Pharmacological Induction of Hypothermia

15

Yinlun Weng, Shijie Sun and Wanchun Tang

Marked protection provided by therapeutic hypothermia after traumatic ischemic-hypoxic damage has been deeply studied, contributing to satisfactory clinic effects. Several physical methods to induce therapeutic hypothermia have been established, and briefly can be divided into two categories: invasive and non invasive. Recently, pharmacological hypothermia is drawing increasing attention as a neuroprotective alternative approach worthy of further clinical development. This chapter reviews the hypothermic effect of several classes of hypothermia-inducing drugs: the cannabinoids, opioid receptor activators, transient receptor potential vanilloid, neurotensins, thyroxine derivatives, dopamine receptor agonists, and cholecystokinin. Recent findings have extended our knowledge of the thermoregulatory mechanisms of the above drugs. A better understanding of the roles of the hypothermia-inducing drugs in neuroprotection may have broad clinical implications. Till date, there is few data that uniquely elicit that pharmacologically induced hypothermia is the sole or specific mechanism on neuroprotection. However, some mechanisms underlying the protection of hypothermia are overlapped with the current evidence on the intrinsic effects of the above drugs.

Y. Weng
Sun Yat-sen Memorial Hospital, Sun Yat-sen University, Yanjiang West Road, 510120, Guangzhou, China
e-mail: yearonyung@126.com

S. Sun · W. Tang (✉)
The Institute of Critical Care Medicine, Bob Hope Drive, Rancho Mirage, CA 92270, USA
e-mail: wanchun.tang@me.com

S. Sun
e-mail: ShijieSun@aol.com

A. Gullo and G. Ristagno (eds.), *Resuscitation*,
DOI: 10.1007/978-88-470-5507-0_15, © Springer-Verlag Italia 2014

15.1 Cannabinoids

There are two main receptors within the cannabinoid system: cannabinoid receptors 1 and 2. In the brain, the cannabinoid receptor 1, one of the most abundant Gi/o-protein-coupled receptors, was found in the hypothalamus responsible for regulation of temperature [1–6]. At the cellular level, cannabinoid receptor 1 is also abundant in the plasma membranes of the axon and axonal terminals, where it typically mediates the release of neurotransmitters [5]. Numerous evidences suggest that cannabinoid 1 receptors participate in the prevention of neurodegenerative disease or protection from ischemic insults [7–10]. The neuroprotective effects of cannabinoid agonists were related either to specific mechanisms played by these agonists or by a cannabinoid-induced hypothermia [11]. Among them, however, cannabinoid-induced hypothermia was the primary mechanism which was principally triggered by activation of cannabinoid receptor 1. Several neurological neurotransmitters were demonstrated to be involved, such as the release of GABA (Gamma-amino Butyric Acid, GABA) [12, 13] and the dopamine [14]. As cannabinoid-induced regulation of body temperature is, however, dose-dependent, further evidence is necessary to establish optimal application standards for the cannabinoid-based hypothermic treatment [15].

It is well documented that cannabinoids may have therapeutic potential in disorders resulting from cerebral ischemia, including stroke, and may protect neurons from injury through a variety of mechanisms [9]. The beneficial mechanisms were related to the decrease of inflammatory factors [16], reduction of apoptotic cell death, maintenance of mitochondrial integrity and functionality [17], activation of extracellular signal-regulated kinases, increase of S-100 protein, and mitigation of glutamatergic excitotoxicity, TNF-alpha release and iNOS expression [18, 19]. These effects are achieved through two parallel CB1-dependent and -independent mechanisms [20, 21].

15.2 Opioid Receptor Agonists

The opioid system was reported to be involved in thermoregulation. Indeed, naloxone has been reported to antagonize the hypothermic effects played by morphine [22–24]. The main subtype of opioid receptors involved in thermoregulation and hypothermia induction is the kappa-receptor, while the mu-receptor is related to hyperthermia. The magnitude of hypothermic effects produced by kappa- opioid agonists is related to the degree of their selectivity for the kappa-receptor [25]. The kappa-opioid receptor is primarily located outside the brain; thus peripheral application of kappa-receptor agonists could produce dose-dependent hypothermia [26, 27].

