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Wenjuan Lin[a]; Nan Sui[a]
[a] Institute of Psychology, Chinese Academy of Sciences, Beijing, China

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Biopsychology research in China

Wenjuan Lin and Nan Sui

Institute of Psychology, Chinese Academy of Sciences, Beijing, China

The early studies on biopsychology in China were classified under the name of physiological psychology and comparative psychology. In 1979 the Division of Physiological Psychology of the Chinese Psychological Society was founded. Fifteen years later, the Brain-Behavior Research Center was founded at the Institute of Psychology, Chinese Academy of Sciences. The objective of the Center was to establish a multidisciplinary scientific environment for conducting experimental research on the relationship between brain and behaviour as well as the interactions of the mind and body. A wide range of studies in biopsychology has been conducted in China. The most major research areas are: (1) Behavioural and physiological studies of stress: Research work includes the effect of early environment on stressful responses, interactions of behavioural and endocrine responses under stress, effects of emotional stress on immune function, stress and hypertension and the related role of interleukin-1. (2) Conditioning and immunity: Studies focus on the effects of conditioning in the modulation of bidirectional immune function. Data from different experiments demonstrate that psychological processes are capable of influencing immune function. The neural substrates are also explored. (3) Memory and learning: Studies mostly concentrate on types of memory formation and training stimulus, effect of light exposure and corticosterone on learning and memory, and the role of the hippocampus in learning and memory. (4) Drug addiction: Work mainly focuses on long-term aspects of addiction, including memory, novelty seeking, motivation-related models, and the brain mechanisms underlying morphine psychological dependence.

Les premières études de biopsychologie en Chine furent classées sous l'appellation de psychologie physiologique et de psychologie comparative. En 1979, la Division de psychologie physiologique de la Société psychologique chinoise fut fondée. Quinze ans plus tard, le Centre de recherche cerveau-comportement fut créé à l'Institut de psychologie de l'Académie chinoise des sciences. L'objectif du Centre était d'établir un environnement scientifique multidisciplinaire pour mener des études expérimentales sur la relation entre le cerveau et le comportement ainsi que sur les interactions entre l'esprit et le corps. Un large éventail d'études en biopsychologie furent menées en Chine. Les principaux secteurs de recherche sont les suivants: (1) Les études comportementales et physiologiques du stress. Les travaux de recherche incluent l'effet de l'environnement premier sur les réponses de stress; les interactions des réponses comportementales et endocriniennes en état de stress; les effets du stress émotionnel sur la fonction immunitaire; le stress et l'hypertension et le rôle relatif de l'interleukine-1. (2) Le conditionnement et l'immunité. Les études sont orientées sur les effets du conditionnement dans la modulation de la fonction immunitaire bidirectionnelle. Les données de différentes expérimentations démontrent que les processus psychologiques peuvent influencer la fonction immunitaire. Les substrats neuraux sont aussi examinés. (3) La mémoire et l'apprentissage. Les études se concentrent surtout sur les types de formation de la mémoire et de stimulus d'entraînement, sur l'effet de l'exposition à la lumière et de la corticostérone sur l'apprentissage et sur la mémoire, sur le rôle de l'hippocampe dans l'apprentissage et la mémoire. (4) La dépendance à la drogue. Les travaux sont principalement axés sur les aspects à long terme de la dépendance, incluant la mémoire, la recherche de nouveauté, les modèles liés à la motivation et les mécanismes cérébraux sous-jacents à la dépendance psychologique à la morphine.

Los primeros estudios sobre Biopsicología en China se clasificaron bajo los nombres psicología fisiológica y psicología comparativa. En 1979 se fundó la División de Psicología Fisiológica en la Sociedad de Psicología China. Quince años después, se fundó el Centro de Investigación Cerebro-Conducta en el Instituto de Psicología de la Academia China de Ciencias. El objetivo del Centro era establecer un ambiente científico multidisciplinario para realizar investigación experimental sobre la relación entre el cerebro y la conducta, así como las interacciones entre la mente y el cuerpo. Se realizó en

Correspondence should be addressed to Dr Wenjuan Lin, Brain-Behaviour Research Center, Institute of Psychology, Chinese Academy of Sciences, Beijing, 100101, China (E-mail: Linwj@psych.ac.cn).

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China un amplio espectro de estudios en biopsicología, las áreas de investigación más importantes son: (1) Estudios conductuales y fisiológicos del estrés: la línea de investigación incluyó los efectos del ambiente temprano sobre respuestas de estrés; interacciones de respuestas conductuales y endocrinas bajo estrés; efectos del estrés emocional en la función inmune; estrés e hipertensión y el papel relacionado que desempeña el interleukin-1. (2) Condicionamiento e inmunidad: estudios que se centran en los efectos del condicionamiento en la modulación de la función bidireccional de la función inmune. Los resultados de diferentes experimentos demuestran que los procesos psicológicos son capaces de influir sobre la función inmune. Los sustratos neuronales también se han explorado. (3) Memoria y aprendizaje: los estudios se concentran principalmente en la formación de los tipo de memoria y los estímulos de entrenamiento, los efectos de la exposición a la luz y la corticoesterona sobre el aprendizaje y la memoria, el papel que desempeña el hipocampo en el aprendizaje y la memoria. (4) Adicción a las drogas: el trabajo atendió básicamente los aspectos de largo plazo de la adicción, incluye la memoria, la búsqueda de novedad, modelos relativos a la motivación, y los mecanismos cerebrales subyacentes a la dependencia psicológica a la morfina.

