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Neuroendocrine response to casino gambling in problem gamblers

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Summary Problematic gambling is thought to be influenced by neurobiological mechanisms. However, the neuroendocrine response to gambling is largely unknown. Therefore, the effect of casino gambling on the sympathoadrenal system, the HPA-axis, and pituitary hormones were analyzed.

Fourteen male problem gamblers and 15 non-problem gamblers were examined in a balanced cross-over design. In the experimental session, participants played blackjack in a casino wagering their own money. During the control session, subjects played cards for accumulation of points. Heart rate and endocrine measures were recorded at baseline, at 30, 60 and 90 min during gambling/card playing, and after the game.

Heart rate and norepinephrine levels increased with the onset of blackjack in both groups, with problem gamblers showing significantly higher levels across the entire gambling session. In addition, dopamine levels were significantly higher in problem gamblers during casino gambling compared to non-problem gamblers. Cortisol levels were transiently increased with the onset of blackjack in both groups.

Casino gambling as a ''real life'' situation induces activation of the HPA-axis and the sympathoadrenergic system, with significantly more pronounced changes

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in problem gamblers. These findings may contribute to a better understanding of neuroendocrine disturbances in problem gambling.

1. Introduction

Recent theoretical models of the development and maintenance of pathological gambling have highlighted the significance of neurobiological mechanisms (Meyer et al., 2000; Potenza, 2001; Sharpe, 2002). Neurotransmitter genes and multiple neurotransmitters are believed to play a major role in mediating acute reinforcement effects in the brain (Comings et al., 2001; Potenza, 2001).

There are ample data suggesting a role for neuroendocrine mechanisms in pathological gambling. For example, pathological gamblers have increased central noradrenergic activity compared to healthy control subjects (Roy et al., 1988, 1989). Basal cortisol remains unaltered (Ramirez et al., 1988), or is elevated during days of intense gambling activity (Schmitt et al., 1998). We have recently demonstrated that regular gamblers experience HPA-axis activation during casino gambling, as shown by an increase in salivary cortisol, in parallel to increased cardiovascular activity (Meyer et al., 2000). Collectively, these observations support the hypothesis that regular gambling induces acute neuroendocrine activation (Blaszczynski et al., 1986), which in turn might contribute to mood alterations and to the reinforcing properties of gambling behavior (Meyer et al., 2000). However, whether and to what extent peripheral neurotransmitters or pituitary hormones, such as β-endorphin or prolactin, are altered by pathological gambling remains unclear (Blaszczynski et al., 1986; Shinohara et al., 1999).

Central monoaminergic systems are implicated in problem gambling. Genetic studies suggest that allelic variants of genes related to function of dopamine, serotonin, and norepinephrine can predispose a risk factor for pathological gambling (Comings et al., 2001). In parallel, altered levels of monoamines (decreased dopamine) and their metabolites (increased 3,4-dihydroxyphenyl-acetic acid and homovanilic acid) in cerebrospinal fluid (CSF) of individuals with addictive gambling behavior have been observed, suggesting altered function of the dopaminergic and noradrenergic system in pathological gambling (Bergh et al., 1997). Serotonergic mechanisms, as measured via 5-hydroxytryptamine and 5-hydroxyindoleacetic acid (5-HIAA), are reported to not be altered in pathological gamblers (Roy et al., 1988, 1989; Bergh et al., 1997). However, when adjusting for between-group differences in CSF flow rates, Nordin and Eklundh (1999) found decreased 5-HIAA levels in male pathological gamblers. Other findings suggest that the noradrenergic system mediates selective attention among pathological gamblers and is related to heightened arousal, readiness for gambling or risk-taking (Roy et al., 1988, 1989; DeCaria et al., 1998; Schmitt et al., 1998; Shinohara et al., 1999; Blanco et al., 2000). Together, these data suggest that catecholamines are involved in gambling behavior. However, the neuroendocrine response pattern to gambling in a field setting has been analyzed by only a few studies. The results have been inconclusive because no control group has been included for comparison.