Moreover, the existence of subtypes of the different receptors may well explain the different effects of one single drug on thermoregulation [28]. Anatomical, histochemical, and pharmacological evidence suggests that the opioid system

probably interacts with the dopaminergic, adrenergic, serotonergic, cholinergic, and other transmitter systems [25–28]. Thus, it can be hypothesized that the opioid system interacts with other neurotransmitter systems known to be involved in thermoregulation. However, studies carried out so far do not present a clear picture of these interrelationships in terms of thermoregulation. In view of the recent findings that several neuropeptides play marked effects on body temperature, exploration of opioid interactions with these systems should prove to be a fruitful approach to deepen the understanding of the opioid system and its function in the thermoregulation.

Kappa-receptor agonists, have been demonstrated effective in preventing brain swelling in parallel with reducing infarction after an ischemic insult [29, 30], but the use of opioid receptor agonist is limited to the early phase of cerebral edema [31, 32]. This was related mainly to the attenuation of ischemia-evoked nitric oxide production [33], the reduction of Na(+)−K(+)-ATPase activity [34], and a significant prolonged neuron survival [35–37].

15.3 Transient Receptor Potential Vanilloid

Studies have demonstrated that many pathophysiological processes were mediated by transient receptor potential (TRP) channels, including pain, respiratory reflex hypersensitivity, cardiac hypertrophy, thermoregulation, and ischemic cell death. The superfamily of mammalian *TRP* channels consists of around 30 proteins which can be divided into six subfamilies: ankyrin (TRPA), canonical, melastatin (TRPM), mucolipin, polycystin, and vanilloid (TRPV). Till date, nine of the proteins are found highly sensitive to temperature and are referred to as the thermo-TRP channels, which include the heat-activated TRPV1 as well as the cold-activated TRPA1 and TRPM8 [38–41].

No consensus in the literature was achieved on the hypothermic response to systemically administered TRPV1 agonists. Most evidence is in support of the central mediation hypothesis: (1) the TRPV1 channel was demonstrated to be widely distributed in the hypothalamus; [42–44], (2) TRPV1 agonist was able to cross the blood–brain barrier; [45, 46], (3) the primary action mode after application of TRPV1 agonist lies on the glutamatergic preoptic anterior hypothalamus neurons; [43, 47], (4) a reduced or low hypothermic response to TRPV1 agonist was observed in rats with decreased hypothalamic sensitivity [48]. Moreover, several authors also suggested a contribution of a peripheral action of TRPV1 agonists to the hypothermic response.

However, there was no definite data illustrating that TRPV1-induced hypothermia could directly contribute to the beneficial neurologic outcomes in rat models of ischemia.

15.4 Neurotensin

At least three subtypes of receptors are involved in pathophysiologic processes of neurotensin: neurotensin-1 and neurotensin-2 receptor, both members of the heptahelical transmembrane domain G protein-coupled receptor superfamily; and neurotensin-3 receptor, which is identical to gp95/sortilin, with only a single transmembrane domain [29–31].

Neurotensin is abundant in the preoptic area of the hypothalamus [49]. Early in the 1980s, neurotensin was first reported to elicit hypothermic effect by acting on the hypothamalus in rodents [50, 51]. Neurotensin-induced hypothermia is thought to be caused by a downward shift of the physiological temperature set point (''regulated hypothermia''). Previous results using neurotensin analogs or peptide nucleic acids suggested that neurotensin receptor 1 was implicated in neurotensin-induced hypothermia, but the nonspecificity of these molecules aroused some doubt. Neurotensin normally does not cross the blood–brain barrier and is quickly metabolized when administered systemically. In terms of wide clinic application, many neurotensin analogs emerge as new options with the ability to penetrate the blood–brain barrier and prolong the hypothermia duration.

Previously, several neurotensin receptor 1 agonists were demonstrated to induce hypothermia in a dose-dependent manner without causing shivering or altering physiological parameters. These analogs ultimately reduced cerebral infarct volumes and improved neurologic outcomes [52–54]. The specific mechanisms involved would be increase in bcl-2 expression, decrease in caspase-3 activation, and suppression of cell death [53, 54].