INTRODUCTION

Biopsychology is the study of the mind and behaviour in biological terms. Mostly, it studies how the brain and the rest of the nervous system generate behaviour and conversely how behaviour modulates the functions of the brain and body (Lin & Singer, 1997). Early studies in this field in China were classified as studies of physiological psychology as well as of comparative psychology (Kuang & Guan, 1997; Shao, 1997). In 1979 the Division of Physiological Psychology of the Chinese Psychological Society was founded. Fifteen years later, the Brain-Behavior Research Center was founded at the Institute of Psychology, Chinese Academy of Sciences. The objective of the Center was to establish a multidisciplinary scientific environment for conducting experimental research on the interactions of the brain and behaviour as well as the mind and body. The establishment of the Brain-Behavior Research Center provided the ground for discussion on recent trends in the development and practice of biopsychology (Singer & Lin, 1995).

The range of biopsychological studies in China is quite broad, including studies of learning and memory (e.g., Gao, Guan, & Kuang, 2001; Xu, Song, & Qu, 1993), attention, cognition and event-related potentials (e.g., Luo & Wei, 1997; Shen, Huang, Wu, & Li, 1998), stress and behaviour, etc. However, this paper makes no attempt to provide a summary of all the literature. It focuses on the most recent major studies of stress, conditioned immunity, learning and memory, and drug abuse.

SCIENTIFIC RESEARCH

Behavioural and physiological studies of stress

"Stress" is a widely used term for describing emotional and biological response to novel or threatening stimulations. Although stress has long been known to affect general health and increase susceptibility to diseases, including behavioural disorders, the knowledge regarding behavioural and physiological effects of stress, psychological stress in particular, as well as the mechanisms underlying these effects, is still not clear. Several lines of behavioural and physiological study of stress are introduced as follows.

The effect of early environment on stressful response

Many factors affect the organism's ability to cope with and respond to stressful stimuli, one of which is early environment. To test this, rats aged 1 month were divided into two groups: a group-housing one and an isolated one. Rats in the former group were housed five rats to a cage. Rats in the isolated group lived individually, without visual or physical contact with other animals. It was found that, compared with the group-housing rats, the isolated rats not only showed less sleep time and greater impairment in learning tasks (Lin & Tang, 1981, 1984), but also had a much higher frequency of seizures induced by acoustic stress and displayed more fighting behaviour induced by electric shocks (Tang & Lin, 1980, 1981). Moreover, when both isolated and group-housing rats were removed from their original home cage and regrouped into groups of four stranger rats per cage, such novel social stress had a greater and longer-lasting impact on food and water intake as well as sleep time of isolated rats than of the group-housing ones (Lin & Tang, 1981). As to the changes of brain neurotransmitters, data showed that when not under stress stimulation, animals reared in different early environments have similar catecholamine levels in the brain; but following stress stimulation, the change in catecholamine level in the brain of isolated animals was different from that of the group-housing animals. Following stress stimulation, both groups of animals showed some decrease in brain norepinephrine level; however, the norepinephrine level in the isolated animals decreased significantly

whereas the decrease in that of the group-housing animals was not significant (Tang & Lin, 1980, 1981). It was further found that the difference between the two groups of animals in the behavioural response to stressful stimulation was related to the difference in changes of catecholamine level to stress due to early rearing environment (Tang & Lin, 1991; Tang, Sun, & Lin, 1984a).

Interaction of behavioural and endocrine responses under stress

The stress effects are not only seen in endocrine reactions, namely hypothalamo-pituitary-adrenal axis (HPA) activation, but also in behavioural reactions, and there might be interactions between the two. To illustrate these interactions, both the role of HPA activation in behavioural actions and the role of behavioural activity in modulation of HPA function were examined in the schedule feeding stress-induced situation in hungry rats. Under this schedule feeding condition, animals showed both excessive activity and activated HPA function, namely increased corticosterone level. For excessive activity, the type of behavioural activity seen is determined by the environment opportunities provided. For example, if water is available, excessive drinking occurs during schedule feeding (Tang, Wallace, Singer, & Mackenzie, 1984b); if a running wheel is available, excessive running develops (Lin, Singer, & Papasava, 1988). Other activities, such as aggression, can be stress-induced only when corresponding opportunities (e.g., paired animals) exist in the experimental chamber. The particular environment opportunity provided here was a running wheel, and therefore the number of wheel revolutions was used as an index of behavioural reactions under stress. To examine the role of adrenal hormone in schedule stress-induced wheel running (SIW), a series of experiments was performed. The effects of adrenalectomy on wheel-running activities were examined under both schedule and nonschedule conditions. For schedule conditions, a FT 120 s noncontingent fixed time food delivery schedule was employed, whereby animals received one 45 mg pellet every 2 minutes. For nonschedule conditions, the same number of pellets used for schedule conditions was given in a single food presentation at the start of each session. The results showed that bilateral adrenalectomy significantly suppressed SIW, but did not significantly influence behavioural activities under nonstressful conditions. These findings indicated that adrenal hormones are involved in stress-induced behaviour. However, since adrenalectomy involves removal of medullary as well as cortical hormones, the question as to which hormone is responsible for the suppressant effect of adrenalectomy on SIW remained unanswered. A hypothesis that cortical hormones, mainly glucocorticoids, exert major hormonal influence on SIW was examined by testing SIW in adrenalectomized rats with or without replacement of corticosterone. The results showed that corticosterone replacement completely reversed the suppressant effect of adrenalectomy (Lin et al., 1988). This indicates that corticosterone, the major glucocorticoid in rats, was the critical hormone influencing SIW. Since adrenalectomy leads to an increased level of ACTH released by the pituitary, it was necessary to turn to manipulations that affect those pituitary-adrenal hormones differently in order to clarify their effects. One such technique is hypophysectomy, which results in low corticosterone as well as low ACTH levels. The effect of hypophysectomy on SIW was further examined. The results showed that hypophysectomy also leads to suppression of SIW. That is, the effect of hypophysectomy is basically the same as that of adrenalectomy. Since both increasing (via adrenalectomy) and decreasing (via hypophysectomy) ACTH levels lead to the suppression of SIW, so long as corticosterone is absent, it is suggested that the hormone responsible for the behavioural effect of both adrenalectomy and hypophysectomy is corticosterone. This contention is strengthened by the results in which corticosterone implantation significantly increased SIW in hypophysectomized rats. Obviously, the two sets of findings, those from the studies of adrenalectomy and corticosterone implantation and of hypophysectomy and corticosterone implantation, demonstrate that SIW is dependent on the function of the pituitary adrenal axis and that pituitary-adrenal involvement is mainly determined by circulating corticosterone levels (Lin, Singer, & Irby, 1990). It was further found that there was a dose–response relationship between levels of corticosterone and levels of SIW. i.e., the greater the circulating corticosterone level, the greater the SIW (Lin, Singer, & Funder, 1989). These results showed that the role of corticosterone in SIW is not only necessary but also regulatory. It was further found that the behavioural action of corticosterone in SIW is mediated through a classical glucocorticoid Type II receptor system in the brain (Lin et al., 1989).