Therefore, this study aimed to analyze the effect of casino gambling on cardiovascular and neuroendocrine activity in problem gamblers in direct comparison to non-problem gamblers. Specifically, we analyzed heart rate, plasma concentration of catecholamines (epinephrine, norepinephrine, and dopamine), ACTH and cortisol and pituitary hormones such as β-endorphin and prolactin before, during, and after a casino session of blackjack and a control condition. Thus, we examined the hypothesis of increased activity of the HPA-axis and the monoaminergic system in problem gambling.

2. Methods and material

2.1. Subjects

Male blackjack players were recruited in casinos through direct approach or through newspaper advertisements. In total, 29 individuals participated (mean age 43.0 ± 10.4 years). Each individual was paid € 150 for their participation and traveling expenses. The protocol of the current study was approved by the local ethics committee of the Medical Faculty of the University of Essen for investigations using human subjects. In addition, participants were screened via a general medical examination and a semistructured clinical interview. Individuals on medication, abusing drugs/alcohol (except nicotine consumption), or exhibiting endocrinological, psychological, or

physical disorder, were excluded from the study because of the potential effects on the endocrine secretion pattern during the experiments. After complete description of the study to the participants, written informed consent was obtained.

2.2. Design and procedure

Specific testing dates were arranged with each participant in accordance with a counterbalanced cross-over design, so as to control habituation effects. All examinations were conducted by a scientist (Ph.D.) together with a M.D. Each subject participated in an experimental session in the casinos of Hannover or Bad Zwischenahn, Germany, and a control session in the University of Hannover, Germany. In the experimental session, the heart rate recorder was fitted in a separate room once the participant arrived at the casino. Baseline data were collected 20 min before gambling by recording each subject's heart rate in a resting position. Heart rate recording took place during the entire session; for each time of measurement, means were taken from the last five minutes of each game period.

Thirty minutes before gambling an i.v. cannula (Versify Granule, 18G) was inserted by a M.D. into a forearm vein for repeated blood sampling. Fifteen minutes before gambling, a baseline blood sample was drawn.

In the experimental session, the subject was seated at the blackjack table and played the game using his own money. The minimum and maximum stake was € 10 and 500, respectively. All participants were able to complete the whole experimental session without running out of money. The second, third and fourth blood samples were collected following 30, 60 and 90 min of play, respectively. A follow-up blood sample and heart rate measurement were taken 20 min after the end of the play, and then the participants completed the final questionnaire (general emotional involvement while gambling, as explained below). The control session was conducted similar to the experimental session. However, participants played a game of cards without monetary stakes in a university environment. The degree of movement exhibited by the participants was the same between control and experimental sessions, and between measurement of baseline, play and after the play (e.g. the same distance between the gambling table/card playing and the separate room for blood sampling). Both the experimental and the control sessions occurred between 19:00 and 23:00 h, with the length of play lasting 1.5 h. Alcohol consumption during the experiments was prohibited.

2.3. Measures

2.3.1. Heart rate measurement

Heart rate was measured continually using a portable heart rate monitor (Accurex Plus, Polar, Büttelborn, Germany). The ECG was transmitted from a chest patch to a receiver worn around the wrist in the mode of a watch. Heart rate was recorded and saved by the receiver in 5 s intervals. Data were transferred from receiver to computer using ''Polar Interface Plus'' software.

2.3.2. Endocrine measures

For repeated blood sampling, an i.v. cannula was inserted into a forearm vein of the nondominant arm. Blood was drawn before, during and after gambling and collected into EDTA tubes (Sarstedt, Nümbrecht, Germany). Blood samples were immediately centrifuged at 4 °C and plasma stored on dry ice during the experiment and latter stored at −70 °C until endocrine analysis.

