Table 1
Pre-neuroleptic era studies

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>No. of controls</th>
<th>Duration, frequency and route of temperature measurements</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cameron (1934)</td>
<td>50</td>
<td>50</td>
<td>3 days: hourly PO/PA</td>
<td>• Baseline temperature lower in patients</td>
</tr>
<tr>
<td></td>
<td>25</td>
<td>25</td>
<td>60 min</td>
<td>• Patients showed less heat loss/vasodilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 min: 3 minutely PO</td>
<td>• Heat stress: no difference</td>
</tr>
<tr>
<td>Gottlieb and Lindner</td>
<td>26</td>
<td>16</td>
<td>3.5 h: 0.5 hourly PR/PO</td>
<td>• Cold stress: patients showed greater increase in temperature</td>
</tr>
<tr>
<td>(1935)</td>
<td></td>
<td></td>
<td></td>
<td>• Patients showed less heat loss/vasodilation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Heat stress: patients showed greater increase in temperature</td>
</tr>
<tr>
<td>Freeman (1939)</td>
<td>20</td>
<td>20</td>
<td>2.5 h: 0.5 hourly skin/PR</td>
<td>• Heat stress: no difference</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>30</td>
<td>7.5 h: 0.5 hourly skin/PR</td>
<td>• Cold stress: patients showed greater decrease in skin temperature</td>
</tr>
<tr>
<td>Freeman (1939)</td>
<td>20</td>
<td>20</td>
<td>Skin/PR</td>
<td>• Baseline skin temperature higher in controls</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Heat stress: controls showed greater increase in skin temperature</td>
</tr>
<tr>
<td>Buck et al. (1950)</td>
<td>40 (38 male, 2</td>
<td>10</td>
<td>4 days: 4 hourly PR</td>
<td>• Baseline temperature lower in patients</td>
</tr>
<tr>
<td></td>
<td>female)</td>
<td></td>
<td></td>
<td>• Temperature range and diurnal change greater in controls, but variation of modal temperature greater in patients</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td></td>
<td>3 h: 15 minutely PR</td>
<td>• Heat stress: no difference</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td></td>
<td>3 h: 15 minutely PR</td>
<td>• Cold stress: controls showed greater decrease in temperature</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Increasing disorder of thermoregulation with increasing illness severity</td>
</tr>
<tr>
<td>Buck et al. (1951)</td>
<td>40</td>
<td></td>
<td>4 days: 4 hourly PR then 6 weeks post-lobotomy</td>
<td>• Greater diurnal change post-surgery</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td></td>
<td>3 h, 15 minutely PR</td>
<td>• Heat stress: no difference</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>• Cold stress: patients closer to controls post-surgery</td>
</tr>
<tr>
<td>Buck et al. (1955)</td>
<td>14 (12 male, 2</td>
<td>10</td>
<td>4 days: 4 hourly PO/PR</td>
<td>• Patients showed less heat loss/vasodilation</td>
</tr>
<tr>
<td></td>
<td>female)</td>
<td></td>
<td></td>
<td>• Differential diminished post surgery</td>
</tr>
</tbody>
</table>

Key: PO = per oral, PR = per rectum, PA = per axilla.
greater increase in skin temperature than the patient group (2.2 cf. 1.3 °C, respectively).

(5) Cold stress was investigated in three studies. Of these, Cameron (1934) found that the patient group had a smaller decrease in body temperature under cold stress than the control group. Buck et al. (1950) found that the patient group was able to compensate more effectively than the control group, as they tended to maintain a comparatively higher body temperature under cold stress. Freeman (1939) found no change in core temperature (but lower skin temperature) in patients, possibly implying more marked vasoconstriction in patients.

Buck et al. (1955) took their findings further, performing a repeat study comparing the differential of core and peripheral temperatures in patients with schizophrenia before and after pre-frontal lobotomy. They found that post-lobotomy, the patient group moved towards the control group with regard to cold stress response and differential between core and peripheral temperature, and that increased derangement of thermoregulation correlated with shorter du-