However, although the level of SIW is determined by the increased level of corticosterone, the ongoing behaviour does not feed back in a way that further increases corticosterone response. Instead, the behavioural activities relieve the increased hormonal response in a stressful situation. Animals that have

developed SIW during stress exhibit a significant reduction in plasma corticosterone level. The animals exposed to stress but without the opportunity to develop SIW showed a higher level of corticosterone than those that had the opportunity to develop SIW. These results showed a good hormone/behaviour interaction, where not only do hormones effect behaviour, but behavioural responses lead to changes in endocrine function. These data showed the dynamics of the behavioural and endocrine responses induced by stress (Lin, 1995).

Effect of emotional stress on immune function

The notion that stress can induce alteration of immune function has been supported by increasing evidence from experimental data. But most investigations dealing with the effects of stress on the immune system in animals employed restraint and electric foot-shock as stressors, which have many components of physiological stress. Recently the impact of psychological stress on immune function has been the subject of extensive research efforts. Although these studies have suggested that psychological stress has effects on various components of immune responses via the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic nervous system (SNS), the major pathway involved in this immunomodulation has not yet been determined. Until now there has been little data on the relationship between the HPA axis or SNS and the immunoregulation (especially humoral immunity) induced by psychological stress. To examine the roles of the SNS and HPA axis in stress-induced immunity, two types of emotional stressors were used. One was a foot-shock apparatus, which delivered a foot-shock signal to make rats that had been given foot-shocks before emotionally stressed; the other was an empty water bottle, used to make rats that had been trained to drink water at two set times each day emotionally stressed. Ovalbumin (OVA), a novel antigen, was used to induce the humoral immune response. The effect of emotional stress on the primary immune function (anti-OVA antibody level and spleen index), the endocrine response (corticosterone level, epinephrine and norepinephrine level), and the behavioural changes (freezing, defecation, grooming, and attacking behaviour) were investigated. It was found that foot-shock signal significantly increased freezing behaviour as well as defecation, indicating fear emotion. Although 10 minutes foot-shock per day for 6 days did not significantly decrease the primary humoral immune response to OVA, foot-shocks plus fear (emotional stress) caused by the foot-shock signal decreased the anti-OVA IgG antibody production and spleen index (spleen weight [mg]/body weight [g]) significantly. Spleen index was correlated negatively with the level of epinephrine (Shao, Lin, Wang, & Zheng, 2000). In the second emotional stress model, experimental animals were randomly assigned to one of the three groups: emotional stress (ES), control 1 (C1), and control 2 (C2) group. Rats in the ES group were irregularly given empty water bottles during one of the two watering periods for 2 weeks to induce emotional stress. Rats in the C2 group were given neither empty water bottles nor water during the same watering periods as for the ES group. This group was used to control the possible effect that an animal, trained to receive water at a particular time of day, is also emotionally stressed if it does not get water at this point in time. Rats in the C1 group were allowed free access to water during all watering periods. It was found that from day 1 to day 14 of the whole experimental sessions, attacking behaviours were exhibited strongly in the rats exposed to emotional stress, but not in the rats of C1 and C2 groups, suggesting that the rats in the ES group were significantly behaviourally stressed. Rats of both the ES and C2 groups expressed significant exploring behaviours compared to rats of the C1 group but there was no difference between rats in the ES group and rats in the C2 group. For rats of the C1 group, grooming behaviours were obvious as compared with rats of the ES and C2 group. Anti-OVA antibody levels decreased significantly in rats of the ES group compared to that in rats of the C2 group. Spleen indices of the rats in ES group were significantly lower than that of the C2 and C1 groups, and there was also no difference between that of the C2 group and C1 groups. Plasma epinephrine levels of the rats in the ES group increased significantly compared to that in the C1 group; norepinephrine levels of rats in the ES group increased significantly compared to that in the two control groups. Corticosterone levels of rats in both the ES and C2 groups increased significantly compared to that in the C1 group. Additional correlation analysis manifested a negative correlation between anti-OVA antibody levels and norepinephrine levels and a negative correlation between the spleen index and epinephrine level. No correlation between corticosterone concentrations and the antibody levels was found (Shao, Lin, Wang, Washington, & Zheng, 2003). The results from the two emotional stress paradigms suggest that SNS may be involved in mediating the effects of emotional stress on humoral immune function (Shao & Lin, 2001a, 2001b)