15.5 Thyroxine Derivatives

Thyroxine is the principal secretion form of thyroid hormone (TH), constituting 95 % of all TH found in human circulation. When deiodinated and decarboxylated, thyroxine is transformed into 3-iodothyonamine (T1AM) and thyronamine (T0AM). It was reported that when injected peripherally, T1AM and T0AM rapidly induced hypothermia through a mechanism independent of gene transcription. T1AM and T0AM are agonists of trace amine associated receptor 1 (TAAR1), a G-protein coupled receptor activated by phenylethylamine, tyramine, methamphetamine, and its congeners. Although T1AM and T0AM can dose-dependently couple TAAR1 to the production of cAMP, it is not yet clear whether TAAR1 is an endogenous receptor for these molecules [55].

There has been data demonstrating that T1AM and T0AM are potent neuroprotectants in neurologic ischemia disease. Hypothermia induced by T1AM and T0AM may partially underlie neuroprotection [55].

15.6 Dopamine Receptor Agonists

Dopamine (DA) is one of the major neurotransmitters in the mammalian central nervous system (CNS). The receptors for DA have been classified into three subtypes: the D1, D2, and D3 receptor subtype [56]. There were data suggesting that hypothermia in mammals are centrally mediated by D2 receptor mechanism, and this centrally mediated D2 receptor mechanism may be modulated by the D1 receptor [57]. Furthermore, the dopamine D1 receptor agonist was also reported to produce hypothermia that was antagonized by D1 receptor antagonists, but not by the dopamine D2/3 receptor antagonists. This supports the evidence that activation of dopamine D1 receptors may play a determinant role in inducing hypothermia in rats [58]. Further evidence finally demonstrated that hypothermia did not result from a selective stimulation of the D3 receptor [59].

There is lack of evidence, however, that D1 or 2 receptor agonist-induced hypothermia would provide protective effects in neurologic ischemic diseases.

15.7 Cholecystokinin

It was first reported in 1981 that centrally administrated cholecystokinin was able to produce hypothermia in rats [38, 60, 61]. Specific mechanisms of cholecystokinin-induced hypothermia after peripheral or central application, however, remain unclear [39, 40, 60]. Hypothermia may either be produced by different mechanisms, such as inhibition of central nervous system function without specific relation to central body temperature control, interruption of afferent or efferent nervous pathways, or a decrease of regulated level of body temperature. The central action of cholecystokinin was not supported by the long latency of the thermoregulatory response observed after central administration of cholecystokinin [39, 40, 60]. An alternative explanation for the cholecystokinin-induced hypothermia after peripheral injection could be a direct skin vasodilatation. Besides, a nervous afferent mechanism, such as the vagal afferentation shown to be an important way of influencing central regulation of food intake could also play relevant roles on specific thermoregulatory sites [41]. The hypothermic action of the peptide in mammals seems to depend on cholecystokinin-1 receptors, since administration of cholecystokinin-1 receptor antagonists attenuated these hypothermic effects, while the cholecystokinin-2 receptor antagonist had no effect on this response [42–45].

Although the concept of pharmacological hypothermia induced by cholecystokinin was not widely raised, there are some data revealing that cholecystokinin to some extent plays a vital role in protecting from brain ischemia disease. Yasui M et al. demonstrated that in rats subjected to stroke, cholecystokinin prevented the dysfunction of CA1 pyramidal neurons [46]. Moreover, in a rat model of global ischemia after cardiac arrest, cholecystokinin octapeptide indeed induced hypothermia, and improved post-resuscitation myocardial dysfunction and overall neurological performance after intravenous injection of CCK8 at a dose of 200 μg/kg [47].