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>No. of controls</th>
<th>Duration, frequency and route of temperature measurements</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morgan and Cheadle (1976)</td>
<td>51 (10 male, 21 female)</td>
<td>33 (21 male, 17 female)</td>
<td>2 days: 1–2 hourly PO</td>
<td>• Baseline temperature greater in patients • Earlier temperature peak for patients • No difference in baseline temperature</td>
</tr>
<tr>
<td>Douglass and Toogood (1987)</td>
<td>16</td>
<td>38 (21 male, 17 female)</td>
<td>Tympanic/Skin</td>
<td>• Heat stress: patients accommodated faster • Patients showed greater increase in skin temperature, less sweat response, and no difference in skin flush • Non-significant correlation between illness acuity and degree of temperature compensation • Haloperidol and clozapine both associated with lower temperatures, the effect being greater with clozapine</td>
</tr>
<tr>
<td>Heh et al. (1988)</td>
<td>8 male in-patients</td>
<td></td>
<td>15 weeks: thrice daily PO</td>
<td>• Baseline temperature higher in patients, with a non-significant lowering of temperature after treatment • No correlation of temperature with pulse peaks (i.e., desynchrony) • Circadian profiles same in all groups • Neuroleptic group had higher mean serum noradrenalin and adrenaline levels • Daily mean TSH lower in both patient groups, and T3 non-significantly lower in both patient groups • Daily means of T4 and cortisol same in all groups</td>
</tr>
<tr>
<td>Madjirova et al. (1995)</td>
<td>146 in-patients</td>
<td></td>
<td>16 h: hourly</td>
<td>• Earlier circadian peak in patients • Baseline temperature higher in patients • Within 24 h drug administration, patient and control groups showed no difference • Skin temperature lower in patients, but greater increase with heat stress • Impaired heat loss/vasodilation or drug effect • Patients showed higher baseline temperature, and greater increase with heat stress • Baseline temperature higher in patients</td>
</tr>
</tbody>
</table>
ration of psychosis. Upon further stratification, this result was found to be significant only in the group with psychosis of 4 years’ duration or less as the more chronic group tended to behave similarly to the control group.

3.2. Later studies

Table 2 summarises studies of thermoregulation conducted on patients with schizophrenia and controls during the neuroleptic era.

(1) Baseline temperatures: The studies of Morgan and Cheadle (1976), Madjirova et al. (1995), Shiloh et al. (2000, 2001, 2003) showed that patients had higher baseline temperatures than controls, but Douglass et al. (1987) found no difference between patients and controls in this regard. Furthermore, Shiloh et al. (2003) showed that apart from the patient group having a corneal temperature that was 1.55 °C higher (p = 0.005), the corneal temperature also had a positive correlation with their severity of symptoms as assessed by the Brief Psychiatric Rating Scale (BPRS) (Overall and Gorham, 1961) score (r = 0.82, p = 0.024). In contrast, the study of Hermesh et al. (2000) showed that patients had lower baseline temperatures than controls. The medication status of patients in these studies was inconsistent, with some being on neuroleptics and some having had a washout period of 24 h or several weeks.

(2) Circadian rhythms: Denisov et al. (1999) and Morgan and Cheadle (1976) confirmed the historical findings that patients had altered circadian temperature variation, both finding that the circadian peaks occurred earlier in the day for the patient group. Madjirova et al. (1995) expanded on this finding, demonstrating that the patient group also had a desynchronous relationship between circadian pulse temperature peaks. In contrast, Rao et al. (1995) found no difference in the circadian rhythms of body temperature between controls and patients, whether treated with neuroleptics or drug-free.

(3) Heat stress tests: In a test of response to heat stress, Hermesh et al. (2000) had subjects walk on a motorised treadmill for two 50 min sessions in a chamber of 40% humidity and 40 °C temperature. They showed that patients on antipsychotic medication had lower initial skin temperature, but demonstrated a faster rate of skin temperature increase, and also a greater increase in core temperature, than controls. Furthermore, Shiloh et al. (2001) employed the same methodology and medication-free patients, also showing that the patients had higher baseline and exertion related per rectal temperatures. In contrast, Douglass and Toogood (1987) had subjects drink 5 ml/kg of 50 °C water as a heat stress. They showed that a medication-free patient group accommodated faster to heat stress than controls, but could not demonstrate a mechanism for this either through vasodilation or sweating. These results contrast with the majority of historical studies of drug-free patients who demonstrated no exaggeration in response to heat stress (see above). The reason for this discrepancy is not clear, but may imply that neuroleptics have a role in impairing heat tolerance or in fact that methodologically, exercise induced heat stress invokes different thermoregulatory responses, compared with passive stresses via heating or water baths.

(4) Effects of medication: Shiloh et al. (2000) compared medicated and non-medicated patients with schizophrenia showing that non-medicated patients had higher basal temperatures than medicated patients, and that these normalised with medication. In contrast, Douglass and Toogood (1987) compared non-medicated patients with controls and showed no difference in baseline temperatures.