Besides the above animal models, controllable versus uncontrollable shocks have been commonly used as psychological stressors. To study their influence on humoral immunity, animals were exposed

to six sessions (0.5 hr per session) of either controllable or uncontrollable shocks. It was found that anti-SRBC IgG of controllable rats was enhanced while that of the uncontrollable rats was suppressed when compared with the control animals (M. Li, Xiao, & Geng, 1997). These results suggest that controllability is an important determinant of the effects of stress on immunity. Wang, Xiao, Geng, and Su (1999) further found that thymopeptdum could improve the suppressed humoral immunity in stressed rats subject to uncontrollable foot-shock.

Effects of stress and interleukin-1 on hypertension

Sharing the characteristics of stress mediation, central interleukin-1 (IL-1) plays an important role in mediating the neural, endocrine, and behavioural responses to stressors. Many stressful stimuli may increase brain IL-1 mRNA and brain IL-1 bioactivity. Cardiovascular and endocrine responses to IL-1β are similar to stress responses. To test roles of central IL-1 in hypertension induced by stress (foot-shock or conditioned fear emotional stress), the hypertension phenomena were observed after intracerebral ventricular (ICV) injection of IL-1β or IL-1ra to male rats. It was found that: (1) ICV injection of IL-1β induced pressor responses; (2) hypertension induced by IL-1β was blocked by ICV injection of an IL-1ra; (3) ICV injection of IL-1ra attenuated the pressor response induced by foot-shock but intravenous injection of IL-1ra did not significantly reduce this response; (4) the hypertensive response to conditioned fear stimuli was reversed by ICV injection of IL-1ra. These results suggested that the pressor response induced by foot-shock or conditioned fear emotional stimuli is mediated by central IL-1 (Zou & Liu, 2001). Since data from the literature showed that the amygdalar, paraventricular, and arcuate nuclei are involved in the cardiovascular responses to stressful or fearful stimuli, and the paraventricular and arcuate nuclei contain immunoreactive IL-1 fibres, it seems likely that, in these nuclei, IL-1 might mediate the pressor effects induced by central amygdaloid nucleus activation. Thus the effects of IL-1β in the paraventricular nucleus or caudal arcuate nucleus on hypertensive and tachycardiac responses induced by activation of the central amygdaloid nucleus were studied. It was found that microinjection of sodium glutamate into the central amygdaloid nucleus resulted in hypertension and tachycardia. Microinjection of IL-1β into the paraventricular nucleus or caudal arcuate nucleus induced significant pressor and tachycardiac responses while pretreatment with microinjection of rabbit anti-rat IL-1β antibody into the paraventricular nucleus or arcuate nucleus attenuated the hypertensive response induced by microinjection of sodium glutamate into central amygdaloid nucleus. These data suggest that the pressor effect is mediated by IL-1β in the paraventricular nucleus or arcuate nucleus (Lu, Chen, & Zou, 2002).

Conditioned immunity

Converging data from different disciplines indicate that central nervous system processes are capable of influencing immune function. The most frequently studied phenomenon is conditioned immunity: i.e., immune response, like other physiological processes, can be modified by classical conditioning. However, until Ader and Cohen's 1975 report, most physiologists believed that the immune system and the nervous system did not interact. The central question as to whether psychological processes affect immune functions has spurred Chinese psychologists to re-examine conditioned immunity and to explore the neural substrates by which psychological process might affect the immune function (Lin, 1997).

Conditioned immunosuppression

To examine conditioning effects on behaviour and immune function, cyclophosphamide (CY), an immunosuppressive agent, was used as an unconditioned stimulus (UCS) in conditioned taste aversion (CTA) paradigms. Following the Pavlovian principles of classical conditioning, the unconditioned stimulus was paired with a neutral conditioned stimulus (CS), saccharin, and both were administered to laboratory animals. When the CS was presented alone to laboratory animals at a designated period of days following the CS-UCS pairing, the animals showed aversive behaviour, associating it with the noxious and ill-inducing effects of the UCS. Moreover, conditioning of changes in immunity, conditioned immuno-suppression of spleen cell proliferation to mitogen, and the number of peripheral leukocytes occurred upon re-exposure to CS alone after two trials of CS-UCS pairing (Lin, Wei, Gao, Tang, & Liu, 1998). When antigen ovalbumin (OVA) was ip injected three days after pairing saccharin with cyclophosphamide, conditioned rats after one trial of CS-UCS pairing and one re-exposure to CS exhibited conditioned taste aversion (CTA) and showed significant lower level of anti-OVA IgG in the peripheral serum than the UCS group. Two trials of CS-UCS pairing and three re-exposures to CS resulted in similar level of CTA, and a similar significant decreased level of anti-OVA IgG as

in the test of one trial of CS-UCS pairing and one re-exposure to CS. These results demonstrated that CS-induced suppression of the primary humoral immune response was stable but marginal even when two trials of CS-UCS pairing and the three re-exposures to CS were used (Zheng, Lin, Shao, & Wang, 2002).