All hormone samples were assayed in duplicate within the same assay. Catecholamine plasma levels were measured by high pressure liquid chromatography (HPLC). Respectively, the intra- and interassay variability for norepinephrine were 6.2% and 8.0%, for epinephrine, 4.0% and 5.1%, and for dopamine, 5.0% and 8.9%. Prolactin and cortisol were detected by the Automated Chemiluminescence-Immunoassay-System 180 (ACS: Centaur, Chiron Diagnostics, Germany). The intra- and interassay coefficients of variance were 2.5% and 3.6% for prolactin, and 4.5% and 6.4% for cortisol, respectively. ACTH plasma levels were detected by a chemiluminescence's immunoassay (Modul LSUBX, DPC Biermann, Germany) with an intra- and interassay coefficient of variance of 8.7% and 10%, respectively. β-Endorphin was measured using an immunoradiometric assay (IRMA; Nichols Institute Diagnostic, California, USA) after alcohol extraction of blood samples. The intra- and interassay coefficients of variance were 4.1% and 9.0%, respectively.

2.3.3. Behavioral measurement

Two instruments were used to assess problem or pathological gambling: a German version of the ''South Oaks Gambling Screen'' (SOGS) (Lesieur and Blume, 1987), which examines gambling behavior over the previous 12 months, and a German short questionnaire for the assessment of gambling characteristics (''Kurzfragebogen zum Glücksspielverhalten'' (KFG); Petry, 1996), which assesses lifetime gambling behavior. The SOGS is a widely used screening instrument based on DSM-III diagnostic criteria for pathological gambling. The majority of the 20 items are in a forced choice

yes/no format. In accordance with established criteria, subjects who scored 3 or 4 points on the SOGS were classified as ''problem gamblers'' while those who scored 5 or more points were classified as ''probable pathological gamblers'' (Volberg, 1996). The KFG is a 20-item questionnaire with statements scored on four-point Likert scales (0–3), producing a maximum score of 60 (Petry, 1996). The items assessed preoccupation with gambling, loss of control, escapism, financial indebtedness, ''chasing one's losses'', illegal acts, feelings of guilt, and suicidal thoughts. Furthermore, the questionnaire can discriminate gamblers in treatment (score ≥ 16) from comparative samples of casual gamblers and bridge players (score < 16), and can diagnose pathological gamblers according to DSM-III-R criteria. A score of 16 or more indicates emerging (16–25), medium (26–45), or severe (45–60) pathological gambling.

In addition, data were collected regarding general emotional involvement both while gambling (seven-point scale: ''not at all'' to ''very strong''), as well as compared to previous casino visits (five-point scale: ''much weaker'' to ''much stronger''). Finally, data were collected on various emotional states (arousal, satisfaction, happiness, disappointment, craving, desire to start/continue gambling) before, during and after gambling (seven-point scale: ''not at all'' to ''very strong''), and the actual result of the particular sequences of gambling was registered (amount of money, won or lost).

2.3.4. Statistical analyses

Following statistical confirmation of normal distribution and variance homogeneity, data were analyzed using two-factor (group $\times$ time) ANOVA with repeated measures, and with Greenhouse–Geisser corrections. Endocrine data from the experimental and the control condition were analyzed separately. In a further step, for each subject, data from the control condition were subtracted from the experimental condition in order to analyze endocrine alterations/differences that are primarily due to the specific condition of gambling in a real life situation. These data are represented as the Δ-value in problem and non-problem gamblers for each time point. Again, ANOVA with repeated measures was carried out for these data, as described above. Post hoc analyses were conducted using Scheffé tests. Statistical significance was set at a probability level of $p < 0.05$. Ranked and nonparametric variables were compared by Mann–Whitney *U*-test. Correlational analyses were performed employing Pearson correlations.