4. Synopsis

Although some of the data are conflicting, and the role of antipsychotic medication is not confirmed, it appears that people with schizophrenia tend to exhibit some degree of dysregulation of temperature including:

- Baseline body temperature was demonstrated to be higher in patients than controls in recent studies. However, these studies maybe complicated by the confounding factor of neuroleptics. In contrast, most older pre-neuroleptic studies showed that patients had lower baseline body temperatures than controls. In addition, one study demonstrated that patients newly commenced on neuroleptics had baseline temperatures that became the same as those already on neuroleptics fairly quickly.
- Abnormal daily range of temperature and diurnal variation, generally showing an earlier peak.
• Four studies demonstrated impaired ability to lose heat, including two more recent ones. One study showed the opposite, whilst others demonstrated no difference.
• Patients were shown to be less affected by cold stress than controls in two early studies; such studies have not been repeated in more recent times.

5. Discussion

The control of body temperature is a homeostatic balance between heat production and heat loss. Heat production is a principal by-product of metabolism, and the metabolic rate of the body is determined by the basal metabolic rate; extra metabolism caused by muscle activity; hormones such as thyroxine; the sympathetic nervous system; and increased cellular chemical activity. This is balanced by heat loss which is determined by how rapidly heat can be transferred from its production site in the body core to the periphery, and how rapidly it can be transferred from skin to the surroundings (Guyton and Hall, 2000).

The role of neurotransmitters in thermoregulation has been investigated in a number of studies. Lovett Doust et al. (1973) found that increasing noradrenaline levels in the brain through administration of oral L-tryptophan in seven subjects lowered body temperature, whilst co-administration with a monoamine oxidase inhibitor (MAOI) tends to favour the accumulation of serotonin in the brain, raising temperatures. Furthermore, Lee et al. (1992) showed that the 5HT1c/5HT2 agonist MK212 did not cause a greater increase in temperature in 23 patients with schizophrenia, than in 22 controls. Evidence for the central dopaminergic system acting in a physiological role in mediating heat loss was presented in a review by Lee et al. (1985); they demonstrated that both the hypothalamic and nigral dopaminergic systems influence thermoregulation via interaction with other components of the central nervous system.

Whilst the evidence presented here leads us to conclude that there is dysregulation of temperature in patients with schizophrenia, the hypotheses of an underlying biochemical or physiological mechanism for this are much less conclusive. Collectively, the studies investigating thermoregulation in schizophrenia that have a biochemical slant have focussed on dopamine, prostaglandins and niacin. Furthermore, most theories concerning dysregulation of temperature in schizophrenia canvass a dichotomy of opinion implicating either central or peripheral biochemical disturbances; and implicating either medications, or the illness itself. The discussion that follows is divided into peripheral and central mechanisms for simplicity. However, it is acknowledged that this division is somewhat “unphysiological” as the peripheral and central arms of thermoregulation are inexorably linked, e.g. in the “fight, flight, fright response” central signals instruct the sympathetic nervous system to vasoconstrict peripheral vasculature.

5.1. Peripheral mechanisms

Boschi et al. (1987) examined the effect of 12 neuroleptics from five classes (phenothiazines, butyrophenones, benzamides, thioxanthenes and diphenylbutylpiperidines) on rectal temperature in mice. They demonstrated that all neuroleptics, apart from the benzamides, induced a dose-dependent decrease in rectal temperature when administered intraperitoneally, but not intracerebroventricularly. This implies that the hypothermic action is more likely to be mediated by a peripheral mechanism. However, this implication must be tempered by the fact that most neuroleptics cross the blood–brain barrier, and thus intraperitoneal administration, which gets absorbed into the vasculature, may result in lower, the same or possibly even higher “central” concentrations of neuroleptics than intracerebroventricular administration. Nevertheless, when phenylephrine, a peripherally acting α adrenoceptor agonist was administered, the hypothermic effect of both chlorpromazine and haloperidol was attenuated, possibly suggesting a role that α adrenoceptor blockade peripherally by neuroleptics may contribute to their hypothermic effect.