The phenomena of conditioned immunosuppression were retested using rabbit anti-rat lymphocyte serum (ALS), a biological immunosuppressant, as the UCS. Data showed that ovalbumine (OVA)-immunized rats conditioned by pairing saccharin solution (CS) with an ip injection of ALS (UCS) showed conditioned immunosuppression in vitro PWM-induced spleen proliferation and in total anti-OVA IgG antibody production as well as in anti-OVA containing cells in the spleen, but did not show conditioned test aversion (Lin, Chen, & Husband, 2002). These results demonstrated that there seems to be no association between the conditioned taste aversion and the conditioned immunosuppressive responses and that conditioned immunosuppression is not the concomitant of behavioural suppression, but the result of the CS-UCS associative learning mediated by the central nervous system.

Conditioned immunoenhancement

Using antigen as the UCS, the conditioned antibody response may be a more effective model for studying the neural mechanism of conditioned immunity, since it is more specific without the participation of immunosuppressive drugs or immune cell activators. To demonstrate conditioned enhancement of specific antibody response, saccharin solution (the CS) was paired with an injection of a protein antigen ovalbumin (OVA) as UCS. It was found that anti-OVA antibody level was elevated by re-exposure to the CS alone or to the CS in the context of re-exposure to a minimally immunogenic dose of OVA, which is insufficient to increase antibody production per se (B. Li, Lin, Wei, Tang, & Guo, 1997; Lin, King, & Husband, 1993). A further study was carried out to observe the kinetic changes of conditioned antibody responses to OVA. It was found that, after a CS-UCS pairing, re-exposure of animals to the CS alone resulted in a sufficiently large enhancement of anti-OVA antibody production that began to be observed at day 15 after the CS presentation. The conditioned enhancement of antibody response achieved a peak at day 20, maintained to day 25, and then attenuated obviously down to baseline. This kinetic change of conditioned anti-OVA IgG production was similar to the regular antibody response after the primary immunization (Chen & Lin, 2002).

Neuronal mechanisms mediating conditioned immunomodulation

To characterize the main brain areas involved in the conditioned immunosuppression and conditioned taste aversion, c-Fos protein expression was observed as an anatomical marker for activated neurons. In the study, saccharin was used as CS and lithium chloride (LiCl) and cyclophosphamide (CY) were used as UCS. Both LiCl and CY are effective UCS in establishing CTA. One difference between the two UCS is that CY, a potent immunosuppressive drug, can also be used as an effective UCS to produce conditioned immunosuppression (CIS) but LiCl, an antidepressant, is immunologically neutral. It was found that after two prior pairings of saccharin with LiCl or CY, CS saccharin induced significantly more c-Fos protein in the forebrain of paired rats than that in saccharin controls or unpaired groups. The activated regions included frontal cortex, cingulate cortex, retrosplenial granular cortex, basolateral amygdaloid nucleus, subfornical organ, median preoptic nucleus, hypothalamic paraventricular nucleus, supraoptic nucleus, etc.

Although the pattern of Fos protein expression was highly similar in both Sac-LiCl and Sac-CY rats, there were some significant differences between the two conditioned groups in the number of c-Fos neurons induced by CS in some regions of the forebrain. Saccharin CS induced significantly higher density of cells with c-Fos expression in the CY-paired group than that in the LiCl-paired group in anterodorsal thalamic nucleus, cingulated cortex, lateral hypothalamic nucleus, subformical organ, supraoptic nucleus, parasubthalamic nucleus, and dysgranular insular cortex . In contrast, saccharin CS in the LiCl-paired rats induced more c-Fos production in accumbens nucleus, basolateral amygdaloid nucleus, ventral part of lateral septal nucleus, and dorsomedial hypothalamic nucleus than in the CY-paired rats. These data suggest that the expression of CTA is not mediated by a few specific brain regions but by a set of cortical and subcortical areas in which aversion behaviour and emotional reaction may take place. The difference between CY-paired and LiCl-paired groups in c-Fos expression after re-exposure to CS in some brain regions may be related to the pharmacological or conditioned pharmacological effects of CY and LiCl on the brain (Yang, Lin, Johansson, Zheng, & Tan, 2000).

To explore the neural mechanisms underlying conditioned enhancement of antibody production, c-Fos immunohistochemistry method was used to map the regional brain activation following the CS representation and during the largest expression of conditioned enhancement of antibody response. It was

found that both CS/UCS conditioning training and re-exposure to CS alone significantly increased c-Fos production in many brain regions throughout numerous cortical, limbic, diencephalic, and medullary areas. When conditioned antibody production was evident on day 20 after re-exposure to CS, higher levels of c-Fos production were detected in conditioned rats than in the controls in the brain areas including granular insular cortex, solitary tract nucleus, etc. (Chen, 2002).

Learning and memory

In human and animals, the most important mechanisms by which the environment alters behaviour are learning and memory. Rapid progress has been made in the study of behavioural principles and neurobiological mechanisms of learning and memory. For example, the study of memory has yielded three generalizations, i.e. memory has different stages, long-term memory is represented in multiple regions of the brain, and explicit and implicit memories involve different neuronal circuits and different cellular and molecular mechanisms. However, studies of learning and memory in China are unsystematic and relatively broad. The work reviewed only focuses on some parts of all the studies.