3. Results

3.1. Group characteristics

Fourteen participants (mean age 42.1 ± 11.6 years) fulfilled the criteria of at least problem gamblers and scored ≥ 3 on the SOGS (four subjects scored 3 or 4; nine scored ≥ 5) and/or ≥ 16 on the KFG (nine subjects scored 16–25; three scored >26). Fifteen participants formed the control group of non-problem gamblers (mean age 43.9 ± 9.5 years). They scored ≤ 1 on the SOGS and ≤ 14 on the KFG. Ten of the problem gamblers gambled once a week or more over the last 12 months, while 10 non-problem gamblers reported casino gambling less than once a month. There were no significant differences in subjective data regarding general emotional involvement in comparison with previous casino visits ($U = 76$; $p = 0.22$). Each group had nine smokers, who smoked during the sessions. Both groups did not significantly differ concerning smoking habit or daily alcohol intake.

3.2. Cardiovascular measures

Casino gambling increased the heart rate of both problem and non-problem gamblers (time effect: $F[4, 108] = 21.39$, $p < 0.001$) (Fig. 1). Problem gamblers had a higher heart rate compared to non-problem gamblers during casino gambling (group effect: $F[1, 27] = 6.43$, $p = 0.017$). This difference was not observed during the control condition (only time effect: $F[4, 108] = 3.29$, $p = 0.014$).

The analysis of the Δ of heart rate showed increasing values throughout the session in both groups (time effect: $F[4, 108] = 14.54$, $p < 0.001$). Although problem gamblers again showed higher heart rate levels than non-problem gamblers, there was no significant group effect.

3.3. Endocrine measures

Peripheral catecholamine levels were analyzed before, during and after gambling. *Epinephrine* levels increased in non-problem gamblers during gambling and declined at the end of the session, whereas epinephrine levels in problem gamblers were already elevated at baseline (time effect: $F[4, 108] = 5.46$, $p < 0.001$). Analysis of the Δ of epinephrine levels also revealed a significant time effect ($F[4, 108] = 8.17$, $p < 0.001$) (Fig. 2A).

Norepinephrine levels increased during gambling, and declined at the end of the session in both groups (time effect: $F[4, 108] = 3.68$, $p = 0.007$). However, higher norepinephrine levels

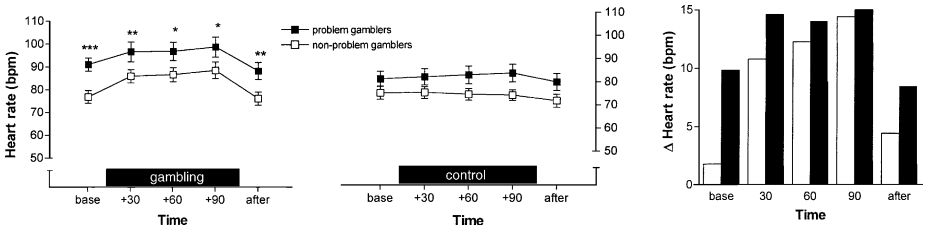

Fig. 1. Heart rate before gambling (base), during 30, 60 and 90 min of gambling, and after gambling in problem gamblers (■) and non-problem gamblers (□). Data are presented for the experimental (left) and control conditions (middle), as well as the △ between both (right). Data represent mean ± SE (except right panel). *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$.

were observed in problem gamblers across the entire session. This was confirmed by analysis of Δ-norepinephrine levels which showed significantly higher plasma norepinephrine concentrations throughout the session in problem gamblers (interaction effect: $F[4, 108] = 2.53$, $p = 0.045$) (Fig. 2B).

In parallel with the enhanced norepinephrine concentrations, problem gamblers had significantly higher *dopamine* levels during the experimental session (group effect: $F[1, 27] = 5.39$, $p = 0.028$), with highest levels after 90 min of gambling. Δ-analysis of dopamine levels demonstrated higher concentrations at all time points for problem gamblers in comparison to non-problem gamblers (group effect: $F[1, 27] = 6.60$, $p = 0.016$) (Fig. 2C).