References

1. Herkenham M, Lynn AB, Little MD, Johnson MR, Melvin LS, de Costa BR, Rice KC (1990) Cannabinoid receptor localization in brain. Proc Natl Acad Sci USA 87:1932–1936
2. Herkenham M, Lynn AB, Johnson MR, Melvin LS, de Costa BR, Rice KC (1991) Characterization and localization of cannabinoid receptors in rat brain: a quantitative in vitro autoradiographic study. J Neurosci 11:563–583 (the official journal of the Society for Neuroscience)
3. Tsou K, Brown S, Sanudo-Pena MC, Mackie K, Walker JM (1998) Immunohistochemical distribution of cannabinoid cb1 receptors in the rat central nervous system. Neuroscience 83:393–411
4. Piomelli D (2003) The molecular logic of endocannabinoid signalling. Nat Rev Neurosci 4:873–884
5. Mackie K (2006) Cannabinoid receptors as therapeutic targets. Annu Rev Pharmacol Toxicol 46:101–122
6. Di Marzo V (2008) Targeting the endocannabinoid system: to enhance or reduce? Nat Rev Drug Discov 7:438–455
7. Jin KL, Mao XO, Goldsmith PC, Greenberg DA (2000) Cb1 cannabinoid receptor induction in experimental stroke. Ann Neurol 48:257–261
8. Sinor AD, Irvin SM, Greenberg DA (2000) Endocannabinoids protect cerebral cortical neurons from in vitro ischemia in rats. Neurosci Lett 278:157–160
9. Nagayama T, Sinor AD, Simon RP, Chen J, Graham SH, Jin K, Greenberg DA (1999) Cannabinoids and neuroprotection in global and focal cerebral ischemia and in neuronal cultures. J Neurosci 19:2987–2995
10. Braida D, Pozzi M, Sala M (2000) Cp 55,940 protects against ischemia-induced electroencephalographic flattening and hyperlocomotion in mongolian gerbils. Neurosci Lett 296:69–72
11. Viscomi MT, Oddi S, Latini L, Bisicchia E, Maccarrone M, Molinari M (2010) The endocannabinoid system: a new entry in remote cell death mechanisms. Exp Neurol 224:56–65
12. Rawls SM, Cabassa J, Geller EB, Adler MW (2002) Cb1 receptors in the preoptic anterior hypothalamus regulate win 55212–2 [(4,5-dihydro-2-methyl-4(4-morpholinylmethyl)-1-(1-naphthalenyl-carbonyl)- 6h-pyrrolo[3,2,1ij]quinolin-6-one]-induced hypothermia. J Pharmacol Exp Ther 301:963–968
13. Rawls SM, Tallarida RJ, Kon DA, Geller EB, Adler MW (2004) Gabaa receptors modulate cannabinoid-evoked hypothermia. Pharmacol Biochem Behav 78:83–91
14. Gonzalez B, Paz F, Floran L, Aceves J, Erlij D, Floran B (2009) Cannabinoid agonists stimulate [3h]gaba release in the globus pallidus of the rat when g(i) protein-receptor coupling is restricted: Role of dopamine d2 receptors. J Pharmacol Exp Ther 328:822–828
15. Sulcova E, Mechoulam R, Fride E (1998) Biphasic effects of anandamide. Pharmacol Biochem Behav 59:347–352
16. Fernandez-Lopez D, Faustino J, Derugin N, Wendland M, Lizasoain I, Moro MA, Vexler ZS (2012) Reduced infarct size and accumulation of microglia in rats treated with win 55,212–2 after neonatal stroke. Neuroscience 207:307–315
17. Alonso-Alconada D, Alvarez A, Alvarez FJ, Martinez-Orgado JA, Hilario E (2012) The cannabinoid win 55212–2 mitigates apoptosis and mitochondrial dysfunction after hypoxia ischemia. Neurochem Res 37:161–170
18. Alonso-Alconada D, Alvarez FJ, Alvarez A, Mielgo VE, Goni-de-Cerio F, Rey-Santano MC, Caballero A, Martinez-Orgado J, Hilario E (2010) The cannabinoid receptor agonist win 55,212–2 reduces the initial cerebral damage after hypoxic-ischemic injury in fetal lambs. Brain Res 1362:150–159