Types of memory formation and training stimulus

The biopsychology of memory has come from progress in distinguishing between different types of memory: short-term memory (STM), immediate-term memory (ITM), and long-term memory (LTM). Many factors influence the formation of memory. One is the strength of stimulus used for training: Zheng, Wang, Weng, and Kuang (1997) found that chicks trained with 5% and 20% methyl anthranilate (MeA), a taste aversion drug, preserved memory for about 15 minutes and 50 minutes respectively, fitting the STM and ITM of the multiple-stage model of memory formation, while those trained with 40% MeA yielded a high retention level up to 8–10 hours. This time-course appeared to correspond with the glycoprotein-synthesis-independent stage of the LTM. Only MeA over 60% resulted in good retention lasting at least 24 hours. These results suggested that the weak-learning paradigm not only dissociated the traditional three main stages of memory formation (STM, ITM, LTM), but could separate the LTM into an early and a later phase (Zheng et al., 1997). Gao, Jin, and Guan (1997b) suggested that there are multiple stages of memory formation in mice, and the stages are very similar to those in chicks.

The structures of the hyperstriatum ventrale (HV) and lobus parolfactorius (LPO) of the brain are known to be the crucial part in the memory formation process in the chick: the former is more important in the stability of memory and the latter is necessary for the store of long-term memory. Hu, Guan, Kuang, Jiang, and Kuang (1998) studied the expression of Jun protein, derived from c-Fos proto-oncogene, during the different learning courses (9, 10, 30, and 70 minutes; 4, 8, and 24 hours) in HV and LPO in 1-day-old chicks trained with 100% concentration of MeA. Data showed that Jun-like protein in both LPO and HV was expressed but more Jun-like protein in LPO was found than that in HV (Hu et al., 1998). The expression of c-Jun in monovisually deprived chicks following a one-trial passive avoidance task was also higher in LPO than in HV. These results suggest that LPO may play a more important role in learning and memory in chicks (Gao, Guan, & Kuang, 1997a).

Effect of light exposure and corticosterone on learning and memory

Chicks are precocious animals. As a relatively independent individual at the moment of its hatch, the chick is capable of feeding and drinking alone, and acquiring and remembering behavioural skills. These abilities require that the chick embryo undergoes a considerable degree of structural and functional development by the time of hatch. Environmental conditions, including light exposure, should have an effect on the post-natal abilities of learning and memory. Sui and Rose (1997) found that dark incubation induced a weak amnestic effect on retention for a passive avoidance task and a diminution in discriminative memory ability in day-old chicks. Light exposure to dark-incubated eggs, especially during embryonic days E19 to E20, alleviated the retention and discrimination deficits. Gao et al. (2001) also found that light-incubated or normal-incubated chicks showed better performance in the passive avoidance test than dark-incubated chicks. It was further found that neural cell adhesion molecules (NCAM) expression was high in the light-incubated chick or normal-incubated eggs at embryonic day 20, while the NCAM level was very low in dark-incubated eggs. These results may suggest that NCAM, which is regulated by light exposure, might be involved in post-hatch learning and memory behaviour (Gao et al., 2001).

Corticosterone is widely known to modulate the organism's adaptive behavioural response, and the expression of proteins in the basis of behavioural plasticity such as that of learning and memory. It is known that there is high level of plasma corticosterone on the day of hatching followed by a gradual reduction over the next few days. To investigate whether intra-embryonic (prior to hatching) or intra-peritoneal (post-hatching) administration of corticosterone could diminish the memory

deficits found for recall of a one-trial passive avoidance task in chicks incubated in the dark, groups of embryos or chicks were divided and injected with 1 ml solution of either corticosterone (60 ng) or vehicle respectively on different days of development from day E17 to Day 1. Chicks were trained using a weak learning paradigm on Day 1 post-hatch. It was found that retention levels in corticosterone-treated, dark-incubated chicks were enhanced when compared with those in vehicle-treated controls. The optimal time points for corticosterone injection were days E19 to E20, which closely resembled those found previously for light exposure. This suggested a possible interaction between light and corticosterone during late embryonic development, with consequent effects on neonatal learning and memory (Sui & Rose, 1997; Sui, Sandi, & Rose, 1997).

Role of hippocampus in learning and memory

Clinical evidence from several patients, as well as studies of experimental animals, suggest that a lesion restricted to any of the major components of the brain can have a significant effect on learning or memory storage. However, different regions of the brain may not have equivalent roles. The hippocampus may be relatively more important for learning and memory.

In 1982, Liu and Kuang observed the effects of the hippocampus damage on the different stages of the establishment of dark avoidance conditioned reflex (DAR). It was found that extensive damage of the hippocampus resulted in difficulty in consolidating the DAR, and the more the conditioned reflex is consolidated, the less it is interfered with by the damage. Bilateral hippocampal damage also resulted in the difficulty to consolidate the jump-table reaction (JAR). However, the damage produced no effect on the retention of JAR once it was consolidated (Liu & Kuang, 1985).

The effect of ventral hippocampus damage on the DAR was more prominent than that of dorsal damage. These results suggest that the hippocampus takes part in different stages of memory, especially the early stage, and that the effects of different parts of the hippocampus are different (Liu & Kuang, 1982). Zhang, Ou, and Xu (1983) suggested that the hippocampus plays a lesser role in the memory of the senses of smell and gestation, whereas it plays an important role in the formation of memory of vision and hearing (Zhang et al., 1983). It was also found that the hippocampus exerted influence on spatial cognitive performance. Sui, Chen, and Kuang (1992) reported that both hippocampal formation (HF) and prefrontal cortex (PFC) lesions lead to spatial cognitive deficits of rats in Morris maze performance. However, the former usually used paretic strategies of "no mapping," which were different from the strategies used by the latter. The different strategies suggested that HF and PFC are at different levels of the spatial cognitive system, and that the role of HF might be more important than that of PFC (Sui et al., 1992). Other factors such as drugs and hyperbaric oxygen resulted in both hippocampal changes and changes in learning and memory (Xu, Guo, & Zhang, 2000; Zhang, Xu, & Wu, 1998).