In order to analyze the gambling-induced activation of the HPA-axis, *ACTH* and *cortisol* plasma levels were analyzed. ACTH and cortisol levels were transiently increased during gambling in either group (time effect: $F[4, 108] = 9.16$, $p < 0.001$ for ACTH; $F[4, 108] = 13.55$, $p < 0.001$ for cortisol) (Fig. 3A and B). Moreover, Δ-analysis of cortisol revealed a significant interaction effect ($F[4, 108] = 4.32$, $p = 0.003$) due to transient increased cortisol levels at the beginning of gambling in problem gamblers (Fig. 3B).

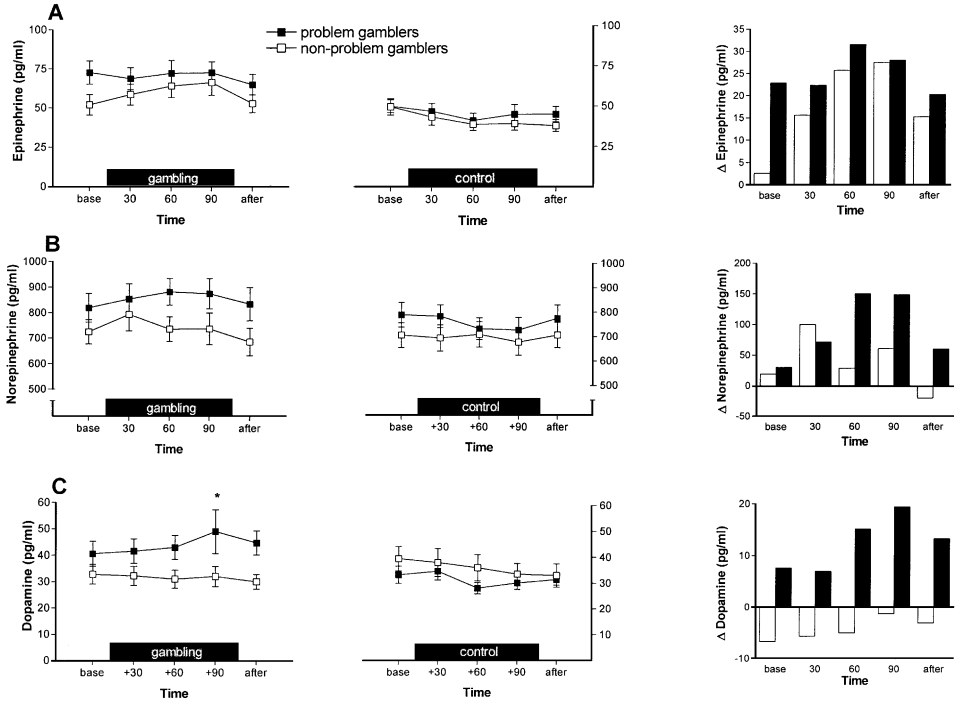

Fig. 2. Epinephrine (A), norepinephrine (B) and dopamine (C) levels before gambling (base), during 30, 60 and 90 min of gambling, and after gambling in problem gamblers (■) and non-problem gamblers (□). Data are presented for the experimental (left) and control conditions (middle), as well as the △ between both (right). Data represent mean ± SE (except right panel). *$p < 0.05$.

