

Brain temperature and brain metabolism measurements: Rapid in vivo markers of mood i.e. mania or depressive disorders

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Background

Recently, scientific interest has increased upon the influence of temperature in the physiopathology of various neurodegenerative and psychiatric disorders. It has been shown that lowering core body and brain temperature has been shown to be beneficial for multiple sclerosis, cardiovascular accidents, traumatic brain injuries and myocardial infarction [1,2].

In 2005 Salerian and Saleri have proposed that a relatively minor alteration in core body or brain temperature may be of significant therapeutic benefit in combating neurodegenerative disorders and prolonging lifespan. In addition, they postulate that brain temperature may rise with mania and fall with depression and propose that therapeutic manipulation of brain temperature may represent a key mechanism in the treatment of mood disorders.

Indeed, studies with rats suggest that lithium increases brain cholinergic activity and heat shock proteins, both resulting in hypothermia [3,4]. Similarly, other neuroleptics such as clozapine, olanzapine and risperdal produce a dose-dependent drop of colon temperature in adult male Wistar rats [5], as well as chlorpromazine induces a drop-in colon temperature in rats [6].

In humans, neuroleptics, with a few exceptions, seem to be hypothermic, i.e. haloperidol, olanzapine and risperdal reduce axillary temperature while clozapine decreases core body temperature and displays a linear relationship between the degree of hypothermia and improvement of psychosis. Overall, it appears that lithium and neuroleptics are hypothermic and that neuroleptic-induced hypothermia is associated with amelioration of psychosis in schizophrenic patients [7]. Accordingly, clinical manifestations such as transient and reversible psychosis with auditory and visual hallucinations that appear when core body temperature rises above 39 °C disappear after core body temperature normalizes [8].

On the other hand, it appears that many antidepressants currently in clinical use (i.e. sibutramine, duloxetine, bupropion, nortriptyline, nortriptyline) have marked thermogenic properties in rodents [9,10]. In particular, bupropion, a dopamine/norepinephrine reuptake inhibitor, increases brain and colon temperature in rats [11]. The studies on the effects of antidepressants on humans have been contradictory; yet there is one study that suggests chronic administration of antidepressants elevates tympanic membrane temperature [12]. In addition, it is interesting that patients with moderate hypothermia experience bradycardia and hypotension (following early and brief tachycardia and hypertension) as well as progressive depression of mental functions starting with apathy, psychomotor retardation, and silence [1].

Proposal

On the basis of the above background, oxymetry (pO_2 and blood flow (BF) together with temperature measurements (Temp-oxymetry) could be used as rapid screener of chemicals with “antidep” (or neuroleptic) capacities [13-19].

Program

Validation and implementation of Temp response of the Temp-oxymetric probe inserted in discrete brain areas of anaesthetized rats via:

- O_2 or CO_2 (various conc.) challenges and parallel analysis of pO_2 , BF and brain Temp changes;
for instance, 2,5%, 5% and 7.5% CO_2 challenge are successfully applicable to the same animal (see Crespi 2013 and also see Figure 1) therefore these experiments can be performed rapidly i.e. within 5days (n=5).
- Controlled changes of body temperature i.e. by means of the “heating pad” and consequent analysis of brain Temp changes;

Again, here experiments should be performed rapidly when obtaining good corresponding parameters between “heating pad” temperature-controlled increases [or decreases] and rat body temperature.

In particular, Salerian claims that small alterations of body temperature (i.e. 1 °C degree) may significantly alter biochemical reactions resulting in mood modification [2,14]. Thus, in our experiments changes of 1, 2 (maximum 3?) °C degrees of body temperature could be applied, then the putative influence of such body temperature changes (i.e. increasing or decreasing) can be monitored upon brain Temp as well pO_2 and BF levels. Again, this study may need a couple of weeks to be performed i.e. n=5 for each degree change.

- Test with known hypothermic [i.e. haloperidol, olanzapine] or thermogenic [i.e. bupropion] compounds.

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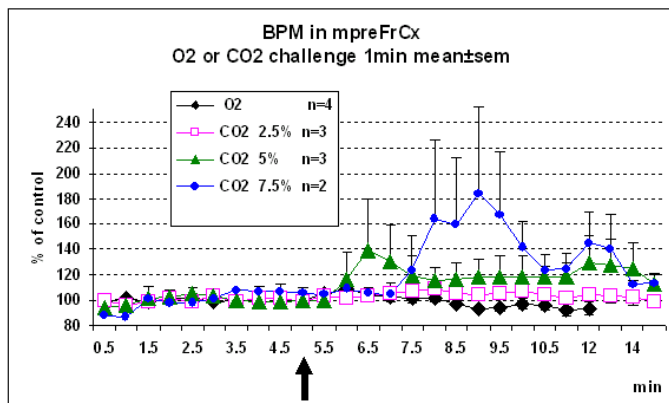


Figure 1. Preliminary data showing the effect of the challenge (arrow) with pure Oxygen (O_2) or carbon dioxide (CO_2) at different doses during 1 min upon blood pressure (BPM) monitored in rat medial prefrontal cortex (mpreFrCx). Similar effects of CO_2 challenge are observed upon BF and Temperature [15]

For instance, experiments to measure Temp changes could be performed with a hypothermic i.e. haloperidol or a thermogenic i.e. bupropion compound within 20 working days ($n=5$ each compound + $n=5$ controls). Parallel oxymetric measurements of pO_2 and blood flow will correlate the metabolic state of the brain region studied.

d) Test with antidepressants such as DOV (TRUI) versus citalopram (for serotonin); reboxetine (for noradrenaline), GBR12909 (for dopamine) to set up METABOLIC FINGERPRINTS OF ANTIDEPRESSANTS [doses obtained from EEG studies] to support and finalize the putative correlation metabolism-depression.

$N=5$ each group i.e. five weeks work (4 treated, 1 control).

Successful data could be supportive of further experiments achievable in conscious rats prepared for Temp-oxymetry [i.e. in frontal cortex] that will be monitored while undergoing acute (i.e. tonic immobility) or chronic (i.e. chronic mild stress) behavioural models used for the characterisation of antidepressants. Each one of these tests could be performed in two groups rats treated with vehicle (control group) or with thermogenic [i.e. bupropion] compounds.

Successful data would then suggest that temperature change may represent a critical mechanism in the patho-physiology of mood disorders and may promise an avenue for therapeutic exploitation, for instance, treatments also inducing hyperthermia may help in depression.

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