Horrobin (1980) postulated that, “schizophrenia is related to excess biological activity of dopamine (DA), deficient synthesis of a prostaglandin (PG) and the presence of normal opioid in excess or production of an abnormal opioid.” These factors are interrelated as opioids inhibit PGE1, and PGE1 and DA inhibit each other’s effects (Horrobin, 1980). Therefore, a low PGE1 level will produce an apparent DA excess. Niacin causes flushing through PGE1,
and patients with schizophrenia require much larger doses of niacin to flush, supporting the hypothesis presented above (Horrobin, 1980). Flushing of the skin may be seen with the naked eye, but is usually measured objectively through the measurement of change in skin temperature. The niacin skin flush lends some support to the contention that patients with schizophrenia have disordered conduction of heat to the periphery because of disordered vasodilatory ability, as this is the mechanism whereby flushing occurs.

Hudson et al. (1999) continued this line of thought by investigating phospholipid metabolism in patients with schizophrenia. Earlier studies had demonstrated that calcium-independent PLA2 is increased in people with schizophrenia, whilst calcium-dependent PLA2 is not significantly different from controls. They found that significantly more patients were niacin insensitive than controls. Furthermore, a niacin sensitive patient subgroup showed a decrease in calcium-dependent PLA2 activity. In animal models, both D2 and D4 DA receptors augment the release of arachidonic acid via calcium-dependent PLA2, which is converted to prostaglandins by cyclo-oxygenase (COX), having anti-dopaminergic effects, whilst indomethacin, a COX inhibitor, has DA stimulatory effects. Hudson et al. (1999) implied that DA, prostaglandins and niacin are somewhat interrelated, lending weight to their involvement in disordered thermoregulation.

Turenne et al. (2001) undertook a study on the effects of haloperidol, nicotine and caffeine on the induction of nicotinic acid (NA) mediated skin vasodilatation in rats. They found that both single or chronic dosing of haloperidol and single dosing of caffeine decreased the effect of NA-induced vasodilatation. Chronic administration of caffeine or either single or chronic administration of nicotine had no effect. The doses used were the equivalent for humans of two cups of coffee or one pack of cigarettes, and chronic administration was undertaken over a period of 14 days. This implicates haloperidol, and possibly neuroleptics in general, impairing mechanisms of heat loss via NA-induced vasodilatation.

Douglass and Toogood (1987) determined the impact of sweat as a mechanism of heat loss. They found that there was no baseline temperature difference but the patient group accommodated faster to heat stress. They found a significantly higher skin temperature in the patient group, a non-significantly lower degree of skin conductance (sweating), and no difference in skin flush or blood flow. Unlike other studies, these results do not point towards increased vasodilatation to explain heat loss and the increased skin temperature, and also Schnur’s (1990) review found that skin conductance was lower in patients with schizophrenia. It also raises the factor of sweat, mediated by sympathetic cholinergic fibres, which appears to have not been the focus of these studies. Additionally, it must be recognised that many neuroleptics have anti-cholinergic properties, and thus add a further potential confounding or causatory factor.

5.2. Central mechanisms

In contrast to the above, Heh et al. (1988) investigated a central role for medications in causing hypothermia in patients with schizophrenia. They built on the work of Chai et al. (1976) that showed that centrally acting chlorpromazine induced hypothermia in monkeys. Heh et al. (1988) studied the oral temperature of eight chronic treatment resistant patients with schizophrenia with a washout phase, followed by 6 weeks single blinded administration of haloperidol and then 6 weeks double-blinded administration of clozapine. They found that clozapine both decreased temperature and improved clinical status measured by the BPRS, to a greater extent than haloperidol. There was also a weak but suggestive linear relationship between the degree of hypothermia and the extent of amelioration of psychosis. These authors proposed that typical antipsychotic medications antagonise post-synaptic DA receptors, whilst blocking pre-synaptic autoreceptors, with the effect of increasing synaptic DA levels until the autoreceptors become “tolerant” of the blockade. The consequent raised level of DA in the synapse becomes a more potent stimulus to negative feedback, resulting in reduced production of dopamine and decreased pre-synaptic firing. The decreased post-synaptic DA firing in the posterior hypothalamus, responsible for heat conservation, putatively results in hypothermia.

Rubinstein (1993) drew on the work of Heh et al. (1988) and Henderson and Wooten (1981) to postulate that the mesolimbic DA system in the brain is...
responsible for both thermoregulation and psychosis. Rubinstein (1993) based her theory on two strains of mice, first described in studies by Lagerspetz et al. (1973), that had differing sensitivity to DA. She postulated that the strain of mice that was more sensitive to DA had more effective thermoregulation, but would be more susceptible to neuroleptic malignant syndrome (NMS), when under DA receptor blockade, and vice versa. Thus neuroleptic medications that block DA receptors ameliorate psychosis but also potentially cause dysregulation of temperature (and potentially NMS) in those who are more sensitive to DA.