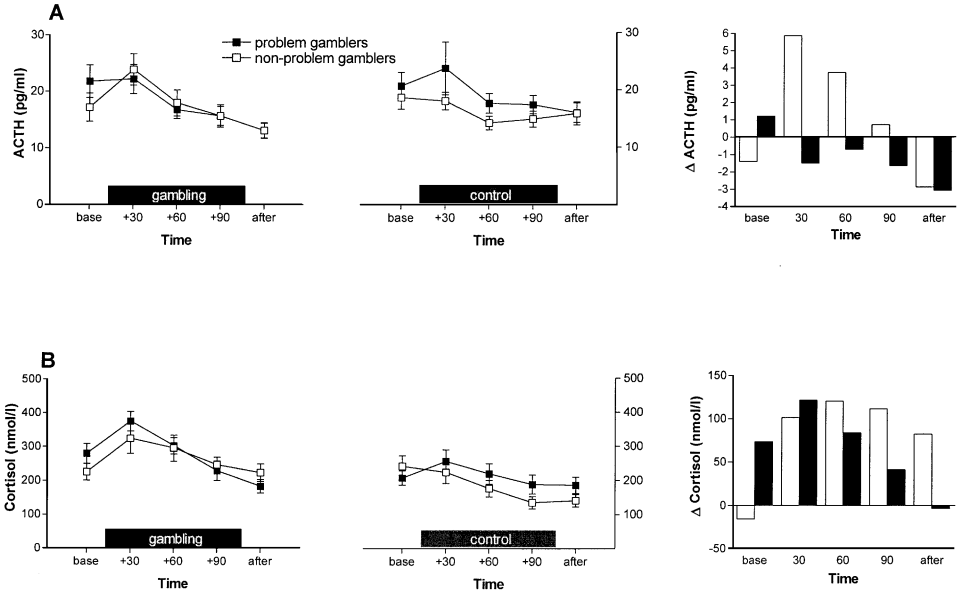

Fig. 3. ACTH (A) and cortisol (B) levels before gambling (base), during 30, 60 and 90 min of gambling, and after gambling in problem gamblers (■) and non-problem gamblers (□). Data are presented for the experimental (left) and control conditions (middle), as well as the △ between both (right). Data represent mean ± SE (except right panel).

Since pituitary hormones, in particular *β-endorphin*, are believed to be associated with pathological gambling, β-endorphin and prolactin plasma concentrations were analyzed. β-Endorphin plasma concentrations tended to be higher in non-problem gamblers in the experimental session (group effect: $F[4, 108] = 3.77$, $p = 0.062$). Similarly, Δ-analysis revealed higher levels in non-problem gamblers but were not statistical significant (group effect: $F[1, 27] = 3.31$, $p = 0.08$) (Fig. 4A). In contrast, *prolactin* levels were not affected by gambling and did not significantly differ between the groups (Fig. 4B).

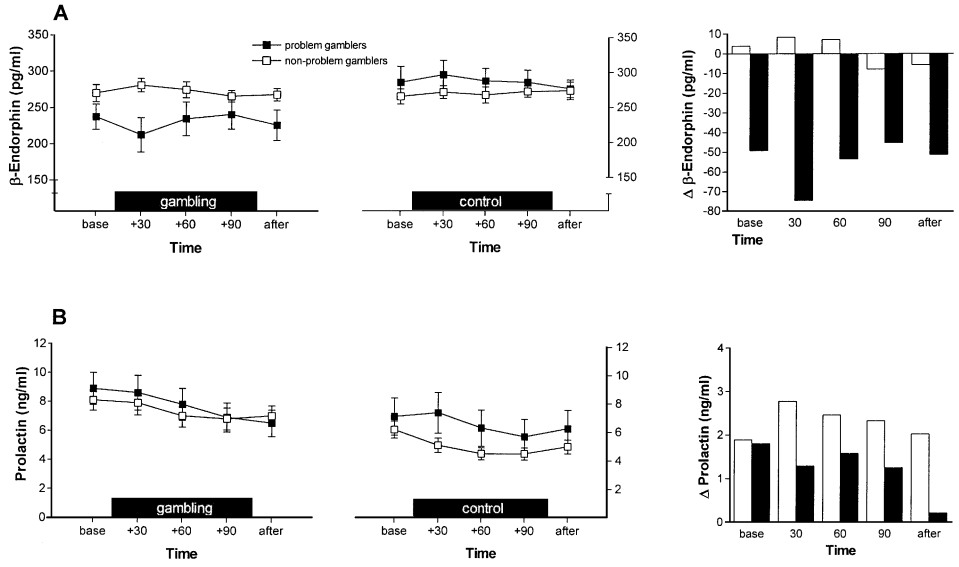

Fig. 4. β-Endorphin (A) and prolactin (B) levels before gambling (base), during 30, 60 and 90 min of gambling, and after gambling in problem gamblers (■) and non-problem gamblers (□). Data are presented for the experimental (left) and control conditions (middle), as well as the △ between both (right). Data represent mean ± SE (except right panel).