19. Hu B, Wang Q, Chen Y, Du J, Zhu X, Lu Y, Xiong L, Chen S (2010) Neuroprotective effect of win 55,212–2 pretreatment against focal cerebral ischemia through activation of extracellular signal-regulated kinases in rats. Eur J Pharmacol 645:102–107
20. Fernandez-Lopez D, Martinez-Orgado J, Nunez E, Romero J, Lorenzo P, Moro MA, Lizasoain I (2006) Characterization of the neuroprotective effect of the cannabinoid agonist win-55212 in an in vitro model of hypoxic-ischemic brain damage in newborn rats. Pediatr Res 60:169–173
21. Martinez-Orgado J, Fernandez-Frutos B, Gonzalez R, Romero E, Uriguen L, Romero J, Viveros MP (2003) Neuroprotection by the cannabinoid agonist win-55212 in an in vivo newborn rat model of acute severe asphyxia. Brain Res Mol Brain Res 114:132–139
22. Clark WG, Cumby HR (1978) Hyperthermic responses to central and peripheral injections of morphine sulphate in the cat. Br J Pharmacol 63:65–71
23. Geller EB, Hawk C, Keinath SH, Tallarida RJ, Adler MW (1983) Subclasses of opioids based on body temperature change in rats: Acute subcutaneous administration. J Pharmacol Exp Ther 225:391–398
24. Rosow CE, Miller JM, Poulsen-Burke J, Cochin J (1982) Opiates and thermoregulation in mice. Ii. Effects of opiate antagonists. J Pharmacol Exp Ther 220:464–467
25. Hayes AG, Skingle M, Tyers MB (1985) Effect of beta-funaltrexamine on opioid side-effects produced by morphine and u-50, 488h. J Pharm Pharmacol 37:841–843
26. Geller EB, Rowan CH, Adler MW (1986) Body temperature effects of opioids in rats: intracerebroventricular administration. Pharmacol Biochem Behav 24:1761–1765
27. Maldonado R, Dauge V, Callebert J, Villette JM, Fournie-Zaluski MC, Feger J, Roques BP (1989) Comparison of selective and complete inhibitors of enkephalin-degrading enzymes on morphine withdrawal syndrome. Eur J Pharmacol 165:199–207
28. Lin MT, Uang WN, Chan HK (1984) Hypothalamic neuronal responses to iontophoretic application of morphine in rats. Neuropharmacology 23:591–594
29. Kusumoto K, Mackay KB, McCulloch J (1992) The effect of the kappa-opioid receptor agonist ci-977 in a rat model of focal cerebral ischaemia. Brain Res 576:147–151
30. Silvia RC, Slizgi GR, Ludens JH, Tang AH (1987) Protection from ischemia-induced cerebral edema in the rat by u-50488h, a kappa opioid receptor agonist. Brain Res 403:52–57
31. Yang L, Wang H, Shah K, Karamyan VT, Abbruscato TJ (2011) Opioid receptor agonists reduce brain edema in stroke. Brain Res 1383:307–316
32. Gueniau C, Oberlander C (1997) The kappa opioid agonist niravoline decreases brain edema in the mouse middle cerebral artery occlusion model of stroke. J Pharmacol Exp Ther 282:1–6
33. Goyagi T, Toung TJ, Kirsch JR, Traystman RJ, Koehler RC, Hurn PD, Bhardwaj A (2003) Neuroprotective kappa-opioid receptor agonist brl 52537 attenuates ischemia-evoked nitric oxide production in vivo in rats. Stroke 34:1533–1538 (a journal of cerebral circulation)
34. Furui T (1993) Potential protection by a specific kappa-opiate agonist u-50488h against membrane failure in acute ischemic brain. Neurol Med Chir 33:133–138
35. Charron C, Messier C, Plamondon H (2008) Neuroprotection and functional recovery conferred by administration of kappa- and delta 1-opioid agonists in a rat model of global ischemia. Physiol Behav 93:502–511
36. Zhang Z, Chen TY, Kirsch JR, Toung TJ, Traystman RJ, Koehler RC, Hurn PD, Bhardwaj A (2003) Kappa-opioid receptor selectivity for ischemic neuroprotection with brl 52537 in rats. Anesth Analg 97:1776–1783
37. Mackay KB, Kusumoto K, Graham DI, McCulloch J (1993) Focal cerebral ischemia in the cat: pretreatment with a kappa-1 opioid receptor agonist, ci-977. Brain Res 618:213–219
38. Zadina JE, Banks WA, Kastin AJ (1986) Central nervous system effects of peptides, 1980–1985: a cross-listing of peptides and their central actions from the first six years of the journal peptides. Peptides 7:497–537