5.3. Conclusions and future directions

A body of evidence has been amassed over time that demonstrates disturbed thermoregulation in people with schizophrenia, although the precise role of medication in these findings is not clear. Biochemical and physiological explanations of the above are inconclusive, with researchers postulating a dichotomy of theories:

- A “peripheral” abnormality related to impaired heat loss through peripheral vasodilatation via abnormalities in niacin and PGE_1;
- A “central” abnormality due to disruption of the mesolimbic dopamine system that is believed to be responsible for temperature regulation and psychosis.

The reality is that the underlying mechanism(s) may well involve a combination of peripheral and central mechanisms, either with equal importance or with one playing a primary or predominating role.

Others have extended these theories, and postulate that medications either act centrally and lead to amelioration of psychosis, with an associated hypothermia, or impair the body’s ability to lose heat through disrupting peripheral vasodilatation or through anti-cholinergic effects.

Furthering our understanding, through larger scale, methodologically sound, controlled studies of thermoregulation, baseline body temperatures and under heat and cold stress, might help in the quest further to elucidate the biochemical and physiological mechanisms underlying the syndrome of schizophrenia. Furthermore, there is still much scope for further study into the effect of neuroleptics on thermoregulation and the central and/or peripheral mechanisms for disturbed thermoregulation.

References

Henderson, V.W., Wooten, G.F., 1981. Neuroleptic malignant syn-
drome: a pathogenetic role for dopamine receptor blockade. 
Neurology 31, 132–137.
Hermesh, H., Shiloh, R., Epstein, Y., Manaim, H., Weizman, A., 
schizophrenia maintained with antipsychotic drugs. Am. J. 
Psychiatry 157, 1327–1329.
Hudson, C., Gotowiec, A., Seeman, M., Warsh, J., Ross, B.M., 
1999. Clinical subtyping reveals significant differences in 
calcium-dependent phospholipase A2 activity in schizophrenia. 
Thermoregulation in group B arbovirus-resistant and arbovirus-
susceptible mice. Am. J. Physiol. 225, 532–537.
Lee, T.F., Mora, F., Myers, R.D., 1985. Dopamine and thermoreg-
ulation: an evaluation with special reference to dopaminergic 
Lee, H.S., Bastani, B., Freidman, L., Ramirez, L., Meltzer, H.Y., 
1992. Effect of the serotonin agonist, MK-212, on body temper-
control of body temperature in man. Int. Pharmacopsychiatry 8, 
239–244.
Madjirova, N.P., Petrova, N.S., Nedelcho, K., 1995. Daily rhyth-
micity of temperature, pulse and blood pressure in schizophrenic 
Morgan, R., Cheadle, A.J., 1976. Circadian body temperature in 
Overall, J.E., Gorham, D.E., 1961. The brief psychiatric rating 
Rao, M.L., Strebel, B., Halaris, A., Gross, G., Brauning, P., Huber, 
G., Marler, M., 1995. Circadian rhythm of vital signs, norepi-
nephrine, epinephrine, thyroid hormones, and cortisol in schizo-
animal model for investigating their interrelationships. Schiz-
Schnur, D.B., 1990. Effects of neuroleptics on electrodermal activity 
in schizophrenic patients: a review. Psychopharmacology 102, 
429–437.
Shiloh, R., Hermesh, H., Weizer, N., Dorfman-Etrog, P., Weizman, 
lowers body temperature in drug-free male schizophrenic pa-
Shiloh, R., Weizman, A., Epstein, Y., Rosenberg, S.L., Valevski, A., 
Dorfman-Etrog, P., Weizer, N., Katz, N., Munitz, H., Hermesh, 
H., 2001. Abnormal thermoregulation in drug-free male schiz-
Shiloh, R., Portuguese, S., Bodinger, L., Katz, N., Sigler, M., Her-
temperature in drug-free male schizophrenia patients. Eur. Neu-
ropsychopharmacol. 13, 49–52.
Taylor, D., McConnell, H., Duncan-McConnell, D., Kerwin, R., 
Prescribing Guidelines, 6th ed. Martin Dunitz, London, 
Turenne, S.D., Seeman, M., Ross, B.M., 2001. An animal model of 
nicotinic-acid-induced vasodilation: effect of haloperidol, caff-
eine and nicotine upon nicotinic acid response. Schizophr. 
Res. 50, 191–197.