As to the mechanisms of the role hippocampus plays in memory, Ou et al. (1988) observed performance of conditioned operant conditioning by injection of scopolamine (M-cholinergic receptor antagonist), GABA, and picrotoxin (GABA receptor antagonist) into the hippocampal area CA_3 through chronically embedded canula. The data showed that injection of either scopolamine or GABA caused a depression in the operant conditioned response. However, after a prior injection of Picrotoxin, the depression of the conditioned response by the administration of GABA was reduced. These results suggested that M-cholinergic receptor and GABA receptor in the hippocampal area CA_3 were involved in the retention of long-term memory (Ou et al., 1988). Microinjection of norepinephrine (NE) into the rat hippocampal dentate gyrus (DG) during the establishment and consolidation of conditioned drinking response significantly enhanced synaptic efficacy, facilitating the development of learning-dependent long-term potentiation response (LdLTP), but the same treatment had no effect on retention of LdLTP, suggesting that NE was involved in the development of LdLTP in DG (Xu et al., 1993). When rats were trained to perform conditioned drinking behaviour, high-frequency stimulation (HFS) of the mammillary body (MB) could elicit a temporary inhibition of population spikes in dentate gyrus (DG). When animals were treated with HFS of MB before the daily training session, the development of LdLTP was suppressed and the conditioned drinking response was delayed. HFS of MB had no effect on retention of LDLTP and the consolidation of conditioned response. These results suggested that MB might exert an inhibitory modulation on the development of LdLTP in DG (Wang, Xu & Ou, 1994).

Drug abuse

Drug abuse is one of the most serious worldwide social problems. Scientific knowledge has been helpful for our understanding of the nature of drug addiction. Based on the results of neurobiological research, the adaptations in specific brain neurons caused by repeated exposure to drug abuse changes the functioning of the neuron circuits at those neurons. As

consequential behaviours, craving and relapse are thought to be critical issues in current or future research.

Effects of morphine on behaviour and electric stimulation inhibition

Chronic-addictive drug exposure induces a series of molecular, cellular, and behavioural changes, which are correlated to dependence, craving, and relapse. The locomotor activity (LA) of rats was tested after morphine was injected ip with 8, 4, 2, or1 mg/kg/day. Results showed that there were significant differences between the groups treated with lower doses of morphine and saline, and 4–2 mg/kg/day was the most suitable dose of morphine for activating LA. The peak effect of 4 mg/kg/day of morphine was found at 15–20 min after injection, and it kept going up for 8 days. It suggested that a low dose of morphine may be more suitable for related behavioural effects such as those of conditioned place preference (CPP) or self-administration (Chen, Hu, Dong, Yang, & Sui, 2000).

CPP is a commonly used model to detect the rewarding effect of drugs. It was found that CPP could be induced by conditioning training with 4 mg/kg dose of morphine for 10 days in rats and peripheral electric stimulation (EAS) with a component of low frequency (2 Hz) could specifically inhibit the expression of morphine-induced CPP (Wang, Luo, Xia, & Han, 2000). To observe whether multiple EAS has a suppressing effect on morphine withdrawal syndrome, rats were injected twice for 10 days with increasing doses of morphine (10–120 mg/kg) and then received multiple electric high-frequency stimuli (100 Hz) (30 min per session). Data showed that rats receiving 2–4 EAS exhibited less spontaneous withdrawal syndrome and the effects of EAS on withdrawal syndrome were cumulative and lasting (Wu, Cui, & Han, 2001).

Effects of scopolamine and physostigmine on acquisition of addictive behaviour

The ultimate behavioural effects of addictive drugs are largely modulated by learning and memory processes. Research has shown that the central cholinergic system plays an important role in memory process, and that it is impaired by the administration of morphine. There are some interactions between central opioid and cholinergic systems through inhibitory effects of opioid-like substances on cholinergic neurons of hippocampus and prefrontal cortex via μ and δ receptors. Opioid-like substances inhibit the cholinergic projection from medial septum to hippocampus, which is regarded as closely associated with spatial learning impairment. To investigate effects of morphine on the learning processes of rats and interactions of opioid and cholinergic systems, a Morris water maze was used to measure the latency of rats receiving drug treatment to find the covered platform. Chronic morphine administration (10 mg/kg) impaired the acquisition process of rats for this task. An appreciable difference was identified for the morphine 10 mg/kg group compared with the morphine 3 mg/kg group. Co-administration of morphine (10 mg/kg) and scopolamine (3 mg/kg) aggravated acquisition impairment induced by morphine 10 mg/kg or scopolamine alone, though scopolamine itself induced no salient changes in the acquisition capabilities of rats. In addition, physostigmine (0.1 mg/kg) could appreciably attenuate morphine-induced acquisition impairment. Morphine 10 mg/kg evidently impaired the acquisition process of rats. There was a close relationship between the acquisition capabilities of morphine-treated rats and the functions of the cholinergic system (Zheng, Li, Yang, & Sui, 2002).