39. Kapas L, Benedek G, Penke B (1989) Cholecystokinin interferes with the thermoregulatory effect of exogenous and endogenous opioids. Neuropeptides 14:85–92
40. Kapas L, Obal F Jr, Alfoldi P, Rubicsek G, Penke B, Obal F (1988) Effects of nocturnal intraperitoneal administration of cholecystokinin in rats: simultaneous increase in sleep, increase in eeg slow-wave activity, reduction of motor activity, suppression of eating, and decrease in brain temperature. Brain Res 438:155–164
41. Palkovits M, Kiss JZ, Beinfeld MC, Williams TH (1982) Cholecystokinin in the nucleus of the solitary tract of the rat: evidence for its vagal origin. Brain Res 252:386–390
42. Szelenyi Z, Bartho L, Szekely M, Romanovsky AA (1994) Cholecystokinin octapeptide (cck-8) injected into a cerebral ventricle induces a fever-like thermoregulatory response mediated by type b cck-receptors in the rat. Brain Res 638:69–77
43. Rezayat M, Ravandeh N, Zarrindast MR (1999) Cholecystokinin and morphine-induced hypothermia. Eur Neuropsychopharmacol 9:219–225 (the journal of the European College of Neuropsychopharmacology)
44. Pullen RG, Hodgson OJ (1987) Penetration of diazepam and the non-peptide cck antagonist, l-364,718, into rat brain. J Pharm Pharmacol 39:863–864
45. Woltman TA, Hulce M, Reidelberger RD (1999) Relative blood-brain barrier permeabilities of the cholecystokinin receptor antagonists devazepide and a-65186 in rats. J Pharm Pharmacol 51:917–920
46. Yasui M, Kawasaki K (1995) 1-cckb receptor activation protects ca1 neurons from ischemia-induced dysfunction in stroke-prone spontaneously hypertensive rats hippocampal slices. Neurosci Lett 191:99–102
47. Weng Y, Sun S, Song F Phil Chung S, Park J, Harry Weil M, Tang W (2011) Cholecystokinin octapeptide induces hypothermia and improves outcomes in a rat model of cardiopulmonary resuscitation. Crit Care Med 39:2407–2412
48. Jancso-Gabor A, Szolcsanyi J, Jancso N (1970) Stimulation and desensitization of the hypothalamic heat-sensitive structures by capsaicin in rats. J Physiol 208:449–459
49. Uhl GR (1982) Distribution of neurotensin and its receptor in the central nervous system. Ann N Y Acad Sci 400:132–149
50. Kalivas PW, Jennes L, Nemeroff CB, Prange AJ Jr (1982) Neurotensin: topographical distribution of brain sites involved in hypothermia and antinociception. J Comp Neurol 210:225–238
51. Martin GE, Bacino CB, Papp NL (1980) Hypothermia elicited by the intracerebral microinjection of neurotensin. Peptides 1:333–339
52. Torup L, Borsdal J, Sager T (2003) Neuroprotective effect of the neurotensin analogue jmv-449 in a mouse model of permanent middle cerebral ischaemia. Neurosci Lett 351:173–176
53. Choi KE, Hall CL, Sun JM, Wei L, Mohamad O, Dix TA, Yu SP (2012) 1-a novel stroke therapy of pharmacologically induced hypothermia after focal cerebral ischemia in mice. FASEB J 26(7):2799–2810 (official publication of the Federation of American Societies for Experimental Biology)
54. Babcock AM, Baker DA, Hallock NL, Lovec R, Lynch WC, Peccia JC (1993) Neurotensin-induced hypothermia prevents hippocampal neuronal damage and increased locomotor activity in ischemic gerbils. Brain Res Bull 32:373–378
55. Doyle KP, Suchland KL, Ciesielski TM, Lessov NS, Grandy DK, Scanlan TS, Stenzel-Poore MP (2007) Novel thyroxine derivatives, thyronamine and 3-iodothyronamine, induce transient hypothermia and marked neuroprotection against stroke injury. Stroke 38:2569–2576 (a journal of cerebral circulation)
56. Kebabian JW, Calne DB (1979) Multiple receptors for dopamine. Nature 277:93–96
57. Nunes JL, Sharif NA, Michel AD, Whiting RL (1991) Dopamine d2-receptors mediate hypothermia in mice: Icv and ip effects of agonists and antagonists. Neurochem Res 16:1167–1174

58. Salmi P, Ahlenius S (1997) Dihydrexidine produces hypothermia in rats via activation of dopamine d1 receptors. Neurosci Lett 236:57–59
59. Perachon S, Betancur C, Pilon C, Rostene W, Schwartz JC, Sokoloff P (2000) Role of dopamine d3 receptors in thermoregulation: a reappraisal. Neuroreport 11:221–225
60. Morley JE, Levine AS, Lindblad S (1981) Intraventricular cholecystokinin-octapeptide produces hypothermia in rats. Eur J Pharmacol 74:249–251
61. Clark WG, Lipton JM (1985) Changes in body temperature after administration of amino acids, peptides, dopamine, neuroleptics and related agents: Ii. Neurosci Biobehav Rev 9:299–371