3.4. Correlational analysis over all participants

Positive correlations were found between the actual result of gambling and the norepinephrine plasma concentrations after the first ($r = 0.434$, $p < 0.05$) and third sequence of gambling ($r = 0.392$, $p < 0.05$) and in the follow-up sample ($r = 0.425$, $p < 0.05$). Additionally, the desire for starting/continuing gambling was positively correlated with plasma norepinephrine at baseline ($r = 0.408$, $p < 0.05$) and after the first ($r = 0.478$, $p = 0.01$) and third sequence ($r = 0.390$, $p < 0.05$). There were no significant correlations between the average bet size, the actual result of the particular sequences of gambling and the SOGS- and KFG-scores indicating that problem gamblers did not put higher wagers or differ in their wins and losses from non-problem gamblers.

4. Discussion

To our knowledge, this is the first study characterizing the neuroendocrine response pattern of casino gambling in problem gamblers in direct comparison to non-problem gamblers in a real life situation. By analyzing heart rate, catecholamines, the HPA-axis and other pituitary hormones before, during and after gambling, these data demonstrate sympathoadrenal activation during gambling with significantly higher heart rates and higher levels of norepinephrine and dopamine in problem gamblers. Furthermore, the onset of casino gambling induced an activation of the HPA-axis, evidenced by increased plasma concentrations of cortisol.

Concurring with our previous study (Meyer et al., 2000), the current data indicate that increases in heart rate as a result of casino gambling are moderate. This finding is also supported by observations from a number of earlier studies (Anderson and Brown, 1984; Leary and Dickerson, 1985; Carroll and Huxley, 1994; Coventry and Norman, 1997; Blanchard et al., 2000). However, the observed increase in heart rate during gambling in problem gamblers compared to non-problem gamblers indicates a higher psychophysiological activation in these subjects. Furthermore, an elevated baseline heart rate in problem gamblers while playing blackjack as compared with non-problem gamblers suggests anticipatory autonomic arousal in problem gambling. Clinically, sustained increases in heart rate in problem or pathological gamblers, together with other comorbid factors, may contribute to cardiovascular disturbances as discussed by Potenza et al. (2002).

The activation of the sympathetic nervous system during gambling is further demonstrated by increased catecholamine levels. Epinephrine concentrations increased during gambling in both groups with a subsequent decline at the end of the session. The higher epinephrine levels at baseline in problem gamblers might be interpreted as a higher level of expectancy, together with anticipatory autonomic activation in these subjects. In contrast, problem gamblers had significantly higher norepinephrine levels after 60 and 90 min of gambling, and in the follow-up sample. These observations correspond to previous reports of higher baseline levels of norepinephrine and its metabolite 3-methoxy-4-hydroxyphenylglycol (MHPG) in CSF, elevated levels of urinary norepinephrine in pathological gamblers (Roy et al., 1988; Bergh et al., 1997), and an increase of plasma norepinephrine during Pachinko play in regular players (Shinohara et al., 1999).

The dopaminergic mesolimbocortical system is another neuroendocrine pathway involved both in addictive behavior as well as reward and reinforcement (Potenza et al., 2002; Breiter et al., 2001; Knutson et al., 2001). However, the central and peripheral monoaminergic systems are separated by the blood–brain barrier which restricts a passage of dopamine and other catecholamines to a high percentage. Therefore, our observation of higher plasma dopamine levels in problem gamblers most likely reflects alterations in sympathoadrenal and cardiovascular activity. Peripheral dopamine, which is mainly synthesized by the adrenal glands and sympathetic nerve endings, has cardiovascular and renal effects. Peripheral dopamine increases myocardial contractility and cardiac output, without changing heart rate and alters diuretic and natriuretic properties (Contreras et al., 2002; Jose et al., 2002). Elevated dopamine levels in problem gamblers during casino gambling further support the observation of altered cardiovascular and sympathetic activity in pathological gambling. Whether increased peripheral dopamine corresponds in any way to the heightened central dopaminergic activity as observed by Bergh et al. (1997) remains to be established in studies that directly compare dopamine and its metabolites in plasma and in CSF of pathological gamblers and non-problem controls.