Corticosterone reinforces motivation for drug-seeking

Steroid hormones seem to be one of the biological substrates mediating stressful action in developing drug intake. Interaction of corticosterone with low dosage morphine on motivational intensity for drug-seeking was investigated. Three continuous phases and a test were included: (1) pre-training: rats were trained on 10 trails (3 min/trail) in the maze for survival in the first 2 days — poor score rats (10% of total) were deleted; (2) addicting training: rats were given peritoneal injections respectively with morphine (2 mg/kg/day), corticosterone (100 ng/kg/day), or morphine plus corticosterone or saline, immediately after every trail in the maze without platform, 2 min/trail, 3 trail/day, 10 min interval, altogether 18 trails in 6 days; (3) reinforcing training: in the maze with platform, given that rats kept on searching for the platform after 1 min, saline, morphine, corticosterone, or morphine plus cortico-sterone were given, or no drugs, for 18 trails in 6 days; (4) test: at different time points of the 4th, 8th, and 16th day after the last training, the latencies of finding the platform for three 10 min-interval trails were respectively tested. Results indicated that the group treated with corticosterone plus morphine significantly increased the latency of finding the platform, and the group with only morphine showed a significant difference only at the 4th day after abstinence, as compared to control groups. Possible mechanisms of the facilitating effects of corticosterone on either increasing sensitivity to morphine or enhancing the propensity of drug intake was discussed (Sui & Chen, 2000; Sui, Hu, Chen, Kuang, & Joyce, 2001).

Effect of naloxone on acquisition and retention of conditioned place aversion

The negative affective state of opiate abstinence plays an important role in craving and relapse to compulsive drug use. To compare the effect of different dose of naloxone and morphine on the acquisition and retention of conditioned place aversion (CPA) in morphine-dependent rats, and to investigate the possible impact of naloxone underlying conditional acquisition of CPA in the different states of morphine dependence or abstinence, rats were made physically dependent, with the initiative dose (6 or 12 mg/kg) of morphine by ip injection with 20% increase every day for 10 days, and were trained to develop CPA induced by naloxone (0.5 or 1.0 mg/kg) in a biased three-compartment conditioned place apparatus. The results showed that morphine-dependent rats with naloxone treatment produced distinct CPA. Though the effects of both high- or low-dose morphine and naloxone on the acquisition of CPA had no significant difference in the morphine-dependent rats, the conditional training with the low-dose naloxone induced longer-lasting CPA than that with the high-dose naloxone. The conditional training with high- or low-dose naloxone produced CPA in the dependent rats, but not in the abstinent rats. This suggests that dose differentials of naloxone played different roles in the acquisition and retention of CPA in morphine-treated or abstinent rats (Xu & Sui, 2002).

Novelty-seeking behaviour and morphine place conditioning

The vulnerability of drug abuse is attributed to the interaction between responsiveness of HPA axis and the function of mesolimbic dopamine system (MLDS). Although different behavioural models have been designed to measure stress-induced locomotion and novelty-seeking behaviour, the clear separation of "escape" and "explore" components of motor response in a novel environment remains a challenge to researchers. Moreover, the reactivity of HPA axis and dopamine system in MLDS undergoes plasticity with development of rodents, causing stressful and relatively "pure" novelty-seeking behaviours to become more interwoven (Zheng et al., 2002; Zheng & Sui, 2001). In the study, the stress-induced locomotion and novelty-seeking behaviour in juvenile rats, as well as conditioned place preference (CPP) with 2 mg/kg morphine 56 days later in their adulthood were tested. Results showed that rats with high response to open-field test (HRS) expressed a statistically equal chance of novelty-seeking behaviour as low responders (LRS). Rats with high response to novelty (HRN) spent longer in the drug-paired side of the shuttle box compared with the low responders to novelty (LRN). Moreover, both HRS and LRS rats expressed equally elevated preference for the drug-paired side in the conditioned place preference (CPP) test. Results suggested that there existed evidence for dissociating open-field locomotion and novelty-seeking behaviour in juvenile rats in contrast to a fading of this effect in their adult counterparts. Meanwhile, juvenile rats with HRN expressed a significant CPP effect of morphine, suggesting that novelty-seeking behaviour during the juvenile period could predict the propensity to CPP effect of morphine in adulthood.

Sensitization of nomifensine, SCH23390, and spiperone on discrimination

To probe the behavioural consequence of dopamine activity mechanism underlying natural reward in the central neural system (CNS), the sensitization and intervention effects on sucrose licking in naïve or chronic morphine-treated rats were investigated. Rats were administrated ip with morphine 10 mg/kg/day or vehicle, dependent on drug-treated or naïve group, for 20 consecutive days. With a restricted water-feeding schedule in all the rats, the volume/time of sucrose or water licking was measured 5 days after morphine withdrawal. When the volumes of fluid intake became relatively stable in 8 days, naïve or chronic morphine-treated rats were administrated ip with nomifensine (DA reuptake blocker), SCH23390 (D1 antagonist), spiperone (D2 antagonist), or SCH23390 or spiperone co-administered with nomifensine 20 min before test. Then, the volumes of sucrose and water licking were recorded and compared pre- or post-intervention. The sucrose intake in all the rats was enhanced by nomifensine, but the effect was more significant in chronic morphine-treated rats. However, the increase of sucrose intake by nomifensine was reversed to baseline by SCH23390, but not by spiperone. These results suggested that chronic morphine treatment sensitized the dopaminergic activity of natural-reward in CNS, which might be modulated by the dopamine system via D1 receptor (Tan , Chen, Yang, & Sui, 2001).

CONCLUDING REMARKS

This paper has reviewed the research and development of biopsychology in China. The major part of the paper summarized the most recent research, including stress, behaviour immunity, learning and memory, and drug addiction. Although efforts have been made to provide

the biological mechanisms that are most relevant to fundamental issues in biopsychology, such as the mind–body interaction, stress, and addictive behaviour, much of the work done is still at an early stage. To what extent psychologically induced changes in stress response, immune function, and drug abuse can be clinically relevant remains to be established.

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