Moderate increases of plasma cortisol concentrations after gambling onset suggests exposure to moderate rather than severe stress. The absence of a prolactin response to gambling, which displays a pronounced increase after acute stress (Richter et al., 1996; Schedlowski et al., 1992), supports the theory of activation-like

responses to casino gambling. The current study found that plasma cortisol levels reach maximal concentrations at the beginning of gambling and decline towards the end of the casino gambling session. This is in contrast to our previous findings of elevated salivary cortisol throughout the gambling session (Meyer et al., 2000). Interestingly, problem gamblers and non-problem gamblers did not differ in their ACTH and cortisol response to casino gambling, indicating comparable activation patterns of the HPA-axis. This observation is supported by other studies which demonstrated either an increase of urinary cortisol on days associated with heavy gambling, in an Australian Aboriginal Community (Schmitt et al., 1998), or normal HPA-function in pathological gamblers, according to a dexamethasone suppression test (Ramirez et al., 1988).

Opioid systems may play a role in mediating levels of pleasure and modulating the mesocorticolimbic dopamine system. However, opioid levels vary with the type of gambling. Shinohara et al. (1999) reported elevated blood levels of β-endorphin during Pachinko play, whereas Blaszczynski et al. (1986) did not find a significant increase of β-endorphin in pathological gamblers. However, the β-endorphin levels of a subgroup of pathological gamblers betting on horse-race were reported to be significantly lower than those playing slot machines (Blaszczynski et al., 1986). The current study revealed lower plasma levels of β-endorphin in problem gamblers compared to non-problem gamblers, although these effects failed to be statistically significant. Thus, it remains equivocal whether diminished β-endorphin plasma levels may represent a state of underarousal in problem gamblers, as hypothesized by Blaszczynski et al. (1986). If this theory is correct, elevated levels of norepinephrine in problem gamblers during casino gambling may represent a compensating factor of states of underarousal or dysphoria in these subjects.

Furthermore, in the recent study, analysis of gambling behavior and the course of gambling revealed positive correlations between the actual result of gambling and norepinephrine levels and between the desire to start or continue gambling and norepinephrine levels at different time points of the experimental session over all participants. Thus, our findings support the assumption that noradrenergic mechanisms play an important role in moderating gambling behavior and are related to heightened arousal, monetary stakes/risk-taking, and readiness for gambling (Blanco et al., 2000; Ibánez et al., 2002; Roy et al., 1988; Zuckerman and Kuhlman, 2000).

Our research design of a quasi-experimental field study had the advantage of high external validity. However, this advantage is challenged by internal validity, as results may be influenced by numerous uncontrollable confounding variables, such as the social context of gambling (changing gamblers at the table with different gambling behavior, behavior of the dealers) or the course of gambling events (wagers, wins and losses). In addition, our study focused on a small number of male gamblers, could not realize the same environment (casino setting) for the experimental and control sessions, and only employed one type of gambling, thereby limiting the generalization of results. According to gamblers, blackjack has a reduced potential of stimulation compared to faster games with higher payoffs (e.g. slot machines or roulette). These forms of gambling might induce more pronounced neuroendocrine responses and should be compared in future studies. As the interpretation of peripheral endocrine changes in problematic gambling is limited, further studies should evaluate more direct measures of neuroendocrine alterations in gambling behavior such as neurochemical analysis by positron emission tomography or direct detection of neurotransmitters and metabolites in CSF.

In conclusion, the present study demonstrates a different gambling-induced catecholaminergic response pattern in problem gamblers compared to non-problem gamblers. This observation supports the hypothesis of altered monoaminergic mechanism in pathological gambling. Supporting this theory, norepinephrine levels were correlated with the urge to gamble.

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